UNIVERSITAT DE BARCELONA

Poliaminas en alimentos, leche materna y fórmulas infantiles

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2021

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Programa de Doctorado
Alimentación y Nutrición

POLIAMINAS EN ALIMENTOS, LECHE MATERNA Y FÓRMULAS INFANTILES

Memoria presentada por Nelly Carolina Muñoz Esparza
para optar al título de doctora por la Universidad de Barcelona

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ABREVIATURAS

Acetil-CoA	Acetil-coenzima A
AdoMetDC	S-Adenosil-Metionina Descarboxilasa
ADN	Ácido Desoxirribonucleico
ARN	Ácido Ribonucleico
ATP	Adenosín Trifosfato
CC	Circunferencia Cefálica
CMB	Circunferencia Media de Brazo
DAO	Diamino Oxidasa
DEXA	Absorciometría de Rayos X de Energía Dual
dcSAM	S-Adenosil-Metionina Descarboxilada
EFSA	Autoridad Europea de Seguridad Alimentaria / European Food Safety Authority
ESPGHAN	Sociedad Europea de Gastroenterología, Hepatología y Nutrición Pediátrica
IMC	Índice de Masa Corporal
5´MTA	5´-metiltioadenosina
ODC	Ornitina Descarboxilasa
OMS	Organización Mundial de la Salud
PAO	Poliamina Oxidasa
PCT	Pliegue Cutáneo Tricipital
PCSE	Pliegue Cutáneo Subescapular
SSAT	Espermidina/Espermina N1-Acetiltransferasa
UHPLC-FL	Cromatografía liquida de ultra alta eficacia con detección fluorimétrica

Resumen

Las poliaminas putrescina, espermidina y espermina son un grupo de moléculas que se encuentran de forma ubicua en todos los organismos vivos. Estos compuestos tienen diversas implicaciones en la salud humana, así como también durante las primeras etapas de la vida, ya que participan en la maduración intestinal y en el desarrollo del sistema inmune. Debido a su efecto antioxidante y antiinflamatorio, las poliaminas juegan un papel importante en la prevención de enfermedades crónicas como en patologías cardiovasculares, obesidad y diabetes, y se asocian con una mayor esperanza de vida.

Los alimentos son la principal fuente exógena de poliaminas en el ser humano, que se suma a la síntesis endógena de las mismas. A pesar de que todavía no existen recomendaciones de ingesta de poliaminas, se ha descrito que sus requerimientos aumentan en etapas de rápido crecimiento celular, como la etapa neonatal o lactante o durante procesos de cicatrización de heridas. Durante el envejecimiento, la síntesis endógena de poliaminas disminuye, y por lo tanto su ingesta adquiere una mayor relevancia. Uno de los objetivos de esta tesis doctoral fue estudiar la composición cuali y cuantitativa de poliaminas en diferentes alimentos y evaluar si se ven afectadas por distintos tratamientos culinarios en su contenido. Los resultados mostraron que el contenido y perfil de distribución de poliaminas en los alimentos fue muy variable, destacando por sus altas concentraciones el germen de trigo, los champiñones, la soja, los quesos y los derivados cárnicos fermentados. También se demostró que los tratamientos culinarios pueden modificar el contenido de poliaminas, siendo el microondas y el sous-vide los que menos afectaron los niveles de estos compuestos.

La leche materna es la primera fuente exógena de poliaminas para el ser humano. Por este motivo, en esta tesis se planteo estudiar también el contenido, perfil y evolución de las poliaminas en leche materna a lo largo de la lactancia. Cuando la lactancia materna no es posible, las fórmulas infantiles son los productos alimenticios adecuados para reemplazarla y por ello se evaluó también el contenido y perfil de poliaminas en diferentes fórmulas infantiles del mercado, y se compararon con la leche materna. Todas las

muestras de leche materna presentaron cantidades variables pero sustanciales de poliaminas, principalmente espermidina y espermina, disminuyendo a lo largo del progreso de la lactancia. En cambio, las fórmulas infantiles mostraron contenidos de poliaminas hasta 30 veces inferiores, siendo la putrescina la mayoritaria.

Otro objetivo de esta tesis fue estudiar la influencia de diversos factores relacionados con la díada madre-hijo y con el propio proceso de lactancia en las poliaminas de la leche materna. Así, se demostró que los niveles de poliaminas de la leche varían dentro de una misma toma (los del final doblan los del inicio), y que el contenido de espermina fue ligeramente más alto en la leche de las madres que dieron lactancia parcial en comparación con las de lactancia completa.

Finalmente, teniendo en cuenta que el tipo de alimentación durante los primeros meses de vida impacta en el crecimiento y composición corporal del lactante, así como la importancia de las poliaminas en el desarrollo del recién nacido y su hipotética implicación en la adipogénesis, también se estudió la influencia del tipo de lactancia y de las poliaminas de la leche materna sobre los parámetros antropométricos del lactante. Los lactantes alimentados con lactancia materna completa presentaron mejores indicadores antropométricos y una mayor ingesta de poliaminas en comparación con los alimentados con lactancia materna parcial. Sin embargo, de todos los parámetros antropométricos evaluados, solo el pliegue cutáneo tricipital y la circunferencia media de brazo mostraron una correlación débil e inversa, pero significativa, con el contenido e ingesta de putrescina y espermina.

Abstract

The polyamines putrescine, spermidine, and spermine are a ubiquitous group of molecules found in all living organisms. These compounds have various implications for human health, and in the early stages of life they contribute to intestinal maturation and the development of the immune system. Due to their antioxidant and anti-inflammatory effects, polyamines play an important role in the prevention of chronic diseases such as cardiovascular diseases, obesity, and diabetes, and are associated with a longer life expectancy.

In humans, food is the main exogenous source of polyamines, which are also available by endogenous synthesis. Although there are still no recommendations for their intake, it has been reported that the need for polyamines increases in stages of rapid cell growth, such as the neonatal or infant stage or during wound healing processes. During aging, the endogenous synthesis of polyamines decreases, and therefore their dietary intake becomes more important. One of the objectives of this doctoral thesis was to study the qualitative and quantitative content of polyamines in different foods and how they are affected by different culinary treatments. The content and distribution profile of polyamines in foods was highly variable, being wheat germ, mushrooms, soybeans, cheeses and dry-fermented sausages the food products with the highest concentrations. It was also demonstrated that certain culinary treatments can modify the occurrence of polyamines, being microwave and sous-vide cooking the methods that least affected the levels of these compounds.

Breast milk is the first exogenous source of polyamines for humans. This thesis also aimed to study the content, profile and evolution of polyamines in human milk throughout lactation. When breastfeeding is not possible, infant formulas provide a suitable alternative. In this sense, the polyamine content and profile of different commercial infant formulas was also evaluated and compared to that of human milk. All human milk samples showed variable yet significant amounts of polyamines, mainly spermidine and spermine,

showing a decrease throughout the lactation progress. In contrast, infant formulas showed polyamine contents up to 30 times lower, putrescine being the main polyamine.

Another objective of this thesis was to study the influence of various factors related to the mother-child dyad and to the lactation process itself on the human milk polyamines. It was shown that the levels of polyamines in human milk vary within a single feed (twice in hindmilk than in foremilk), and that the spermine content was slightly higher in the milk of mothers providing partial, rather than full, breastfeeding.

Finally, taking into account that the type of feeding during the first months of life affects the growth and body composition of the infant, and the importance of polyamines in the development of the newborn, including their hypothetical implication in adipogenesis, the Influence of the type of breastfeeding and the human milk polyamines on the anthropometric parameters of the infant was also studied. Fully breastfed infants showed better anthropometric indicators and a higher polyamine intake than those partially breastfed. However, among all evaluated anthropometric parameters, only the tricipital skinfold and the mean upper arm circumference showed a weak and inverse correlation, but significant, with the content and intake of putrescine and spermine.

1| Introducción

1 Introducción

1.1 Poliaminas, salud y alimentación

Las poliaminas son compuestos nitrogenados de bajo peso molecular, que están presentes de forma ubicua en todos los organismos vivos (Larqué et al., 2007; Kalač, 2014). La presencia de estos compuestos se describió por primera vez en materiales biológicos hace más de 300 años. En 1678, A. Leeuwenhoeck descubrió la existencia de cristales en el semen humano, aunque no fue hasta 1865 que Boettcher sugirió que estos cristales estaban formados por una proteína, a la que denominó espermatina (Leeuwenhoeck van, 1678; Bachrach, 2010). En 1878, P. Schreiner determinó que estos cristales no eran una proteína, si no que consistían en un compuesto básico en forma de sal de fosfato (Schreiner, 1878). Pocos años después, A. Landenburg y J. Abel, denominaron espermina a esta base orgánica por encontrarse en cantidades particularmente altas en el semen humano (Landenburg, 1888). Finalmente, en 1926, O. Rosenheim estableció la estructura química de la espermina (N,N-bis(3-aminopropil)-1,4-butano diamina), una poliamina alifática formada por cuatro grupos amino (Rosenheim, 1924). Años más tarde, se identificó la espermidina (N-(3-aminopropil)-1,4-butano diamina), en tejidos de animales, de plantas y en microorganismos (Herrera et al., 2014; Mendez, 2017). La putrescina (1,4-butano diamina), denominada así por las elevadas concentraciones encontradas en carnes putrefactas, fue descrita por primera vez en 1885 por L. Brieger en tejido animal (Mendez, 2017).

La putrescina, la espermidina y la espermina son poliaminas que se caracterizan por la presencia de dos o más grupos amino (Figura 1). Debido a su estructura, son compuestos relativamente estables, capaces de resistir condiciones tanto ácidas como alcalinas, y de establecer puentes de hidrógeno con solventes hidroxílicos como el agua y el alcohol (Moinard et al., 2005; Agostinelli et al., 2010). En el organismo, a pH fisiológico las poliaminas están completamente protonadas y pueden unirse fuertemente a biomoléculas como el ADN, el ARN, el ATP, proteínas y fosfolípidos, estabilizando sus cargas negativas y, en muchos casos, modulando su función (Handa et al., 2018; Hirano et al., 2021). A nivel celular, las poliaminas se almacenan principalmente en el citosol y el núcleo, donde participan en procesos de transcripción del ADN y traducción del ARN (Moinard et al., 2005; Larqué et al., 2007).

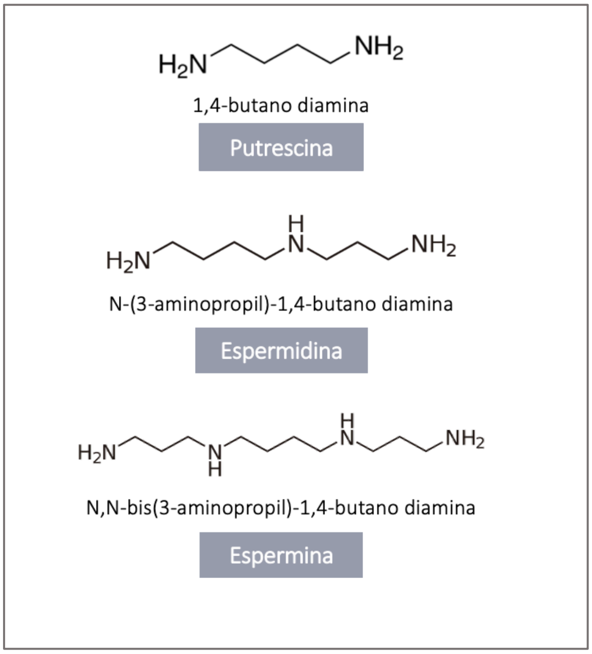

Figura 1. Estructura química de las poliaminas.

En los seres humanos, las poliaminas tienen un papel esencial en la regulación de diversos procesos celulares, tales como el crecimiento y la diferenciación celular, y la síntesis de proteínas y de ácidos nucleicos (Kalač, 2014; Bae et al., 2018). Además, las poliaminas también participan en la regulación de la respuesta inmune, en la regulación de los canales iónicos, particularmente bloqueando los canales de potasio y en la apoptosis celular (Larqué et al., 2007; Ruiz-Cano, 2012; Kalač, 2014). Otro aspecto importante por el que también se han estudiado las poliaminas es por su capacidad antioxidante, con un efecto similar al de otros compuestos con reconocida actividad (α-tocoferol, palmitato de ascorbilo y galato de octilo) (Toro-Funes et al., 2013). En este sentido, el principal mecanismo antioxidante es su capacidad para quelar metales, lo que evita la formación de hidroperóxidos y compuestos de oxidación secundaria (Løvaas, 1991; Toro-Funes et al., 2013). La espermina es la poliamina con mayor capacidad antioxidante debido a la mayor cantidad de cargas positivas en su estructura química, seguida de la espermidina (Toro-Funes et al., 2013). Además, las poliaminas también actúan protegiendo al ADN frente al daño oxidativo, al eliminar los radicales libres, especialmente en medios lipofílicos (Farriol et al., 2003; Toro-Funes et al., 2013).

Las poliaminas tienen implicaciones importantes en la salud humana, principalmente en las primeras etapas de la vida, ya que participan en la maduración intestinal y en el desarrollo del sistema inmune (Dandrifosse et al., 2000; Pérez-Cano et al., 2010; Gómez-Gallego et al., 2014). Debido a su efecto antioxidante y antiinflamatorio, las poliaminas también juegan un papel importante en la prevención de enfermedades crónicas no transmisibles como ciertas patologías cardiovasculares, la obesidad y la diabetes (Soda et al., 2009; Eisenberg et al., 2016; Kiechl et al., 2018). Asimismo, la implicación de estos compuestos en procesos de apoptosis celular y en la prevención de la metilación del ADN, hace que se las haya asociado con una mayor esperanza de vida (Nishimura et al., 2006; Madeo et al., 2018; Soda et al., 2021).

Las poliaminas se encuentran en todos los seres vivos y por ello se pueden encontrar en una gran variedad de alimentos, tanto de origen animal como vegetal. Sin embargo, la composición cuali y cuantitativa de las tres poliaminas puede variar en función del tipo de producto (Kalač, 2014). Además, la leche humana también es fuente de poliaminas, constituyendo el primer aporte exógeno de estos compuestos en el ser humano (Larqué et al., 2007). A pesar de que todavía no existen recomendaciones de ingesta de poliaminas, se sabe que en etapas de rápido crecimiento celular, como la etapa neonatal o lactante, así como durante procesos de cicatrización de heridas, los requerimientos de poliaminas aumentan (Atiya-Ali et al., 2011). Durante el envejecimiento la síntesis endógena de poliaminas disminuye, por lo que las poliaminas dietéticas adquieren una mayor importancia (Nishimura et al., 2006).

En los siguientes apartados de esta introducción se tratarán detalladamente la homeostasis de las poliaminas en el organismo humano, la relación de las poliaminas con la salud y, por último, los aspectos relacionados con las poliaminas en los alimentos.

1.2 Homeostasis de las poliaminas en el organismo

La homeostasis celular de las poliaminas en el organismo está fuertemente regulada y depende del equilibrio entre la síntesis endógena, el aporte dietético y su catabolismo (Moinard et al., 2005; Kalač, 2014). La ornitina descarboxilasa (ODC) y la S-adenosil-metionina descarboxilasa (AdoMetDC) son las dos enzimas claves en las biosíntesis de las poliaminas. Por otro lado, la espermidina/espermina N1-acetiltransferasa (SSAT) y la poliamina oxidasa (PAO) controlan la interconversión y el catabolismo de las poliaminas (Büyükuslu & Öztürk, 2018). La figura 2 muestra esquemáticamente las rutas metabólicas de síntesis, interconversión y catabolismo de las poliaminas.

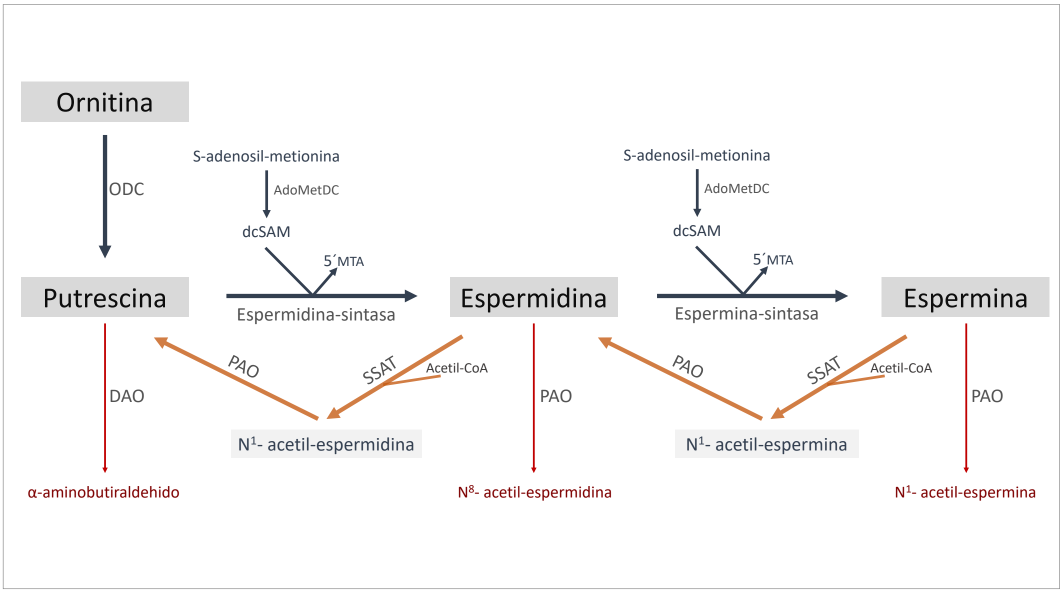

Figura 2. Síntesis *de novo*, interconversión y catabolismo de las poliaminas en el organismo. ODC: ornitina descarboxilasa, AdoMetDC: S-adenosil-metionina descarboxilasa; dcSAM: S-denosil-metionina descarboxilada, 5´MTA: 5´-metiltioadenosina, SSAT: espermidina/ espermina N1-acetiltransferasa, Acetil-CoA: Acetil coenzima A, PAO: poliamina oxidasa, DAO: diamino oxidasa. (Adaptado de Moinard et al., 2005; Larqué et al., 2007; Miller-Fleming et al., 2015).

1.2.1 Síntesis endógena de poliaminas

Las concentraciones intracelulares de poliaminas están reguladas principalmente por la síntesis *de novo* (Figura 2). La putrescina se sintetiza a partir del aminoácido ornitina por la acción de la enzima ODC. La espermidina se obtiene a partir de la putrescina por acción de la enzima espermidina-sintasa, que cataliza la adición de un grupo propilamino procedente de la descarboxilación de la S-adenosil-metionina. Finalmente, la enzima espermina-sintasa es la encargada de transformar la espermidina en espermina mediante la adición de un segundo grupo propilamino (Moinard et al., 2005; Miller-Fleming et al., 2015).

Además de la formación *de novo*, también es posible la interconversión entre poliaminas, el cual es un proceso cíclico que controla el recambio de poliaminas y regula su homeostasis intracelular (Figura 2). La interconversión se inicia con la acetilación de la espermina o la espermidina, por acción de la enzima SSAT y con la participación de acetil coenzima-A. Posteriormente, la enzima PAO elimina un grupo propilamino, obteniendo putrescina a partir del metabolito acetilado de la espermidina, o bien espermidina a partir del metabolito acetilado de la espermina (Larqué et al., 2007; Minois et al., 2011; Kalač, 2014).

1.2.2 Origen exógeno de poliaminas

Las poliaminas también pueden tener un origen exógeno, principalmente procedente de los alimentos. Las secreciones intestinales y pancreáticas, así como los productos del catabolismo de las células intestinales también contribuyen al *pool* total de poliaminas intestinales (Larqué et al., 2007). Las poliaminas dietéticas y luminales se absorben en el intestino delgado, principalmente en el duodeno y en el primer segmento del yeyuno, a través de mecanismos de absorción transcelular con la participación de transportadores, o pasivamente a través de la ruta paracelular, siendo esta última la principal vía de absorción (Figura 3) (Larqué et al., 2007; Bae et al., 2018; Ramos-Molina et al., 2019; Hirano et al., 2021). A pesar de que no existe mucha información acerca de los transportadores de poliaminas en células de mamíferos, se han identificado dos transportadores transmembranales de la Familia de Transportadores de Solutos (SLC por sus siglas en inglés) (Lenis et al., 2017; Bae et al., 2018). Las poliaminas exógenas se incorporan a la célula a través del transportador de carnitina SLC22A16, mientras que el transportador SLC3A2 es responsable de la excreción de poliaminas acetiladas, especialmente putrescina y espermidina (Bae et al., 2018; Ramos-Molina et al., 2019).

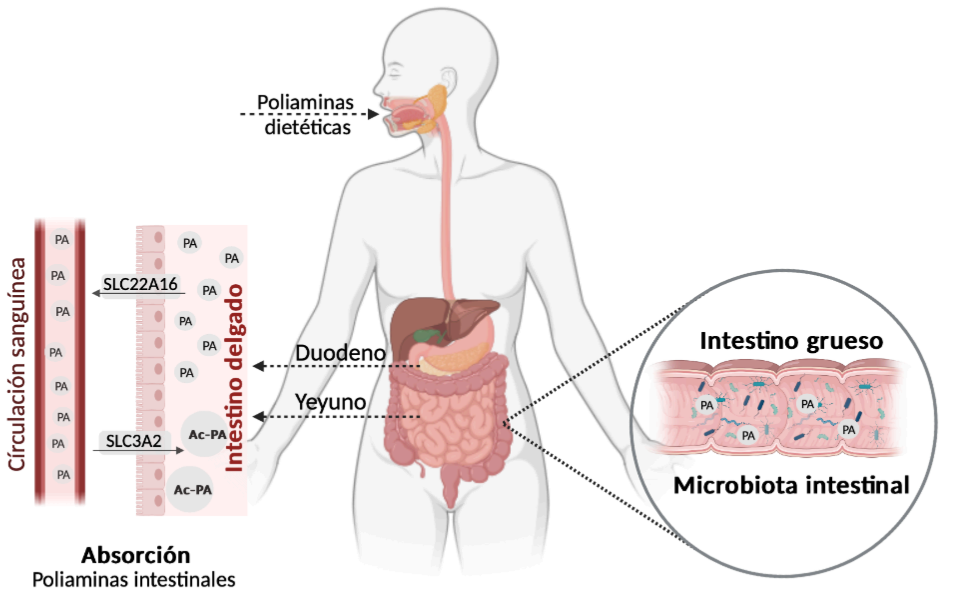

Figura 3. Absorción de poliaminas dietéticas e intestinales.
SLC3A2: Familia de Transportadores de Solutos; SLC22A16: transportador de carnitina; PA: poliaminas; Ac-PA: poliaminas acetiladas.

Una vez que las poliaminas alcanzan la circulación sistémica, se distribuyen a los diferentes tejidos, principalmente a aquellos con una alta tasa de renovación celular, como el cerebro, hígado, corazón, páncreas, timo y tejido adiposo; en los cuales pueden ser utilizadas directamente por la célula o experimentar reacciones de interconversión (Larqué et al., 2007; Ramos-Molina et al., 2019).

Otro posible origen exógeno de poliaminas en el organismo seria la microbiota, aunque todavía existen muy pocos trabajos sobre este tema. Estos estudios han relacionado diferentes especies microbianas intestinales, principalmente Bacteroides y Fusobacterias con la síntesis de putrescina y espermidina (Ramos-Molina et al., 2019; Tofalo et al., 2019). Además, Tofalo et al. (2019) describen también cómo la presencia de fibras fermentables en el intestino grueso estimula la producción de poliaminas por parte de estos microorganismos de la microbiota intestinal. Según los mismos autores, parte de las poliaminas sintetizadas por la microbiota colónica pasarían al organismo, mientras que el resto serían excretadas a través de las heces (Ramos-Molina et al., 2019; Tofalo et al., 2019). Sin embargo, hoy en día, sigue siendo incierta cuál es la contribución de la microbiota intestinal al *pool* global de poliaminas, siendo necesaria la realización de más estudios enfocados a conocer la capacidad de los microorganismos para formar poliaminas, de las posibles vías biosintéticas y mecanismos o vías de absorción.

1.2.3 Catabolismo de las poliaminas

La degradación de poliaminas en el organismo se lleva a cabo mediante reacciones de desaminación oxidativa, principalmente por acción de las enzimas PAO y diamino oxidasa (DAO). Concretamente, la putrescina es metabolizada a alfa-aminobutiraldehido por la DAO y este aldehído puede ser posteriormente oxidado a ácido gamma-aminobutirico (GABA) (Moinard et al., 2005; Herrera et al., 2014). La PAO participa en la degradación de la espermina y la espermidina, ya sea para su interconversión o para eliminarlas de la célula. Por tanto, es posible detectar metabolitos de las poliaminas en la orina, ya sea en sus formas acetiladas o como productos oxidados (Minois et al., 2011; Ruiz-Cano, 2012; Ramos-Molina et al., 2019).

1.3 Poliaminas y salud

En las últimas décadas se han publicado diversos estudios que avalan la implicación de las poliaminas en la salud humana, principalmente en las primeras etapas de la vida y durante el envejecimiento (Moinard et al., 2005; Kalač, 2014; Handa et al., 2018; Hirano et al., 2021). Asimismo, también se ha descrito un impacto positivo de las poliaminas en la prevención de enfermedades crónicas no transmisibles, tales como obesidad, enfermedades cardiovasculares, diabetes o cáncer (Kiechl et al., 2018; Soda et al., 2009, 2010, 2021).

1.3.1 Poliaminas en las primeras etapas de la vida

Las poliaminas participan en diferentes procesos biológicos a lo largo de los primeros años de la vida. Durante las etapas neonatal y lactante, las poliaminas promueven el crecimiento y la maduración del tracto gastrointestinal y participan en el desarrollo del sistema inmune (Romain et al., 1992; Buts et al., 1995; Dandrifosse et al., 2000; Sabater-Molina et al., 2009; Pérez-Cano et al., 2010; Gómez-Gallego et al., 2014). Así, los requerimientos de poliaminas durante estas etapas son mayores, debido a la rápida tasa de crecimiento celular (Gómez-Gallego et al., 2008; Plaza-Zamora et al., 2013).

En relación al efecto de las poliaminas en la maduración intestinal postnatal, existen diversos estudios que han demostrado como la administración oral de estos compuestos induce ciertas modificaciones morfológicas y bioquímicas a nivel intestinal, aunque todos estos trabajos se han realizado con modelos animales. Concretamente, algunos autores han señalado que la administración de espermina y espermidina en ratones, incrementó la expresión de proteínas y modificó la actividad de las disacaridasas, marcadores de la maduración del intestino delgado (Buts et al., 1993; Dandrifosse et al., 2000; Peulen et al., 2004). Además, también se ha descrito como las poliaminas intervienen en la maduración de otros órganos, como el hígado y el páncreas (Dandrifosse et al., 2000). Biol-N'garagba et al. (2002) sugieren que los cambios postnatales en la fucosilación de las glucoproteínas intestinales, como parte del proceso de maduración intestinal, podrían relacionarse en gran parte con la ingesta de poliaminas. Concretamente, estos autores demostraron en ratones que la administración oral de 10 μmol/día de espermina y espermidina aumentó la actividad de la α-1,2-fucosiltransferasa provocando una mayor concentración de α-1,2-fucoproteínas en la membrana del borde en cepillo. En esta línea, otros autores también han reportado cambios bioquímicos asociados a la maduración del intestino delgado, como un incremento de la actividad enzimática de la fosfatasa alcalina y de la gama glutamil-transferasa (Peulen et al., 2004; Sabater-Molina et al., 2009).

A nivel morfológico, Sabater-Molina et al. (2009) demostraron cómo la suplementación de poliaminas en lechones recién nacidos, a las dosis fisiológicas en las que se encuentran en la leche de este animal, aumentó significativamente la profundidad de la cripta en el intestino delgado en comparación con el grupo no suplementado. Además, Pérez-Cano et al. (2010) observaron que la administración de espermina y espermidina en ratas recién nacidas se relacionaba con un mayor peso y longitud del intestino, lo que indicaba una estructura intestinal más madura.

Desde el punto de vista de la respuesta inmunitaria, estudios realizados en modelos animales señalan que la administración oral de espermina y espermidina en el período postnatal se traduce en una mejora en la maduración de las células inmunitarias intestinales e incrementa los niveles de inmunoglobulina A (Buts et al., 1993; Ter Steege et al., 1997; Dandrifosse et al., 2000; Pérez-Cano et al., 2010). Concretamente, Ter Steege et al. (1997) demostraron que la ingesta de espermina aumentó el porcentaje de linfocitos intraepiteliales (CD4, CD5 y CD54) y consecuentemente los niveles de expresión de estos anticuerpos. Asimismo, Pérez-Cano et al. (2010) observaron que la suplementación diaria de espermidina y espermina incrementaba significativamente la maduración de linfocitos intraepiteliales CD8 y la presencia de células asesinas naturales (natural killer cells), lo que se relaciona con un aumento de la inmunidad innata.

Durante los primeros meses de vida, el intestino es más permeable a macromoléculas, aumentando así el riesgo de desarrollar alergia (Dandrifosse et al., 2000). En esta línea, Dandrifosse et al. (1991) demostraron que la administración de espermina indujo un aumento en la actividad de las proteasas del páncreas, lo que mejoró la digestión de proteínas y, por tanto, disminuyendo la probabilidad de alergenicidad. Además, es conocido que los lactantes alimentados con leche materna tienen un menor riesgo de desarrollar alergia en comparación con los alimentados con fórmulas infantiles (Matsumoto et al., 2020). Esto se puede atribuir principalmente a la presencia de compuestos bioactivos en la leche materna, como inmunoglobulinas, factores de crecimiento, nucleótidos, citoquinas, así como también poliaminas (Pérez-Cano et al., 2010; Matsumoto et al., 2020). En este sentido, Peulen et al. (1998) reportaron que un mayor contenido de espermina en la leche materna durante el primer mes postparto, se asoció con una menor presencia de alergia a los cinco años de edad del niño. Además, como se ha mencionado anteriormente, la presencia de poliaminas promueve la maduración intestinal, lo que, en último término, se asocia con una menor permeabilidad intestinal. Esto limita el paso de antígenos del lumen hacía la circulación sanguínea, reduciendo así el riesgo de alergia en el lactante (Romain et al., 1992; Pérez-Cano et al., 2010; Gómez-Gallego et al., 2014). Con todo esto, se ha señalado la importancia de suplementar con poliaminas las fórmulas infantiles para ayudar a la prevención del desarrollo de alergias (Peulen et al., 1998; Dandrifosse et al., 2000).

Por último, además de las funciones mencionadas sobre la maduración e inmunidad intestinal, las poliaminas se han relacionado también con cambios en la composición de la microbiota (Gómez-Gallego et al., 2012; Gómez-Gallego et al., 2017). Los estudios realizados por estos autores en ratones recién nacidos demostraron que la administración de una fórmula infantil adicionada con poliaminas tuvo un impacto significativo en la composición y actividad de la microbiota. Específicamente observaron un incremento significativo en el número de especies de *Bifidobacterias* en el intestino en comparación con el grupo no suplementado con poliaminas. Estas bacterias tienen un papel biológico en la relación entre la mucosa del huésped y la microbiota, en la regulación inmune y en el control de la inflamación. Además, estos autores también encontraron un aumento en la concentración de la bacteria *Akkermansia muciniphila*, una especie común de la microbiota intestinal que promueve tanto el desarrollo de las respuestas inmunes innata como el de la adaptativa.

1.3.2 Poliaminas y envejecimiento

Durante el envejecimiento, las concentraciones celulares de espermina y espermidina, así como también de la actividad enzimática de la ODC tienden a disminuir, por lo que el aporte exógeno de poliaminas se vuelve relevante (Minois et al., 2011; Nishimura et al., 2006; Soda, 2020). Recientemente, las poliaminas se han asociado a un efecto protector contra el proceso de envejecimiento, e incluso se han descrito como posibles compuestos promotores de la esperanza de vida (Soda, 2020). Este potencial efecto de las poliaminas se relaciona principalmente con su capacidad de estimular la autofagia, en la que eliminan proteínas y orgánulos dañados de las células. Se ha descrito que las poliaminas son capaces de inhibir varias acetiltransferasas, especialmente la proteína p300 asociada a E1A, que es uno de los principales reguladores negativos de la autofagia (Eisenberg et al., 2009; Mariño et al., 2014; Madeo et al., 2018).

Por otro lado, también se ha relacionado el metabolismo de las poliaminas con la regulación del proceso de metilación del ADN (Soda, 2020). La S-Adenosil-metionina descarboxilada (dcSAM) es un sustrato fundamental para la síntesis de poliaminas que, a su vez, también participa en la regulación de la metilación del ADN. Cantidades elevadas de dcSAM se han relacionado con un incremento de metilación aberrante del ADN, lo cual se relaciona con la aparición de patologías asociadas a la edad. Algunos estudios, tanto *in vitro* como en animales de experimentación, han demostrado que una inducción del proceso de síntesis de poliaminas mantiene las concentraciones de dcSAM bajas, inhibiendo así la metilación aberrante del ADN (Soda et al., 2013; Soda, 2020).

Se ha sugerido que el enriquecimiento de la dieta con poliaminas durante el envejecimiento disminuye el riesgo de presentar patologías asociadas a la edad y promueve la longevidad. En este sentido, Soda et al. (2009) demostraron en animales de experimentación que una dieta rica en poliaminas reducía la aparición de atrofia glomerular renal relacionada con la edad, así como también la tasa de mortalidad. Posteriormente, estos mismos autores observaron, en una cohorte de población japonesa, que la ingesta a largo plazo de espermidina (1880 nmol/g) y espermina (390 nmol/g) a través del consumo de alimentos a base de soja (p.ej. natto) comportó un aumento de las concentraciones de espermina en sangre (Soda et al., 2021). A la vez, esta espermina se relacionó con una reducción de la metilación aberrante del genoma (Soda et al., 2021). En cuanto a la espermidina, el estudio realizado por Kiechl et al. (2018) en una cohorte de 829 participantes durante 20 años, relacionó una dieta rica en este compuesto con una disminución en el riesgo de mortalidad. Concretamente, de entre los 146 nutrientes investigados (p.ej. vitaminas, putrescina, espermina, etc.), la espermidina fue la que mostró la mayor relación inversa con la mortalidad, con un efecto dosis-dependiente. Los autores atribuyen estos resultados al hecho de que la espermidina induce la autofagia y reduce la acetilación de histonas, un proceso también crítico en la homeostasis celular durante el envejecimiento.

Los trastornos neurodegenerativos son otro tipo de afectaciones que frecuentemente se asocian con el envejecimiento. Las poliaminas, y en particular la espermidina, parecen ejercer efectos neuroprotectores según varios estudios realizados en modelos animales (Guo et al., 2011; Gupta et al., 2013; Minois et al., 2014; Q. Yang et al., 2016). Por ejemplo, se demostró que la alimentación adicionada con espermidina protegía las moscas del deterioro de la memoria inducido por la edad (Gupta et al., 2013), así como también de la pérdida de la actividad locomotora (Minois et al., 2014). De nuevo, estos efectos se explicarían por el efecto protector de la autofagia, que mantiene la flexibilidad y plasticidad sináptica (Gupta et al., 2016). Asimismo, en un modelo de ratón con esclerosis múltiple, la suplementación con espermidina atenuó la progresión de la enfermedad y mejoró las funciones visuales mediante la reducción de la desmielinización del nervio óptico y la médula espinal (Guo et al., 2011; Q. Yang et al., 2016). También la espermina se ha relacionado con una mejora del déficit de memoria de reconocimiento y del aprendizaje espacial en modelos de roedores (Velloso et al., 2009).

Una de las características del envejecimiento es la disminución de la función de las células madre, lo que da como resultado una deficiente regeneración tisular (López-Otín et al., 2013). La administración de espermidina en ratones de edad avanzada, revirtió la disminución de la autofagia asociada a la edad en células madre musculares, previniendo su senescencia y mejorando la regeneración muscular (García-Prat et al., 2016). Asimismo, la espermidina (sola o en combinación con ejercicio) inhibió con éxito la atrofia del músculo esquelético en ratas, debido también como en el anterior estudio a la inducción de la autofagia (Fan et al., 2017).

1.3.3 Poliaminas en la prevención de enfermedades crónicas no transmisibles

Las enfermedades crónicas no transmisibles son el resultado de una combinación de factores genéticos, fisiológicos, ambientales y del comportamiento. Las principales enfermedades no transmisibles son la obesidad, las enfermedades cardiovasculares, la diabetes y el cáncer (OMS, 2020). Cada año mueren 41 millones de personas a causa de estas enfermedades, lo que equivale a 71% de todas las muertes en el mundo (OMS, 2020).

1.3.3.1 Obesidad

La obesidad es un problema de salud pública, que afecta a millones de personas en el ámbito mundial y se asocia con el desarrollo de diversas patologías como diabetes tipo 2, esteatosis hepática, enfermedades cardiovasculares, ictus e incluso cáncer (Ma et al., 2021). En las últimas décadas, la prevalencia de obesidad en niños y adolescentes ha aumentado hasta diez veces, por lo que la investigación sobre su etiopatogenia, tratamientos efectivos y comorbilidades también ha incrementado. En esta línea, se ha descrito que las poliaminas pueden tener un papel esencial en la adipogénesis. Diversos estudios han demostrado que la enzima espermidina/espermina-N1-acetiltransferasa (SSAT), un regulador metabólico clave en la homeostasis de las poliaminas se encuentra fuertemente implicada con la adipogénesis. La SSAT cataliza la transferencia de grupos acetilo procedentes del acetil-CoA a la espermidina o espermina, ya sea para su interconversión o excreción (Figura 2). Por lo tanto, una sobreexpresión de esta enzima incrementa la biosíntesis de poliaminas, reduciendo así las concentraciones de acetil-CoA y, consecuentemente, inhibiendo la formación de malonil-CoA y la síntesis de ácidos grasos (Büyükuslu & Öztürk, 2018; Liu et al., 2014). Pirinen et al. (2007) demostraron también que la sobreexpresión de la enzima SSAT en ratones provocaba una mejor tolerancia a la glucosa y sensibilidad a la insulina, así como una menor acumulación de triglicéridos en el hígado y en el músculo esquelético y una disminución del tejido adiposo blanco. Años más tarde, el estudio realizado por Liu et al. (2014) confirmó la relación entre el metabolismo de las poliaminas y la lipogénesis. Diversos estudios han demostrado que la desregulación del metabolismo de las poliaminas podría afectar la homeostasis de la glucosa, los lípidos y el gasto energético y, por tanto, contribuir al desarrollo de la obesidad (Ishii et al., 2012; Brenner et al., 2015; Ramos-Molina et al., 2018).

Más allá de los trabajos que intentan elucidar la relación entre las poliaminas y los mecanismos de la obesidad, hasta la fecha existen pocos trabajos que hayan evaluado el efecto del aporte exógeno de poliaminas en el tratamiento de esta patología, y que todos los trabajos se han realizado únicamente con modelos animales. En 2014, Sadasivan et al. estudiaron el efecto de la administración exógena de espermina (5mg/kg y 10mg/kg) durante cuatro semanas en ratones con obesidad inducida por una dieta hipercalórica. La suplementación con espermina provocó una disminución del peso corporal (24%) y de la masa grasa (52%), siendo mayor el efecto en el grupo con más aporte de espermina. Además, otros parámetros como la lipolisis y la tolerancia a la glucosa se vieron aumentados. En otro estudio realizado por Fernández et al. (2017) se observó que la administración intraperitoneal de espermidina (50 mg/kg) reducía significativamente la ganancia de peso, la grasa visceral, el diámetro de los adipocitos y la esteatosis hepática. Asimismo, los ratones también mejoraron significativamente su tolerancia a la glucosa y la sensibilidad a la insulina. El estudio publicado recientemente por Ma et al. (2021) ha demostrado que la suplementación de espermidina (20 mg/kg) en ratones con obesidad también reduce el peso corporal y la masa grasa, así como diferentes marcadores relacionados con la obesidad (esteatosis hepática, concentraciones séricas de triglicéridos, colesterol total, glucosa e insulina).

A pesar de que la evidencia científica disponible hasta el momento apunta a un papel protector de las poliaminas frente a la obesidad, todavía son necesarios más estudios que ayuden a entender los mecanismos que sustentan esta relación para, en un futuro, poder considerar la suplementación con poliaminas como herramienta en la prevención y tratamiento de la obesidad.

1.3.3.2 Enfermedades cardiovasculares

De todas las enfermedades no transmisibles, el grupo integrado por las enfermedades cardiovasculares es el que provoca uno de los mayores impactos en términos de morbilidad y mortalidad, ocasionando 17,9 millones de muertes cada año entre los 30 y los 69 años. Más de 85% de estas muertes ocurren en países de ingresos bajos y medianos (OMS, 2020). En España, de acuerdo con el Instituto Nacional de Estadística, en el período de enero a mayo del 2020, las enfermedades cardiovasculares fueron la primera causa de muerte (23%), seguido de las enfermedades infecciosas, que incluye la enfermedad COVID-19 causada por el coronavirus SARS-CoV-2 (20%).

Algunos autores han investigado el papel que desempeñan las poliaminas en la prevención de enfermedades cardiovasculares, principalmente por sus propiedades antioxidantes y antiinflamatorias (Gugliucci & Menini, 2003; Soda et al., 2009; Soda, 2011). El efecto antioxidante y antiinflamatorio de las poliaminas frente al estrés oxidativo se ha estudiado tanto *in vitro* como *in vivo*, demostrando que las poliaminas eran capaces de reducir significativamente la producción de mediadores pro-inflamatorios, como el óxido nítrico, la prostaglandina E2 y las citocinas, así como la acumulación de especies reactivas de oxígeno (Choi & Park, 2012; Jeong et al., 2018).

Una mayor ingesta de poliaminas a través de la alimentación se ha correlacionado con una menor incidencia de enfermedades cardiovasculares y una disminución de la presión arterial y de la insuficiencia cardíaca (Soda, 2010; Soda et al., 2012; Madeo et al., 2018). Estudios en animales, principalmente en ratones envejecidos, han demostrado que la administración de espermidina disminuye la rigidez arterial inducida por la edad y el daño oxidativo de las células endoteliales, además atenúa el envejecimiento cardíaco mediante la activación de la biogénesis mitocondrial (LaRocca et al., 2013; Michiels et al., 2016; Madeo et al., 2018; Wang et al., 2020). Asimismo, Eisenberg et al. (2016) demostraron que la espermidina prolonga la vida de los ratones y ejerce efectos cardio-protectores, reduciendo la hipertrofia cardíaca y la presión arterial. En la misma línea, el trabajo realizado por Zhang et al. (2017) comprobó que la suplementación con espermina y espermidina durante seis semanas en ratones revertía los cambios en la morfología del miocardio asociados con la edad (fibrosis miocárdica) (Zhang et al., 2017).

De hecho, según Soda et al. (2012) es probable que la eficacia de las poliaminas en la prevención y tratamiento de la enfermedad cardiovascular sea similar a la de los ácidos grasos poliinsaturados (PUFA 3-n) y las estatinas (Soda, 2010; Soda et al., 2012). De confirmarse, las poliaminas podrían devenir en una innovadora aproximación dietética para la prevención de la enfermedad cardiovascular.

1.3.3.3 Diabetes

Con respecto a la diabetes tipo 2, la glicación tiene un efecto importante en la génesis de las complicaciones de esta patología, por lo que aquellos compuestos que la retarden o contrarresten serían deseables para el tratamiento. Las poliaminas, debido a su estructura química, podrían funcionar como agentes antiglicantes retrasando la acumulación de productos resultantes de esta reacción (Moinard et al., 2005; Bjelakovic et al., 2010). Se ha propuesto que el efecto protector de las poliaminas se podría explicar por la interacción de sus grupos amino libres con los compuestos carbonílicos, altamente reactivos (Gugliucci & Menini, 2003; Gugliucci, 2004). Estudios *in vitro* han demostrado que concentraciones milimolares de espermina presentes en el núcleo de la célula pueden proteger el ADN y las histonas de la glicación (Gugliucci & Menini, 2003). Modelos animales a los que se les ha inducido farmacológicamente la diabetes, han permitido demostrar también que la administración exógena de espermidina y espermina reduce las concentraciones de hemoglobina glucosilada y la formación de productos finales de glicación avanzada, mejorando además el perfil de lípidos (Méndez & Leal, 2004; Jafarnejad et al., 2008).

1.3.3.4 Cáncer

Las elevadas concentraciones de poliaminas en pacientes con cáncer están asociados con el crecimiento tumoral (Casero et al., 2018; Gerner et al., 2018). La desregulación en la biosíntesis de poliaminas, debido principalmente al aumento de la actividad de la enzima ODC, conduce a un alto contenido de poliaminas intracelulares en las células cancerosas (Soda et al., 2012; Kalač, 2014; Gerner et al., 2018). Por tanto, el control de la síntesis de poliaminas podría ser útil en la terapia antineoplásica. De acuerdo a diferentes estudios experimentales y ensayos clínicos, el tratamiento combinado con DFMO (difluorometilornitina), un inhibidor potente e irreversible de la ODC, con fármacos inhibidores del transporte de poliaminas, redujo eficazmente la carcinogénesis al inhibir la síntesis de poliaminas y estimular el catabolismo y exportación de poliaminas (Casero et al., 2018; Gerner et al., 2018).

En pacientes que padecen cáncer se ha observado un aumento de los metabolitos acetilados de las poliaminas en orina y/o en sangre. Este aumento de las poliaminas acetiladas en orina podría explicarse ya sea por un incremento de las poliaminas celulares y de la actividad de la enzima SSAT, o por una disminución de su degradación oxidativa por acción de la enzima PAO, aunque los mecanismos moleculares no están del todo aclarados (Park & Igarashi, 2013). En la última década, el desarrollo de técnicas metabolómicas más sensibles ha permitido detallar perfiles metabólicos de las poliaminas asociados con ciertos tipos de cáncer (Casero et al., 2018). De hecho, se ha encontrado un incremento de las concentraciones de poliaminas acetiladas en orina o sangre, particularmente de N1, N12-diacetilespermina, de N1, N8-acetilespermidina, de N1-

acetilespermina y de N8-acetilespermidina en pacientes con cáncer de ovario, de próstata, de colon, de páncreas, de mama y de pulmón (Umemori et al., 2010; Casero et al., 2018; DeFelice & Fiehn, 2019). Entre las poliaminas acetiladas, se ha descrito a la N1, N12-diacetilespermina como el biomarcador urinario más eficaz en diversos tipos de cáncer y en el seguimiento de la progresión tumoral.

A pesar de los avances en la comprensión del papel de las poliaminas en el cáncer, son necesarios aún más estudios sobre las bases moleculares en las que participan las poliaminas. Determinar cómo intervenir de manera óptima en el metabolismo y la función de las poliaminas podría generar beneficios terapéuticos en el tratamiento del cáncer.

1.4 Poliaminas en los alimentos

Como se ha mencionado anteriormente, los alimentos son la principal fuente exógena de poliaminas en el ser humano. Estos compuestos se encuentran en prácticamente todos los alimentos, tanto de origen animal como vegetal, ya sea en forma libre o conjugada (Larqué et al., 2007; Gómez-Gallego et al., 2008; Kozová et al., 2009). En general, en alimentos de origen vegetal los contenidos de espermidina suelen ser más elevados que los de espermina, y viceversa para los de origen animal (Kalač, 2014). La leche materna es la primera fuente exógena de poliaminas para el ser humano.

La presencia de espermidina y espermina en los alimentos tiene principalmente un origen natural, ya que proceden de los tejidos animales y vegetales que los constituyen, mientras que la putrescina puede tener también un origen bacteriano, formándose por la actividad aminoácido descarboxilasa de microorganismos fermentativos y/o alterantes (Kalač & Krausová, 2005; Bover-Cid et al., 2014; Sánchez-Pérez et al., 2018). Se ha postulado que la espermidina y la espermina también podrían tener un origen bacteriano, especialmente en productos fermentados, aunque los estudios que lo describen son aún muy escasos (Atiya-Ali et al., 2011; Kalač, 2014; Kobayashi et al., 2016). Por lo tanto, las condiciones de procesado y almacenamiento de los alimentos pueden influir en su contenido total de poliaminas.

1.4.1 Leche materna

La lactancia materna es el estándar de oro para la nutrición humana durante los primeros seis meses de vida, ya que satisface todos los requerimientos del lactante para lograr un crecimiento y desarrollo óptimo (WHO, 2009; Mosca & Giannì, 2017; Garwolińska et al., 2018). La leche materna humana es un fluido complejo y altamente variable que, además de los nutrientes que aporta, contiene otros componentes como nucleótidos, hormonas, factores de crecimiento, inmunoglobulinas, oligosacáridos, citocinas, anticuerpos y bacterias, entre otros, que participan en el desarrollo del sistema inmunológico y que proporcionan protección contra enfermedades infecciosas (Figura 4) (Pérez-Cano et al., 2010; Andreas et al., 2015; Garwolińska et al., 2018). A pesar de que se había descrito que la leche materna era estéril, ahora es conocido que contiene una comunidad compleja de bacterias que ayudan a establecer la microbiota intestinal del lactante, impactando en su futura salud (p.ej. prevención de alergia, asma, obesidad, etc.) (Gómez-Gallego et al., 2016; Fitzstevens et al., 2017; Moossavi et al., 2019). Entre los compuestos presentes en la leche materna, también se encuentran las poliaminas, putrescina, espermidina y espermina (Buts et al., 1995; Atiya-Ali et al., 2014). Las poliaminas se sintetizan en la glándula mamaria durante el embarazo y la lactancia, y se han relacionado con la regulación hormonal de los procesos lactogénicos (Gómez-Gallego et al., 2017). Además, como se ha mencionado en apartados anteriores, las poliaminas entre otras funciones, también participan en la maduración intestinal y en el desarrollo del sistema inmune del lactante (Romain et al., 1992; Buts et al., 1993; Dandrifosse et al., 2000; Sabater-Molina et al., 2009; Pérez-Cano et al., 2010; Gómez-Gallego et al., 2017).

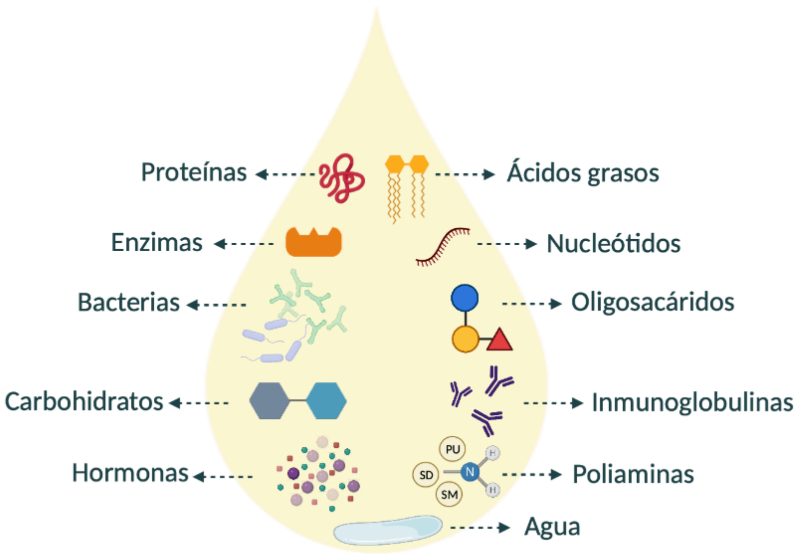

Figura 4. Composición cualitativa de la leche materna.

En la actualidad son escasos los estudios disponibles sobre la presencia de poliaminas en leche materna (Tabla 1). Además, los contenidos reportados muestran una amplia variabilidad, con concentraciones de poliaminas totales que oscilan entre 145 nmol/dL y 948.5 nmol/dL. Tampoco hay coincidencia en cuanto al perfil de distribución de las poliaminas en leche humana, ya que mientras algunos autores describen la espermidina como la poliamina principal (Romain et al., 1992; Atiya-Ali et al., 2013; Plaza-Zamora et al., 2013; Atiya-Ali et al., 2014), otros señalan a la espermina como la mayoritaria (Pollack et al., 1992; Buts et al., 1995; Gómez-Gallego et al., 2017). Por el contrario, sí existe unanimidad en que la putrescina es la poliamina minoritaria en leche materna. La variabilidad de los contenidos de poliaminas podría explicarse, en parte, por las diferentes fases de la lactancia en las que se ha realizado la toma de muestra, desde la primera semana hasta los seis meses de vida del lactante. Esto es relevante ya que se ha descrito que las concentraciones de poliaminas disminuyen a lo largo de la lactancia (Pollack et al., 1992; Romain et al., 1992).

Tabla 1. Contenidos medios de poliaminas (nmol/dL) en leche materna reportados en la literatura.

Leche materna	Fase de lactancia	Poliaminas totales	Putrescina	Espermidina	Espermina	Referencias
Término	1 semana	396.1	20.5	185.4	190.2	(1)
		713.3	82.4	457.5	173.4	(2)
	1 mes	861.5	61.5	351.2	448.8	(1)
		881.0	21.0	352.0	508.0	(3)
		25.7	2.9	12.4	10.4	(4)
	2 meses	819	90.0	385.0	344.0	(5)
		145.8	Nd	73.6	72.2	(1)
		659.1⁺	85.3⁺	414.0⁺	159.8⁺	(6)
		567.7*	73.0*	348.6*	146.1*	(6)
	4 meses	745	79.0	316.0	350.0	(5)
	6 meses	618	87.0	298.0	233.0	(5)
	Promedio	557	24.0	220.0	313.0	(7)
Pretérmino	1 semana	948.5	165.6	615.2	167.7	(2)
	1 mes	82.2	5.8	46.2	30.2	(8)

Nd: no detectable. Leche de madres con ⁺normo peso y con *obesidad. Promedio: no especifica mes de lactancia. [1]Pollack et al., 1992; [2]Ali et al., 2014; [3]Gómez-Gallego et al., 2017; [4]Plaza Zamora et al., 2013; [5]Romain et al., 1992; [6]Atiya-Ali et al., 2013; [7]Buts et al., 1995; [8]Plaza Zamora et al., 2013.

Por otro lado, también se ha sugerido que factores relacionados con la madre, el lactante y/o la propia lactancia pueden influir en la presencia de poliaminas de la leche materna (Figura 5). Sin embargo, los datos experimentales que apoyan estas relaciones son aún muy escasos o inexistentes. Por ejemplo, Gómez-Gallego et al. (2017) describió que la región geográfica influye en el contenido de poliaminas en la leche materna, esto se explicaría porque la región geográfica incluye factores como el origen étnico, la genética y los patrones dietéticos. En cuanto a la influencia de la dieta, el estudio realizado por Atiya-Ali et al. (2013) mostró que una mayor ingesta de poliaminas por parte de las madres, especialmente procedente de frutas y verduras, se asoció con un mayor contenido de poliaminas en la leche materna. Estos autores también reportaron que las concentraciones de poliaminas fueron más bajas en la leche de madres con obesidad en comparación con las madres con normo peso, aunque los autores no especifican el posible motivo de este resultado. En cuanto al tipo de nacimiento, existen dos estudios que señalan un mayor contenido de poliaminas en la leche de madres de recién nacidos prematuros en comparación con la leche de madres con recién nacidos a término (Plaza-Zamora et al., 2013; Atiya-Ali et al., 2014). Además, Gómez-Gallego et al. (2017) describen una menor concentración de poliaminas en la leche de madres que tuvieron a su bebé por cesárea en comparación con las de parto natural.

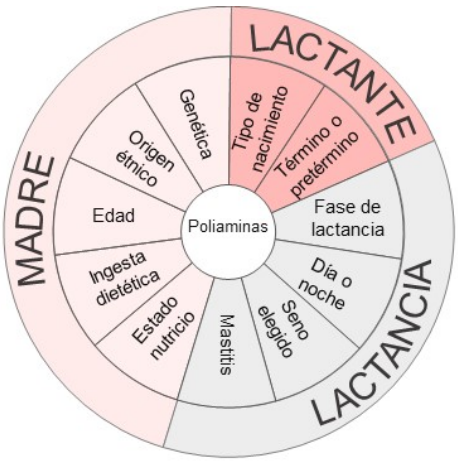

Figura 5. Factores que influyen en el contenido de poliaminas de la leche materna (Löser, 2000; Plaza-Zamora et al., 2013; Perez et al., 2016; Gómez-Gallego et al., 2017).

Con respecto a los factores relacionados con la propia lactancia, solo dos trabajos realizados en 1992 por Romain et al. y Pollack et al. han descrito una disminución progresiva de poliaminas durante el curso de la lactancia (Pollack et al., 1992; Romain et al., 1992). Los altos contenidos de poliaminas en la leche materna se han asociado con el rápido crecimiento durante los primeros meses de vida, siendo los contenidos de poliaminas hasta 28% más bajos a los seis meses de lactancia (Pollack et al., 1992; Romain et al., 1992; Plaza-Zamora et al., 2013).

Además, se ha descrito que la presencia de ciertas infecciones, como es el caso de la mastitis, puede potencialmente modificar los contenidos de poliaminas y provocar la aparición de otras aminas biógenas. Concretamente, Pérez et al. (2016) detectaron concentraciones más altas de putrescina, junto con la presencia de tiramina e histamina en la leche de madres con mastitis en comparación con madres sanas. Estos autores señalaron que el aumento de los niveles de putrescina y la aparición de otras aminas, podría atribuirse en gran medida a la actividad aminogénica de las bacterias infecciosas (p.ej. especies de estafilococos, estreptococos y/o corinebacterias), que son responsables del proceso inflamatorio de la glándula mamaria y dan lugar a la mastitis.

1.4.2 Fórmulas infantiles

La Organización Mundial de la Salud (OMS) recomienda la lactancia materna exclusiva durante los primeros seis meses de vida, y continuarla hasta los dos años de edad con alimentación complementaria adecuada (WHO, 2009). Sin embargo, la alimentación con fórmulas infantiles durante el primer año de vida continua siendo muy frecuente, ya sea en combinación con la lactancia materna o como el único alimento del lactante (Libuda et al., 2017).

Las fórmulas infantiles o sucedáneos de leche materna, son productos alimenticios adecuados para sustituir ya sea parcial o totalmente a la lactancia materna (Koletzko et al., 2005). En 1977 el Comité de Nutrición de la Sociedad Europea de Gastroenterología, Hepatología y Nutrición Pediátrica (ESPGHAN) estableció la composición nutrimental que debían tener las fórmulas infantiles, para que estas cubrieran los requerimientos nutrimentales del lactante y fueran lo más similares posible a la leche humana (Koletzko et al., 2005). A lo largo de los años, la formulación de estos preparados alimenticios infantiles se han modificando en función a la adquisición de nuevos conocimientos sobre la composición de la leche humana y en beneficio a la salud y nutrición del lactante, adaptándose a los estándares establecidos por la ESPGHAN y la Academia Americana de Pediatría (Moreno-Villares, 2011; Lönnerdal, 2014; Almagro-García, 2017).

Los sucedáneos de leche materna se clasifican en dos tipos, los que proceden de la leche de vaca, conocidas como fórmulas lácteas de uso estándar y las fórmulas de uso médico especial (Tamayo-López et al., 1997; Vásquez-Garibay et al., 2011). Las fórmulas lácteas incluyen las fórmulas de inicio, que están dirigidas a lactantes durante los primeros seis meses de edad (EU 609/2013), y las fórmulas de continuación, dirigidas a lactantes de más de seis meses de edad que han iniciado la alimentación complementaria (EU 609/2013) (EFSA, 2014). Las fórmulas de uso médico están dirigidas a lactantes con problemas de digestión, de absorción, de intolerancia o a aquellos que por razones religiosas o preferencias no consumen proteína animal. Los preparados de uso especial incluyen las fórmulas para prematuros, las fórmulas modificadas en hidratos de carbono, en proteínas y/o en grasas (p.ej. sin lactosa, a base de soja, hidrolizados de proteína y elementales), así como las fórmulas antirreflujo adicionadas con espesantes (p.ej. algarrobo) (Tamayo-López et al., 1997; Vásquez-Garibay et al., 2011).

Hasta la fecha, son escasos los trabajos que han estudiado la presencia de poliaminas en fórmulas infantiles, y estos se han enfocado especialmente en preparados lácteos de inicio y de continuación (Pollack et al., 1992; Romain et al., 1992; Buts et al., 1995; Atiya-Ali et al., 2014; Gómez-Gallego et al., 2016; Spizzirri et al., 2019). Solo dos trabajos han considerado las fórmulas para prematuros (Pollack et al., 1992; Atiya Ali et al., 2014), mientras que solo uno ha evaluado las fórmulas a base de soja (Romain et al., 1992). Además, debido a los cambios en la formulación de estos productos en los últimos años, los datos de la presencia de poliaminas pueden no ser el reflejo de la realidad actual.

La Tabla 2 muestra los contenidos de putrescina, espermidina y espermina en fórmulas infantiles disponibles en la literatura (Pollack et al., 1992; Romain et al., 1992; Buts et al., 1995; Atiya-Ali et al., 2014; Gómez-Gallego et al., 2016; Spizzirri et al., 2019). En general, se observa que tanto los contenidos como el perfil de distribución de las distintas poliaminas son muy variables entre estudios. La mayoría de las fórmulas infantiles muestran contenidos relevantes de putrescina, con valores de entre 1.8 nmol/dL hasta 964 nmol/dL. Igualmente, la espermidina también se encuentra en concentraciones importantes, con valores que van de los 10 nmol/dL a los 923 nmol/dL, mientras que la espermina es la poliamina minoritaria en prácticamente todos los preparados infantiles (nd – 739 nmol/dL).

Tabla 2. Contenidos medios de poliaminas (nmol/dL) en fórmulas infantiles reportadas en la literatura.

Tipo de fórmula	Poliaminas Totales	Putrescina	Espermidina	Espermina	Referencias
Inicio	136.0	94.0	27.0	15.0	(1)
	213.0	192.0	10.0	11.0	(1)
	20.5	1.8	18.7	Nd	(2)
	313.3	80.4	188.2	44.7	(2)
	78.4	23.9	39.4	15.1	(3)
	333.6	17.6	213.0	103.0	(4)
	441.3	359.6	51.6	30.1	(5)
	2599	964.0	923.0	712.0	(6)
Continuación	83.3	13.7	56.5	13.1	(3)
	354.1	11.0	280.0	63.1	(4)
	1970	749.0	482.0	739.0	(6)
Para prematuros	144.4	105.7	21.5	17.2	(2)
	649.9	154.5	433.1	62.3	(4)
A base de soja	361.0	84.0	233.0	44.0	(1)
	385.0	64.0	278.0	43.0	(1)

Nd: No detectado. [1]Romain et al., 1992; [2]Pollack et al., 1992; [3]Buts et al., 1995; [4]Atiya-Ali et al., 2014; [5]Gómez-Gallego et al., 2016; [6]Spizzirri et al., 2019.

Esta variabilidad observada en el contenido de poliaminas en las fórmulas infantiles se podría atribuir principalmente a la concentración de estos compuestos en la materia prima (p.ej. leche de vaca), pero también al proceso de fabricación (Gómez-Gallego et al., 2016). Además, Gómez-Gallego et al. (2016) demostraron que la actividad de la enzima poliamina oxidasa (PAO) de la leche cruda, puede ser responsable de cambios en las concentraciones de poliaminas ya que parece ser resistente a los procesos tecnológicos utilizados en la elaboración de las fórmulas infantiles.

A pesar de la gran variabilidad en los contenidos de poliaminas tanto en las fórmulas infantiles como en la leche materna humana, se observa claramente que el contenido y el perfil de poliaminas en las fórmulas infantiles es diferente al de la leche materna. Por ejemplo, en las fórmulas infantiles la poliamina principal es la putrescina, con contenidos generalmente más altos que los de la leche materna, mientras que los niveles de espermidina y espermina son hasta 60 veces más bajos en las fórmulas infantiles.

1.4.3 Alimentos de origen vegetal

En la Tabla 3 se presentan los contenidos de putrescina, espermidina y espermina en alimentos de origen vegetal procedentes de diferentes estudios disponibles en la literatura. Como se ha mencionado anteriormente, la espermidina es la poliamina mayoritaria en los alimentos de origen vegetal, aunque en ciertos alimentos la putrescina puede alcanzar niveles superiores. En cuanto a los contenidos de cada una de las poliaminas, se observa una gran variabilidad, no solo entre categorías sino también entre los diferentes productos de una misma categoría (Tabla 3).

Los productos vegetales que destacan por su riqueza en poliaminas son el germen de trigo y la soja, con niveles totales de 500 mg/kg y 211 mg/kg, respectivamente (Okamoto et al., 1997; Kalač & Krausová, 2005; Nishibori et al., 2007; Nishimura et al., 2006; Toro-Funes et al., 2015). Igualmente, los champiñones, guisantes, castañas, pistachos, espinacas, brócoli, coliflor y judías verdes también presentan cantidades importantes de poliaminas, especialmente espermidina (28 – 58 mg/kg). Por otro lado, la putrescina es la poliamina más abundante en alimentos como las frutas cítricas (137 mg/kg), el pimiento verde (70 mg/kg) y los brotes de soja (44 mg/kg) (Eliassen et al., 2002; Kalač & Krausová, 2005; Nishimura et al., 2006; Toro-Funes et al., 2015).

Tabla 3. Intervalos de contenidos medios de poliaminas (mg/kg) en alimentos de origen vegetal reportados en la literatura.

Categorías de alimentos	Putrescina	Espermidina	Espermina	Referencias
Verduras y hortalizas Brócoli, col, coliflor, zanahoria, apio, pepino, berenjena, judías verdes, pimiento verde, lechuga, champiñón, cebolla, patata, espinaca, tomate, brotes de soja.	0.5 – 70.0	1.0 – 57.8	Nd - 10.9	(1 - 13)
Frutas y derivados Manzana, aguacate, plátano, cereza, kiwi, mandarina, naranja, pera, melocotón, piña, fresa, zumos de frutas.	Nd – 137.0	1.0 – 14.2	Nd – 5.1	(3, 4, 11, 12)
Legumbres y derivados Garbanzos, lentejas, guisantes, alubias, soja, bebida de soja, tofu, salsa de soja, miso.	Nd - 46.3	8.7 - 50.5	Nd – 13.0	(2, 3, 5 - 8, 11, 10, 14, 15)
Frutos secos y semillas Almendras, castañas, avellanas, cacahuates, pistachos, semillas.	3.0 – 43.0	26.3 – 55.6	12.7 – 33.4	(6, 11)
Cereales y derivados Arroz, avena, germen de trigo, salvado, pan blanco, pasta.	0.2 – 62.1	0.4 – 354.0	Nd – 146.0	(3, 8, 10, 11)

Nd: No detectable. [1]Bardócz, 1995; [2]Ziegler et al., 1994; [3]Okamoto, et al., 1997; [4]Eliassen, et al., 2002; [5]Kalač et al., 2002; [6]Moret et al., 2005; [7]Kalač, et al., 2005; [8]Cipolla, et al., 2007; [9]Lavizzari, et al., 2007; [10]Nishibori, et al., 2007; [11]Nishimura, et al., 2006; [12]DIONEX, 2016; [13]Preti, et al., 2017; [14]Byun et al., 2013; [15]Toro-Funes, et al., 2015.

La variabilidad en los contenidos de poliaminas en los alimentos de origen vegetal puede deberse a diferentes factores, que incluyen el origen, el tipo de cultivo (especie, variedad, etc.), los factores ambientales (temperatura, disponibilidad de agua, etc.) y las condiciones específicas de cosecha, recolección y/o almacenamiento (Glória et al., 2005; Kobayashi et al., 2017; Sagara et al., 2017). Así, algunos trabajos han reportado un aumento en los niveles de poliaminas en leguminosas en respuesta al estrés inducido por las altas temperaturas o la sequía (Menéndez et al., 2019 Shao et al., 2015). La contribución de las poliaminas en los procesos de regulación del crecimiento de las plantas, así como su capacidad para incrementar la actividad de algunas enzimas antioxidantes, pueden explicar el rol de las poliaminas en ciertas situaciones de estrés causado por factores ambientales (Chen et al., 2019).

Por otro lado, los elevados niveles de putrescina que se pueden encontrar en algunos productos de origen vegetal, frecuentemente junto con otras aminas biógenas como la histamina, pueden estar asociados a la actividad microbiana. Lavizzari et al. (2007) atribuyeron los altos contenidos de putrescina en espinacas a la actividad aminoácido-descarboxilasa de bacterias alterantes durante el almacenamiento, pertenecientes principalmente a los grupos *Enterobacteriaceae* y *Clostridium spp*. Asimismo, Kalač (2014) atribuye que las elevadas cantidades de putrescina encontradas en guisantes congelados se debían a la actividad bacteriana que tuvo lugar durante el período comprendido entre la recolección y la congelación o durante la descongelación.

1.4.4 Alimentos de origen animal

En los alimentos de origen animal, al igual que en los de origen vegetal, los contenidos de poliaminas descritos en la literatura son muy variables (Tabla 4). En este tipo de alimentos, el cociente espermina/espermidina es superior al de los alimentos de origen vegetal. Los cárnicos y derivados se caracterizan por presentar los contenidos más elevados de espermina, con valores medios alrededor de los 30 mg/kg (Hernández-Jover et al., 1996, 1997; Nishimura et al., 2006; Nishibori et al., 2007). En pescados y mariscos los contenidos medios de espermina y espermidina tienden a ser inferiores a los de los cárnicos (<15mg/kg y <9mg/kg, respectivamente). En los productos lácteos, los contenidos de poliaminas son bajos, a excepción de los quesos. En este último tipo de productos, la presencia de espermidina es normalmente superior a la de espermina.

En cuanto a la putrescina, su origen bacteriano en productos de origen animal hace que los alimentos fermentados (embutidos y quesos) sea susceptibles de alcanzar niveles elevados de esta amina, asociados a la actividad de microorganismos no solo fermentativos sino también a posibles bacterias alterantes. Diferentes autores han asociado el uso de materias primas cárnicas con una calidad higiénica deficiente y/o condiciones de producción y/o almacenamiento inadecuadas con una alta acumulación de putrescina en embutidos fermentados (Kalač, 2006; Bover-Cid et al., 2014). En el caso de los quesos de larga maduración, en los que el uso de leche cruda es una práctica autorizada, este sería también un factor que podría incrementar la presencia de putrescina. El tratamiento térmico de la leche constituye una herramienta útil no solo para garantizar la ausencia de microrganismos patógenos sino también para evitar la formación de putrescina y otras aminas biógenas ya que disminuye: a) la carga de microrganismos alterantes con capacidad aminoácido- descarboxilasa, b) la presencia de los aminoácidos precursores libres al retrasar la proteólisis durante la maduración y c) el piridoxal fosfato, cofactor necesario del enzima aminoácido-descarboxilasa, al ser termolábil (Novella-Rodríguez et al., 2003).

Tabla 4. Intervalos de contenidos medios de poliaminas (mg/kg) en alimentos de origen animal reportados en la literatura.

Categorías de alimentos	Putrescina	Espermidina	Espermina	Referencias
Carne fresca Ternera, cordero, cerdo, pollo, conejo, pavo, pato.	0.1 – 10.1	1.2 – 13.4	1.6 – 69.2	(1 - 8)
Carne cocida y derivados Jamón cocido, mortadela, salchicha Viena, Frankfurt, butifarra.	0.4 – 1.0	1.2 – 4.0	2.1 – 17.9	(2, 4, 6)
Derivados cárnicos curados y fermentados Jamón curado y embutidos fermentados crudos curados.	0.4 – 156.1	1.2 – 9.0	10.1 – 35.8	(1, 2, 6, 7, 9)
Pescado fresco y mariscos Pescado blanco, bacalao, merluza, salmón, atún, anchoas, sardinas, camarón, cangrejo, calamar, ostras, vieiras.	Nd – 43.0	Nd – 24.3	Nd – 22.4	(5 - 7, 10)
Huevo	0.1 – 0.9	Nd – 0.6	Nd – 0.2	(5, 7)
Leche y yogurt	Nd – 0.3	0.1 – 0.7	Nd – 0.8	(4, 6, 11)
Queso Queso fresco, madurado, queso duro curado, queso de cabra, roquefort, gorgonzola, queso azul, camembert, brie, comté, emmental suizo, queso amarillo.	0.1 – 130.0	Nd – 38.0	Nd – 3.5	(4 - 6, 11, 12)

Nd: no detectable. [1]Hernández-Jover, et al., 1996; [2]Hernández-Jover, et al., 1997; [3]Bover-Cid, et al., 2014; [4]Eliassen, et al., 2002; [5]Nishimura, et al., 2006; [6]Cipolla et al., 2007; [7]Nishibori, et al., 2007; [8]Kozová et al., 2009; [9]Miguélez-Arrizado et al., 2006; [10]Veciana-Nogués et al., 1997; [11]Novella-Rodríguez et al., 2000; [12]Novella-Rodríguez, et al., 2003.

Finalmente, cabe destacar que la mayoría de los datos disponibles en la literatura sobre los contenidos de poliaminas en alimentos se refieren a alimentos crudos, y solo unos pocos autores han considerado la influencia del proceso de cocción en el contenido de poliaminas. Se ha descrito como algunas prácticas culinarias, como el hervido, el asado o la brasa pueden reducir la presencia de poliaminas, aunque estos datos son aún muy limitados y en ocasiones contradictorios (Eliassen et al., 2002; Krausová et al., 2007; Kozová et al., 2009; Kozová et al., 2009b; Preti et al., 2017). En este ámbito, son necesarios más estudios que ayuden a conocer la influencia de diferentes procesos tecnológicos y culinarios en el contenido de estos compuestos bioactivos.

1.5 Ingesta de poliaminas

La ingesta diaria de poliaminas se ha estimado en diferentes países europeos, Japón y Estados Unidos (Tabla 5). La ingesta media de poliaminas por la población europea adulta se estimó en 354 µmol/día, con diferencias entre los estados miembros, siendo el Reino Unido el que presentó una menor ingesta y los países del área mediterránea, Italia y España, los que mostraron un mayor consumo diario de estos compuestos (Ralph et al., 1999). Posteriormente, estudios realizados en países mediterráneos, como España y Turquía, estimaron valores de ingesta de poliaminas mucho más bajos para estas poblaciones (Buyukuslu et al., 2014; Comas-Basté et al., 2017). Estas diferencias podrían estar relacionadas, en parte, con la disminución del consumo de alimentos de origen vegetal debido al progresivo abandono del patrón tradicional de consumo de la dieta mediterránea observado en los últimos veinte años (Arroyo et al., 2018). Las estimaciones de ingesta de poliaminas para la población adulta de Japón y Estados Unidos se encuentran entre la media europea y los valores correspondientes al área mediterránea. El único estudio disponible sobre estimación de ingesta en población adolescente es el realizado por Atiya-Ali et al. (2011) en Suecia. Los resultados de la estimación de ingesta en este grupo de edad fueron muy similares a los reportados previamente para la población adulta sueca por Ralph et al. (1999).

Las diferencias entre las estimaciones de ingesta de poliaminas se pueden atribuir no sólo a los diferentes patrones dietéticos de cada población, sino también al grupo de edad estudiado, a la metodología de recolección de datos y/o la variabilidad en el contenido de poliaminas en los alimentos. Por ejemplo, los datos de consumo de alimentos utilizados para la estimación de la ingesta de poliaminas de Japón y España procedían de datos publicados en encuestas nacionales, los de Estados Unidos de un cuestionario de frecuencia de consumo, los de Suecia de un registro de alimentos de siete días y los de Turquía de un recordatorio de 24 horas. Los contenidos de poliaminas provenían en algunos casos de los análisis realizados específicamente para los estudios de estimación de ingesta (Nishibori et al., 2007; Zoumas-Morse et al., 2007; Comas-Basté et al., 2017), mientras que otros utilizaron datos ya publicados en la literatura (Atiya-Ali et al., 2011; Buyukuslu et al., 2014).

Tabla 5. Ingesta estimada promedio de poliaminas (µmol/día) en diferentes estudios.

Referencias	Población de estudio	Poliaminas totales	Putrescina	Espermidina	Espermina
Unión Europea (1)		353.6	211.9	87	54.7
Reino Unido	Adultos	315.1	160.3	96.7	58.1
Finlandia	Adultos	343.6	222.6	71.9	49.1
Suecia	Adultos	362.9	250.5	70.0	42.3
España	Adultos	384.3	211.7	103.1	69.5
Italia	Adultos	387.7	247.4	83.6	56.7
Japón (2)	Niños y adultos J-NNS	200	90	74	36
Estados Unidos de América (3)	Adultos 40 a 80 años	249.5	159.1	54.7	35.7
Suecia (4)	Adolescentes 17 años	316	215.5	66	34.5
Turquía (5)	Adultos 40 ± 19 años	139.9	93.1	33.1	13.7
España (6)	Adultos ENALIA II	170	-	-	-

[1]Ralph et al., 1999; [2]Nishibori et al., 2005; [3]Zoumas-Morse et al., 2007; [4]Atiya-Ali et al., 2011; [5]Buyukuslu et al., 2014; [6]Comas-Basté et al., 2017. 2J-NNS: Nationwide Nutrition Survey in Japan. ENALIA II: Encuesta Nacional de Alimentación en población adulta, mayores y embarazadas.

Todos los estudios coinciden en que la poliamina que más contribuye a la ingesta total es la putrescina, procedente principalmente del consumo de frutas y verduras, y en Japón también de los cereales y de la salsa de soja. En el caso de la espermidina también fueron las frutas, las verduras y los cereales los alimentos que mayoritariamente contribuyeron a la ingesta de esta poliamina. El principal aporte de la espermina procede del consumo de la carne y de pescado, excepto en Suecia, que proviene de las verduras y los cereales.

En la actualidad no existen recomendaciones de ingesta diaria de poliaminas, pero sí algunas sugerencias por parte de algunos autores. Atiya-Ali et al. (2011) propusieron que, teniendo en cuenta las pautas de una alimentación saludable que fomente el consumo elevado y suficiente de frutas, verduras y cereales, la ingesta de poliaminas debería ser del orden de 540 µmol/día. Esta recomendación es de dos a tres veces mayor que las ingestas reportadas en los estudios revisados. Por tanto, sería importante esclarecer los requerimientos dietéticos en los diferentes grupos de edad, con la finalidad de poder definir dietas ricas o restringidas de poliaminas cuando sea necesario.

Fruto de la revisión bibliográfica realizada en el marco de esta tesis doctoral, se ha publicado un artículo de revisión en acceso abierto y un capítulo de libro que revisan los contenidos de poliaminas en alimentos, así como las implicaciones de estos compuestos bioactivos para la salud humana.

PUBLICACIÓN 1

Polyamines in food

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Frontiers in Nutrition. 11;6:108. DOI: 10.3389/fnut.2019.00108.

Factor de impacto (SJR 2019): 1.013
Categoría "Food Science": Q1 (40/344)

PUBLICACIÓN 2

Polyamines in soybean food. Potential benefits for the elderly. Phytochemicals in Soybeans: Bioactivity and Health Benefits

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frontiers in Nutrition

REVIEW
published: 11 July 2019
doi: 10.3389/fnut.2019.00108

Polyamines in Food

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The polyamines spermine, spermidine, and putrescine are involved in various biological processes, notably in cell proliferation and differentiation, and also have antioxidant properties. Dietary polyamines have important implications in human health, mainly in the intestinal maturation and in the differentiation and development of immune system. The antioxidant and anti-inflammatory effect of polyamine can also play an important role in the prevention of chronic diseases such as cardiovascular diseases. In addition to endogenous synthesis, food is an important source of polyamines. Although there are no recommendations for polyamine daily intake, it is known that in stages of rapid cell growth (i.e., in the neonatal period), polyamine requirements are high. Additionally, *de novo* synthesis of polyamines tends to decrease with age, which is why their dietary sources acquire a greater importance in an aging population. Polyamine daily intake differs among to the available estimations, probably due to different dietary patterns and methodologies of data collection. Polyamines can be found in all types of foods in a wide range of concentrations. Spermidine and spermine are naturally present in food whereas putrescine could also have a microbial origin. The main polyamine in plant-based products is spermidine, whereas spermine content is generally higher in animal-derived foods. This article reviews the main implications of polyamines for human health, as well as their content in food and breast milk and infant formula. In addition, the estimated levels of polyamines intake in different populations are provided.

Keywords: spermidine, spermine, putrescine, polyamines, human health, food, breast milk

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Specialty section:
This article was submitted to Nutrition and Food Science Technology, a section of the journal Frontiers in Nutrition

Received: *10 April 2019*
Accepted: *28 June 2019*
Published: *11 July 2019*

Citation:
Muñoz-Esparza NC, Latorre-Moratalla ML, Comas-Basté O, Toro-Funes N, Veciana-Nogués MT and Vidal-Carou MC (2019) Polyamines in Food. Front. Nutr. 6:108. doi: 10.3389/fnut.2019.00108

INTRODUCTION

In 1678, Antoni van Leeuwenhoeck discovered the presence of crystals in human semen, which 200 years later (1888) were named spermine by A. Landenburg and J. Abel. The chemical structure of spermine and spermidine was determined in 1924 (1). The polyamines spermidine (N-(3-aminopropyl)-1,4-butane diamine), spermine (N,N-bis (3-aminopropyl)-1,4-butane diamine), and putrescine (1,4-butane diamine) have a low molecular weight and are characterized by having two or more amino groups. They are found in all living cells, including microorganisms, plants, and animals. Due to their structure (**Figure 1**), polyamines are relatively stable compounds, capable of resisting acidic and alkaline conditions and they can establish hydrogen bond with hydroxyl solvents such as water and alcohol (2–6). In the organism, at physiological pH they are completely protonated and strongly bound to polyanionic macromolecules such as DNA and RNA (2, 7, 8). On the other hand, polyamines can also be found in food of both animal and plant origin. An important source of polyamines for humans is breast milk and infant formula (2, 4).

Polyamines and Health

Polyamines play an essential role in cell growth and proliferation, the stabilization of negative charges of DNA, RNA transcription, protein synthesis, the regulation of the immune response, apoptosis, the regulation of ion channels, particularly by blocking potassium channels, and as antioxidants (2, 4, 5, 7, 9–12).

The antioxidant activity of polyamines mainly affects membrane lipids and nucleic acids. Spermine is the polyamine with the strongest antioxidant properties, associated with its higher number of positive charges. The main mechanism of polyamine antioxidant action is metal chelation, which prevents the formation of hydroperoxides and delays the generation of secondary oxidation compounds (13–16). It has also been proposed that polyamines can eliminate free radicals, especially in lipophilic media (14, 16).

Polyamine Homeostasis

The *de novo* synthesis of polyamines in the organism begins with the formation of putrescine from the amino acid ornithine, catalyzed by the enzyme ornithine decarboxylase (ODC) (**Figure 2**). Putrescine is converted to spermidine by spermidine synthase through the addition of a propylamine group derived from the decarboxylation of S-adenosyl-methionine. Subsequently, spermidine is transformed into spermine by spermine synthase, which adds a second propylamine group (2, 4, 7, 12, 17).

The interconversion of polyamines is a cyclic process that controls their turnover and regulates intracellular homeostasis (**Figure 2**). This process begins with the acetylation of any of the three polyamines, which is catalyzed by an N-acetyl-transferase enzyme with the participation of acetyl coenzyme-A. Subsequently, the enzyme polyamine oxidase (PAO) removes a propylamine group, and putrescine is obtained from the acetylated metabolite of spermidine, or spermidine from the acetylated metabolite of spermine (2, 10, 12, 17, 18).

The elimination of polyamines from the organism is carried out by the oxidative deamination of a primary amino group, mainly by the action of diamine oxidase (DAO) and PAO. Both enzymes can act on polyamines and their acetylated derivatives (2, 4, 7, 10, 17).

Besides endogenous synthesis, polyamines also have an exogenous origin, mainly food and breast milk (2). In addition, gut microbiota is also described as a source of polyamines, mainly forming in the large intestine (2, 19, 20). Some recent studies have been linked different intestinal microbial species with the synthesis of these compounds (20). However, more information is still needed on the capability to form polyamines of the gut microbiota and the corresponding biosynthetic pathways. Finally, intestinal and pancreatic secretions and catabolism products of intestinal cells also contribute to the polyamines in the gut (2). Polyamines are absorbed in the duodenum and in the first portion of the jejunum by various mechanisms, including transcellular (through passive diffusion and transporters) and paracellular pathways (2, 4, 21). Polyamines are partly metabolized in the intestinal wall before reaching the blood circulation, and those that pass into the circulation are distributed throughout the organism and captured by the tissues, where they can undergo interconversion reactions.

The highest concentrations of polyamines are found in the intestine, thymus and liver (2, 4). A diet enriched with polyamines raises plasma levels in experimental animals and humans (22).

Potential Effects of Polyamines

Postnatal Stage

Several studies describe the importance of polyamines in humans, especially in the early stages of life. It is known that during rapid cell growth, particularly in the neonatal stage, the need for polyamines increases (4, 5, 21, 23, 24). Requirements are also higher after surgery or during periods of wound-healing and aging (2, 23, 25).

Polyamines (spermine and spermidine) promote the proliferation and maturation of the gastrointestinal tract and are involved in the differentiation and development of the immune system (5, 21, 25–31). In addition, due to their antioxidant properties, these compounds can participate in the regulation of the inflammatory response (12, 22).

Several studies have demonstrated that oral administration of polyamines in mice induces early postnatal maturation of the intestine and acts in the repair of the intestinal mucosa and in the immune and inflammatory response. Spermine and spermidine modified protein expression and the activity of disaccharidases and accelerated postnatal intestinal maturation, producing morphological changes in the intestinal epithelium and mucosal permeability (29). They also participate in the maturation of associated organs such as the liver and pancreas. In another study with mice, the oral administration of polyamines, mainly spermidine, was found to promote the early maturation of glycoprotein fucosylation. A dose of 10 μmol/day of each polyamine increased the activity of α-1,2-fucosyltransferase and α-L-fucosidase and induced the synthesis of α-1,2-fucoprotein (32, 33). The authors of this study suggest that postnatal changes in the fucosylation of intestinal glycoproteins could be related mainly to the intake of polyamines, especially spermidine and spermine. Another study showed that oral administration of spermine in mice increases the activity of alkaline phosphatase and disaccharidase, and subsequently alters intestinal maturation (34). The administration of spermine and spermidine in newborn rats increased the intestinal weight and length and accelerated its maturation (21). Regarding the immune response at the intestinal level, various studies in animals have indicated that the oral administration of spermine and spermidine in the postnatal period improves the maturation of the intestinal immune cells and increases the levels of immunoglobulin A in the villi and crypts of the intestine (21, 29).

In humans it is widely reported that breast milk enhances the maturation of immune cells and decreases intestinal permeability to antigenic macromolecules, reducing the risk of food hypersensitivity in the infant (21, 25, 26, 29, 35, 36).

Aging

In the aging process, the cellular levels of spermine and spermidine and the enzymatic activity of ODC tend to decrease

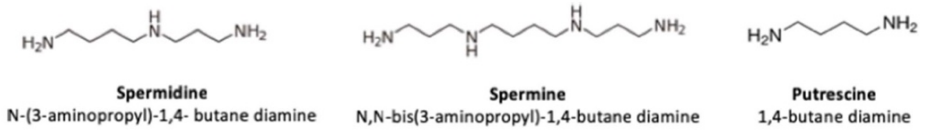

FIGURE 1 | Chemical structure of polyamines.

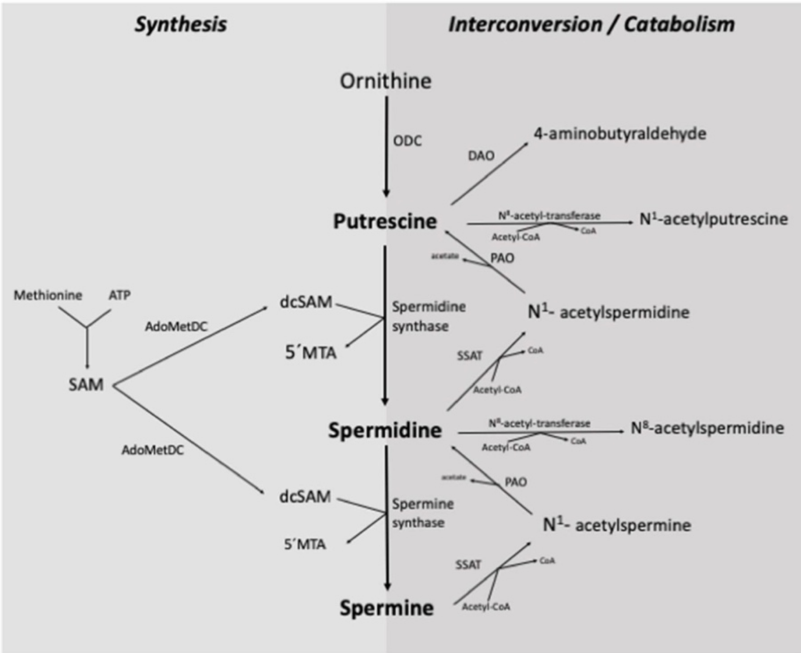

FIGURE 2 | Synthesis and interconversion/catabolism of polyamines in the organism. ODC, ornithine-decarboxylase; SSAT, spermidine/spermine N^1-acetyl-transferase; PAO, polyamine-oxidase; DAO, diamine-oxidase; SAM, S-adenosyl-methionine; AdoMetDC, S-adenosyl-L-methionine-decarboxylase; dcSAM, decarboxylated S-adenosyl-methionine; 5′MTA, 5′-methylthioadenosine; Acetyl-CoA, Acetyl coenzyme-A [Adapted from (7) and (2)].

(17, 37, 38). Enrichment of the diet with polyamines during this stage can reduce the risk of age-associated pathologies and promote longevity (39, 40). In a study in aging mice, a diet with high levels of spermine and spermidine (374 and 1,540 nmol/g, respectively) increased the concentrations of these compounds in the blood and reduced levels of pro-inflammatory markers, age-associated DNA methylation, renal glomerular atrophy and mortality (39). It has also been observed that spermidine increases autophagy, which involves the removal of damaged proteins and organelles from cells, thus inhibiting the aging process (6, 41–43). In a follow-up study of a cohort of 829 participants during 20 years, spermidine showed the strongest inverse relation with mortality among 146 nutrients investigated. This effect was dose-dependent, and the authors explain that spermidine effectively induced autophagy and can reduce the acetylation of histones, which are critical processes for cell homeostasis in aging. In this sense, a diet rich in spermidine, mainly from foods of vegetable origin (green pepper, wheat grain, mushrooms, etc.), was associated with a decrease in the risk of all-cause mortality in the general community (42).

Cardiovascular Disease

The antioxidant and anti-inflammatory effects attributed to polyamines can play an important role in the prevention of chronic inflammatory pathologies, such as cardiovascular diseases (22). A higher intake of spermidine has been correlated with a lower incidence of cardiovascular diseases and a decrease in blood pressure and heart failure (44). It is likely that the anti-inflammatory role of polyamines in the prevention and treatment of cardiovascular disease is similar to that of polyunsaturated fatty acids (PUFA 3-n) and statins (22, 45). In animal studies, mainly in aging mice, spermidine has been shown to decrease age-induced arterial stiffness and oxidative damage of endothelial cells (44). In addition, 6 week supplementation of spermine and spermidine in mice reversed age-associated changes in myocardial morphology (myocardial fibrosis) and inhibited cellular apoptosis of the heart (46).

Diabetes

Glycation has an important role in the development of diabetes complications, so compounds that can counteract this reaction are desirable. Due to their chemical structure, polyamines could function as antiglycan agents, delaying the accumulation of advanced glycation end-products (AGEs) (7, 47). This effect would be due to the interaction between the free amino groups of polyamines and the highly reactive carbonyl compounds (10, 18). *In vitro* studies have demonstrated that the millimolar concentrations of spermine present in the cell nucleus can protect DNA and histones from glycation (18).

On the other hand, some authors have observed a higher PAO activity in children with diabetes mellitus type 1, which could induce an increased production of free radicals and subsequent oxidative damage (47). Therefore, more studies are needed to clarify the role of polyamines in diabetes and establish recommended levels of polyamine intake for the diabetic population.

Cancer

Elevated levels of polyamines in cancer patients are associated with tumor growth (48, 49). A deregulation in polyamines biosynthesis, mainly due to an increase in the activity of the ODC enzyme, leads high intracellular polyamine content in cancer cells (12, 39, 45, 49). Therefore, controlling polyamine synthesis could be useful in antineoplastic therapy. According to different experimental studies and clinical trials, the combined treatment using difluoro-methylornithine (DFMO), a potent and irreversible inhibitor of ODC, with polyamine transport inhibitor drugs or non-steroidal anti-inflammatory drugs (NSAIDs), efficiently reduced the carcinogenesis by inhibiting polyamines synthesis and stimulating polyamines catabolism and export (48, 49).

An increase of the acetylated metabolites of polyamines has been observed in urine or blood in patients suffering cancer disease. The rise of acetylated polyamines in urine may be explained by an increase of cellular polyamines, an increase of the SSAT activity, a major excretion of acetylated metabolites from cells or by a decrease of their oxidative degradation by PAO enzyme, although the molecular mechanisms are not well-elucidated (50). The development of more sensitive metabolomic techniques in the last decade has allowed detailed polyamine metabolic profiles to be associated with certain types of cancer (48). In fact, increased levels of acetylated polyamines in urine or blood, particularly, N1,N12-diacetylspermine, N1,N8-acetylspermidine, N1-acetylspermine, and N8-acetylspermidine have been found in patients with ovarian, prostate, colorectal, pancreatic, breast and lung cancers. Among them, N1,N12-diacetylspermine has been extensively described as the most effective urinary biomarker for several types of cancer and to monitor tumor's progression (48, 51, 52).

Despite advances in understanding the role of polyamines in cancer, more research is required on the molecular basis in which polyamines participate. Determining how to optimally intervene in polyamine metabolism and function could lead to therapeutic benefits in cancer treatment.

Polyamines in Food

Polyamines are found in foods of both animal and plant origin, either in a free or conjugated form. Conjugated polyamines are found in plant-derived foods mainly linked to phenolic compounds (4, 24). In foods, spermidine and spermine are primarily naturally present, coming from raw plant and animal tissues, whereas putrescine may also be formed by the activity of fermentative or contaminating microorganisms (12, 53). It has also been described that spermidine and spermine may partly have a bacterial origin, especially in fermented products (12, 54, 55). Therefore, processing and storage conditions can influence the total content of polyamines.

Breast Milk and Infant Formula

The first dietary exposure to polyamines is through breast milk. **Table 1** shows the contents of polyamines in breast milk and infant formula reported in the literature, with all results expressed in nmol/ml to facilitate comparison. All the studies reviewed agree that the content and profile of these compounds can vary depending on factors such as genetics, the lactation phase, and the age, nutritional status and dietary intake of the mother.

The major polyamines in breast milk are spermidine and spermine and their contents differ considerably, with coefficients of variation >68 and 53%, respectively. Spermine values are generally higher, except in two studies by the same author, in which higher values are reported for spermidine (11, 25). As indicated in **Table 1**, the breast milk analyzed in different studies corresponds to different phases of lactation, which could contribute to the high variability observed. In this sense, some authors have described that the polyamine content tends to decrease over the course of lactation (26, 56). Additionally, two studies found higher polyamine contents in the milk of mothers of preterm infants compared to full-term (25, 31). Also, as preliminary information it should be noted that milk from obese mothers was found to contain fewer polyamines than milk from those with normal weight (11).

In infant formula the variability among results of different studies is even higher than for breast milk, with coefficients

TABLE 1 | Average contents of polyamines in breast milk and infant formula.

	Putrescine nmol/ml	Spermidine nmol/ml	Spermine nmol/ml	References
Full-term breast milk	0.896	3.849	3.440	(26)[a]
	0.615	3.512	4.490	(56)[b]
	0.238	2.196	3.128	(27)
	0.030	0.124	0.104	(31)[b]
	0.851[1]	4.138[1]	1.596[1]	(11)[a]
	0.726[2]	3.470[2]	1.463[2]	
	0.824	4.578	1.735	(25)[c]
	0.658	3.993	4.077	(57)
	0.204	3.520	5.080	(5)[b]
Range	0.030–896	0.124–4.578	0.104–5.080	
Pre-term breast milk	0.058	0.462	0.302	(31)[b]
	1.655	6.151	1.677	(25)[c]
First formula	14.300	0.186	0.129	(26)
	0.018	0.187	nd	(56)
	0.374	0.912	0.675	(27)
	3.880	2.265	0.363	(25)
	3.596	0.516	0.302	(57)
	10.323	6.933	7.339	(58)
Range	0.018–14.300	0.186–6.933	0.129–7.339	
Follow-on formula	12.796	0.138	0.158	(26)
	0.263	1.198	0.458	(27)
	5.349	2.382	0.363	(25)
	7.533	4.241	6.227	(58)
Range	0.263–12.796	0.138–4.241	0.158–6.227	
Pre-term formula	1.057	0.215	0.172	(56)
	15.451	4.331	0.623	(25)

[1] *Milk from mothers of normal weight.*
[2] *Milk from obese mothers.*
[a] *Breast milk 2 months postpartum.*
[b] *Breast milk 1 month postpartum*
[c] *Breast milk 1 week postpartum.*
nd, not detected.

of variation of 89% for putrescine, 116% for spermidine, and 160% for spermine. Despite this variability, it can be extrapolated that the polyamine content and profiles in infant formula differ from those of breast milk. For example, the major polyamine in infant formula is putrescine, its content usually higher than in breast milk, whereas spermidine and spermine levels tend to be lower. When first and follow-on formula are compared, no differences can be observed in the mean contents of polyamines. Likewise, the few available data on polyamines in infant formulas for premature babies do not allow to observe differences with other types of formulas.

The available data on polyamine content in breast milk and infant formula are scarce and, in some cases, outdated. More studies are needed to clarify whether the variability observed both in breast milk and infant formula is due to the use of different analytical methodologies or to other factors that have not been sufficiently investigated.

Food of Plant Origin

Polyamines are ubiquitous in foods of plant origin, although their content and distribution vary depending on the type of food (**Table 2**). Spermidine, present in all plant-derived foods, is generally the predominant polyamine. The food categories with the highest contents of spermidine and spermine are cereals, legumes and soy derivatives. Wheat germ and soybeans stand out in particular, with respective values of 2,437 and 1,425 nmol/g for spermidine and 722 nmol/g and 341 nmol/g for spermine (37, 59). Mushrooms, peas, hazelnuts, pistachios, spinach, broccoli, cauliflower and green beans also contain significant amounts of both polyamines. The lowest levels are found in the fruit category. For example, in apples, pears, cherries, oranges or tangerines, reported values for spermidine are lower than 21 nmol/g and <1.98 nmol/g for spermine.

Like spermidine, putrescine is found in virtually all foods of plant origin, and is particularly abundant in fruits and vegetables, notably citrus fruits (1,554 nmol/g) and green peppers (794 nmol/g) (9, 61). There are also high amounts of putrescine in wheat germ (705 nmol/g) and soybean sprouts (507 nmol/g) (37, 70).

The variability in polyamine contents in plant-derived products can be due to different factors, including their origin, growing conditions, harvesting, or storage. In this sense, different stress situations of the plant could affect the polyamine content. For example, polyamine levels in plants can increase in response to stress brought by high or low cultivation temperatures or drought (71). Studies show that the application of polyamines pre- and post-cultivation can compensate for the negative effects of cold or drought, thereby favoring germination, plant growth or survival (72–74). Another factor that could explain the high levels of putrescine in some vegetables, such as spinach and peas, is the presence of spoilage bacteria, mainly *Enterobacteriaceae* and *Clostridium spp.*, which can form putrescine from its amino acid precursor ornithine by their amino acid-decarboxylase activity (12, 62, 75).

Food of Animal Origin

In animal-derived foods, like those of plant origin, the contents of polyamines are extremely variable (**Table 3**). Meat and its derivatives may contain high levels of spermidine and spermine, particularly the latter. Spermine values >148 nmol/g have been described in samples of beef, pork, chicken, cured ham, and sausages, without significant differences between fresh meats and derivatives (37, 63, 76, 77). In fish and its derivatives, the contents of spermine and spermidine are generally lower than in meat products, but clearly higher than in milk and eggs, where their levels are low. In most cheeses the values of spermine and spermidine are <10 and 69 nmol/g, respectively, with the exception of a blue cheese with a very high spermidine content (262 nmol/g) (37).

In fresh products of animal origin (meat, fish, milk, and eggs) the putrescine contents are generally lower than in plant-derived foods. However, the highest levels of putrescine are found in products subjected to a fermentation process involving potentially aminogenic microorganisms. The wide range of putrescine contents could also be explained by the

TABLE 2 | Ranges of average polyamine content (nmol/g) in foods of plant origin.

Food categories	Putrescine	Spermidine	Spermine	References
Fruits				
Apple, avocado, banana, cherry, kiwi, mandarin, orange, pear, peach, pineapple, strawberry, fruit juices.	nd–1,554	6.9–98	nd–25	(9, 37, 59, 60)
Vegetables				
Broccoli, cabbage, cauliflower, carrot, celeriac, courgette, cucumber, eggplant, green beans, green pepper, lettuce, mushroom, onion, potato, spinach, tomato.	5.7–794	6.9–398	nd–54	(9, 37, 59–69)
Legumes and soybean products				
Chickpeas, lentils, peas, white beans, red kidney beans, soybean, soybean sprouts, soybean milk, tofu, soy sauce, miso	nd–525	1.0–1,425	nd–341	(37, 55, 59, 61, 63, 64, 66–68, 70)
Nuts and oilseeds				
Almonds, chestnuts, pistachios, seeds	34–488	41–383	63–165	(37, 64)
Cereals				
Rice, wheat germ, white bread	2.3–704	2.8–2437	nd–722	(37, 59, 63, 68)

nd, not detected.

TABLE 3 | Ranges of average polyamine content (nmol/g) in foods of animal origin.

Food categories	Putrescine	Spermidine	Spermine	References
Fresh meat				
Beef, veal, lamb, pork, chicken, rabbit, turkey, duck.	1.1–47	1–92	1–342	(9, 37, 53, 63, 68, 76–78)
Cooked meat derivatives				
Cooked ham, mortadella, wiener sausage, frankfurter, botifarra	4.5–11	15–28	11–99	(9, 68, 77)
Cured and fermented meat derivatives				
Dry-cured ham, dry-fermented sausage	5–1771	8–62	11–177	(63, 68, 76, 77, 79)
Fresh fish and seafood products				
White fish, cod, hake, salmon, tuna, sardine, shrimp, crab, calamari, oysters, scallops	nd–487	nd–167	nd–111	(37, 63, 68, 80)
Semi-preserved and canned fish				
Canned tuna, anchovies	1.1–47	6.2–28	12–53	(80, 81)
Egg	3.1–10	1–4	nd–1	(37, 63)
Milk and dairy products				
Milk, yogurt	nd–3	0.41–5	nd–4	(9, 68, 82)
Cheese				
Matured cheese, hard-ripened cheese, goat cheese, roquefort, gorgonzola, blue cheese, camembert, brie, comté, Swiss emmental, yellow cheese.	1.5–1470	nd–262	nd–17	(9, 37, 68, 82, 83)

nd, not detected.

decarboxylase activity of spoilage bacteria. Studies show that the hygienic state of raw materials has an important influence on the formation of putrescine and other amines during the elaboration of different food products. For example, a greater accumulation of amines was reported in dry-fermented sausages when these were produced from raw materials of low microbial quality (78). This factor could also be responsible for increasing putrescine levels in long-maturing cheeses for whose manufacture the use of raw milk is an authorized practice. In this sense, the previous thermal treatment of milk is a useful tool, not only to guarantee the absence of pathogenic microorganisms but also to avoid the formation of putrescine and other biogenic amines, as it decreases a) the load of spoilage microorganisms with amino acid-decarboxylase capacity; b) the presence of free amino acid precursors by delaying proteolysis during ripening; and c) levels of the thermolabile pyridoxal phosphate, a necessary cofactor of the amino acid-decarboxylase enzyme (83).

Effects of Culinary Treatment

Culinary treatment can potentially decrease the polyamine content in foods by two possible mechanisms: (a) transfer to the cooking water or (b) due to the high temperatures reached in some types of cooking. The few studies evaluating the effect of culinary treatment on polyamines report variable results, depending on the type of cooking and the food studied. Polyamine contents after the boiling of certain vegetables (spinach, cauliflower, and potatoes) were significantly reduced by transfer to the cooking water, especially putrescine, as this is the most water-soluble polyamine. However, the same cooking process did not induce losses in other types of food (peppers, peas, and asparagus) (84). Another study found no significant differences in polyamine levels between raw and boiled vegetables (carrots, broccoli, cauliflower, and potatoes), although the low number of samples analyzed (two per food type) was a limiting factor (9). In meat subjected to a cooking process involving a large amount of water (stewing and boiling), no significant losses of spermidine and spermine were observed either (23, 53). In the case of some cooking techniques that involved higher temperatures (53) described that roasting, grilling, or frying produced losses of up to 60% of spermidine and spermine in chicken meat.

Antioxidant Potential of Polyamines in Food

Studies of the antioxidant role of polyamines in food are scarce compared to those in biological substrates. The protective effect of polyamines against oxidation when added to a lipid matrix has been demonstrated *in vitro*, mainly acting as metal chelators. A concentration-dependent antioxidant capacity was reported for spermine and spermidine (13). Later, Toro Funes et al. (16) also described an antioxidant effect for each of these polyamines at a wide range of concentrations (from 30 to 1,250 µg/mL). Specifically, spermine and spermidine delay the formation of peroxides and secondary oxidation compounds, the effects of spermine being greater due to a higher number of amino groups. In addition, these two studies showed that antioxidant activity of both polyamines is equal to or even higher than that of some antioxidant additives commonly used in foods, such as octyl gallate, alpha-tocopherol, ascorbyl palmitate, or tert-butylhydroquinone, among others.

Foods with high contents of polyamines, such as wheat germ, soya, mushroom, or citrus fruits, could be used as natural antioxidant ingredients in the form of powdered concentrates or polyamine-rich extracts. Prior to the use of these extracts or concentrates of polyamine-rich foods as natural antioxidants, effective and safe doses would need to be determined.

Analysis of Polyamines in Food

The analytical methodologies to determine polyamines in food are mainly based on the chromatographic separation coupled with distinct detection techniques due to their high resolution, sensitivity and versatility. Gas chromatography, thin-layer chromatography and high-performance liquid chromatography have been applied for the analysis of polyamines in food (85–87). Concretely, high or ultra high-performance liquid chromatography with ion-exchange columns or reverse-phase columns to separate polyamines are the most frequently reported techniques in the literature (88).

Different detection techniques coupled to chromatographic separation systems have been described such as UV, fluorescence and mass spectrometry. Polyamines have low absorption coefficients or quantum yields and require derivatization when the method involve UV or fluorescent detection. Chemical derivatization of these compounds can be carried out with a variety of reagents, mostly 5-dimethylamino-1-naphtalene-sulfonyl chloride (dansyl chloride) that forms stable compounds after reaction with both primary and secondary amino groups and *o*-phthaldialdehyde (OPA), which reacts rapidly (i.e., 30 seg) with primary amines. Amine derivatives can be formed before (pre-column), during (on-column) or after (post-column) the chromatographic separation. Pre-derivatization comprises a series of time- consuming manual steps and may introduce imprecision to the overall analytical procedure. Post-column derivatization has the advantage that it is automatically performed online, thereby avoiding sample manipulation and shortening the time required for the analysis (89). In recent years, the determination of polyamines through liquid chromatography coupled to mass spectrometry (MS) or tandem mass spectrometry (MS/MS) has emerged as an alternative analytical technique, very specific and sensitive and without the need of derivatization (52, 87, 88, 90).

Electrochemical sensors or biosensors are an alternative to the analytical procedures described above, being less expensive, less time-consuming, and analytically simpler, especially for routine screenings. Electrochemical biosensors usually consist on immobilized amino-oxidases, which catalyze the oxidative deamination of polyamines present in foods, and a working electrode that detects the production or the consumption of the redox species produced by the enzymatic activity. Different electrochemical sensors developed for the rapid determination of polyamines in food showed low detection limits and good selectivity toward these compounds (86).

Polyamine Intake

The daily intake of polyamines has been estimated for different European countries, Japan and the United States (**Table 4**). The mean polyamine intake in the European adult population was estimated as 354 µmol/day, with differences among the member states, being lowest in the United Kingdom and highest in the countries of the Mediterranean area, Italy and Spain (91). Subsequent studies carried out in Mediterranean countries, such as Spain and Turkey, have estimated much lower intake values for these populations (94, 95), which could be partly related to a decrease in the consumption of plant-derived foods due to the progressive abandonment of the traditional Mediterranean diet observed in the last 20 years (96). The polyamine intake estimates for the adult population of Japan and the United States lie between the European mean and the values corresponding to the Mediterranean area. The only study estimating the intake in an adolescent population was carried out in Sweden (93) and the results were very similar to those previously reported for the Swedish adult population (91).

The differences between intake estimates can be attributed not only to the different dietary patterns of each population, but also to the age group studied, the methodology of data collection and/or to the variability in food polyamine content. For example, the food consumption data used to estimate polyamine intake was obtained from published national surveys (Japan and Spain), a frequency-of-consumption questionnaire (United States), a 7 day food record (Sweden) and a 24 h dietary recall (Turkey). In some studies, the data on polyamine content were obtained from analyses carried out specifically for the intake estimation studies (63, 64, 95), whereas others used data already published in the literature (93, 94).

TABLE 4 | Estimated average intake of polyamines (μmol/day) in different studies.

References	Study population	Total polyamines	Putrescine	Spermidine	Spermine
European Union[a] (91)	Adults	353.6	211.9	87	54.7
United Kingdom		315.1	160.3	96.7	58.1
Finland		343.6	222.6	71.9	49.1
Sweden		362.9	250.5	70.0	42.3
Spain		384.3	211.7	103.1	69.5
Italy		387.7	247.4	83.6	56.7
Japan (63)	Children and adults J-NNS[b]	200	90	74	36
United States of America (92)	Adults 40 to 80 years	249.5	159.1	54.7	35.7
Sweden (93)	Adolescents 17 years	316	215.5	66	34.5
Turkey (94)	Adults 40 ± 19 years	139.9	93.1	33.1	13.7
Spain (95)	Adults ENALIA II[c]	170	–	–	–

[a]*European Union: United Kingdom, Italy, Spain, Finland, Sweden, and the Netherlands.*
[b]*J-NNS: Nationwide nutrition survey in Japan.*
[c]*Spanish national dietary survey in adults, elderly and pregnant women.*

All the studies agree that the polyamine contributing most to the total intake is putrescine, mainly from the consumption of fruits and vegetables, or in Japan also from cereals and soy sauce. Fruits, vegetables and cereals are also the main sources of spermidine. The main origin of dietary spermine is meat and fish, except in Sweden, where it is vegetables and cereals.

At present there are no official recommendations for the daily intake of polyamines, but some suggestions have been made. Atiya Ali et al. (93) proposed an intake around of 540 μmol/day, taking into account the guidelines of a healthy diet that promotes a high consumption of fruits, vegetables and cereals (93). This estimate is two to three times higher than the intakes reported in the studies reviewed.

CONCLUSIONS

There is extensive knowledge about the physiological functions of polyamines and their importance for human health. Several studies indicate the importance of dietary polyamines at different stages and situations of life, such as in the postnatal period or aging, when requirements are higher. In addition, the antioxidant and anti-inflammatory effects described for polyamines can play an important role in the prevention of chronic conditions such as cardiovascular diseases and diabetes. On the other hand, cancer is associated with high levels of polyamines, brought about by an alteration in their homeostasis.

The contents of polyamines in food, even within the same type, are highly variable. Breast milk provides the first dietary exposure to these compounds. Despite the scarcity and variability of available data, the content and profile of polyamines in breast milk are clearly different from those observed in infant formula. Among plant-derived foods, cereals, legumes and soybean derivatives are the categories with the highest contents of spermidine and spermine, whereas the highest putrescine levels are found in vegetables and fruits, especially citrus fruits. In animal-derived foods, meat and derivatives have the highest polyamine contents, with the exception of some cheeses. A range of factors could be responsible for the high variability in the polyamine content in food, notably origin and conditions of cultivation of plants, as well as the conditions of processing and storage. The wide range of putrescine contents could be also explained by the decarboxylase activity of spoilage or fermentative bacteria.

Polyamines have been associated with a high antioxidant activity in foods matrices, especially spermine. Therefore, foods rich in polyamines such as wheat germ, soybean, mushroom, or citrus fruits, in the form of extracts or concentrated powders, could be used as natural antioxidant ingredients. Such application will require previous studies to determine safety and effective dosage.

The few studies estimating polyamine intake have published highly variable results. This inconsistency could be attributed not only to the different diets of the studied populations, but also to methodological differences that could be related to the absence of consensus guidelines for the estimation of polyamine consumption. There are currently no official recommendations for daily polyamines intake, although some authors have proposed levels well above the intake estimates made in different countries. The dietary polyamine requirements in the different age groups should also be establish in order to be able to define a rich or low diet in polyamines.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

NM-E is a recipient of a doctoral fellowship from the University of Guadalajara, Mexico.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6 Polyamines in Soybean Food and Their Potential Benefits for the Elderly

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CONTENTS

6.1 INTRODUCTION

Polyamines are a group of aliphatic molecules that are ubiquitously distributed in all living organisms. These compounds were firstly described in 1678 by Antoni van Leeuwenhoek and later named spermidine and spermine due to their presence in particularly high amounts in human semen (Miller-Fleming et al., 2015). In humans, polyamines are involved in the regulation of several cellular processes, including cell proliferation, signal transduction, and membrane stabilization (Hunter & Burrit, 2012). Polyamines have important implications in human health, playing an important role in the prevention of diseases associated with age and thus favoring lifespan (Muñoz-Esparza et al., 2019).

These compounds are synthesized endogenously, starting from the decarboxylation of ornithine, or exogenously supplied through diet. It is known that their synthesis decreases with age, which is why polyamines from food acquire greater importance in the elderly population (Nishimura et al., 2006). In this sense, soybean food can be considered a good source of polyamines (Nishibori et al., 2007; Toro-Funes et al., 2015). This chapter reviews the content of polyamines found in soybeans and in soy-derived foods, as well as the implications of polyamines during aging and in the prevention of chronic diseases.

DOI: 10.1201/9781003030294-7

6.2 POLYAMINES' CHEMICAL AND BIOCHEMICAL PROPERTIES

Spermidine (N-[3-aminopropyl]-1,4-butanediamine), spermine (N,N-bis[3-aminopropyl]-1,4-butane diamine), and putrescine (1,4-butanediamine) are low-molecular-weight aliphatic polycations that are widely distributed in nature, including microorganisms, plants, and animals (Lenis et al., 2017). Spermidine and spermine possess three and four amino groups, respectively, while putrescine may be considered a diamine (Figure 6.1). Polyamines are relatively stable compounds, capable of resisting acidic and alkaline conditions, and can establish hydrogen bonds with hydroxyl solvents such as water and alcohol. Likewise, they can strongly bind to biomolecules such as DNA, RNA, proteins, and phospholipids, stabilizing their negative charges and, in many cases, modulating their function (Gómez-Gallego et al., 2017; Handa et al., 2018; Hirano et al., 2021).

Polyamines are involved in several important cellular processes, especially in cell proliferation and differentiation. They also participate in the synthesis of proteins, the modulation of the immune response, and the regulation of ion channels, particularly by blocking potassium channels (Gómez-Gallego et al., 2017; Tofalo et al., 2019). Another important aspect for which polyamines have been studied is their antioxidant capacity, spermine being the polyamine with the greatest antioxidant potential due to the higher amount of positive charges in its chemical structure. The main antioxidant mechanism would be its ability to chelate metals, which prevents the formation of hydroperoxides and secondary oxidation compounds (Lovaas, 1991; Toro-Funes et al., 2013). In addition, polyamines also act as DNA protectors from oxidative damage by eliminating free radicals, especially in lipophilic media (Farriol et al., 2003; Toro-Funes et al., 2013).

Intracellular polyamine levels are mainly regulated by *de novo* synthesis (Figure 6.2). Putrescine is synthesized from the amino acid ornithine by the action of the enzyme ornithine decarboxylase. Spermidine is subsequently obtained from putrescine by the action of the enzyme spermidine-synthase, which catalyzes the addition of a propylamine group coming from the decarboxylation of

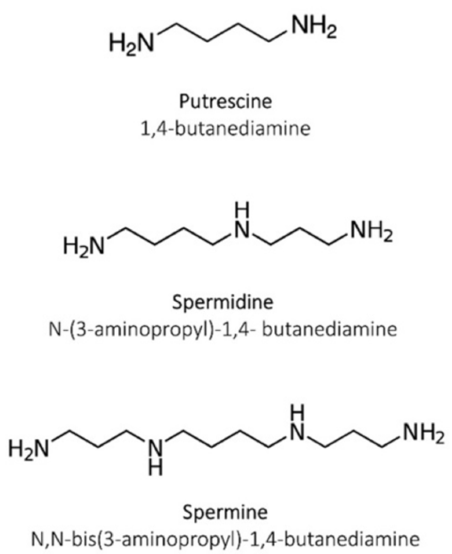

FIGURE 6.1 Chemical structure of polyamines.

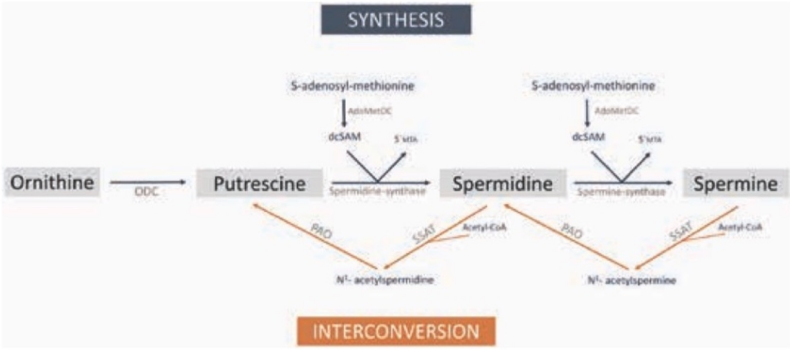

FIGURE 6.2 Synthesis and interconversion of polyamines. ODC = ornithine-decarboxylase; AdoMetDC = S-adenosyl-L-methionine-decarboxylase; dcSAM = decarboxylated S-adenosyl-methionine; 5´MTA = 5´-methylthioadenosine; SSAT = spermidine/spermine N1-acetyl-transferase; Acetyl-CoA = Acetyl coenzyme-A; PAO = polyamine-oxidase. Source: adapted from Munoz-Esparza et al. (2019).

S-adenosyl-methionine. Finally, the enzyme spermine-synthase is in charge of transforming spermidine into spermine by the addition of a second propylamine group (Miller-Fleming et al., 2015; Muñoz-Esparza et al., 2019).

In addition to *de novo* formation, interconversion among polyamines is also possible. This cyclical process controls the turnover of polyamines and regulates their intracellular homeostasis. The interconversion begins with the acetylation of either spermine or spermidine, which is catalyzed by an N-acetyl-transferase enzyme with the participation of acetyl coenzyme-A. Then, the enzyme polyamine oxidase removes a propylamine group. In this way, putrescine and spermidine may be obtained from the acetylated metabolite of spermidine and spermine, respectively (Larqué et al., 2007; Ruíz-Cano et al., 2012; Kalač, 2014).

In humans, polyamines can also have an exogenous origin mainly proceeding from food and/or the intestinal microbiota (Ramos-Molina et al., 2019; Tofalo et al., 2019). However, the contribution of the colonic microbiota to the global pool of polyamines is still uncertain and more information is needed on the polyamine-forming capacity of the intestinal microbiota and the possible biosynthetic pathways (Ramos-Molina et al., 2019). These bioactive compounds from the diet are absorbed in the small intestine, mainly in the duodenum and in the first segment of the jejunum, through transcellular mechanisms (i.e. passive diffusion and transporters) and by paracellular pathways (Pérez Cano et al., 2010; Ruíz-Cano et al., 2012; Hirano et al., 2021). Polyamines reaching systemic circulation are distributed to different tissues, such as adipose tissue, brain, liver, heart, pancreas, and thymus, in which they can be directly used by the cell or undergo interconversion (Larqué et al., 2007; Ramos-Molina et al., 2019).

6.3 POLYAMINES AND HEALTH IN THE ELDERLY

Polyamines are involved in a wide range of vital cellular processes, playing essential roles in cell growth and differentiation, metabolism, and physiological functions that may contribute to the inhibition of age-associated pathological changes (Minois et al., 2011; Soda et al., 2009a).

No age-related changes in polyamine levels in the blood have been reported so far, either in humans or animals. In blood cells, three separate mouse experiments did not find aging-associated changes in blood polyamine concentrations (Soda et al., 2009a; Soda et al., 2009b; Soda et al., 2013).

In human blood, an age-related decrease in polyamines has not been observed either (Elworthy & Hitchcock, 1989; Soda et al., 2005). Similarly, Pucciarelli et al. (2012) reported that healthy human nonagenarians and centenarians retain whole-blood polyamines concentration in comparison with middle-aged individuals.

However, it has been evidenced that the levels of polyamines present in some tissues tend to decrease with age. In this sense, Nishimura et al. (2006) found that polyamine concentrations in various organs were significantly lower in 10- and 26-week-old mice than in 3-week-old mice. Similarly, Liu et al. (2008) observed a decrease in polyamine concentrations in different age-related memory-associated structures of the brain in rats. In human brains, Vivó et al. (2001) reported a negative correlation between spermidine and spermine content and age in several areas of the basal ganglia. The decline of polyamine concentrations with age in tissues may result from a decrease in the biosynthetic activities of polyamine-producing enzymes, especially ornithine decarboxylase (Yoshinaga et al., 1993).

Overall, to overcome the potential decrease in the synthesis of polyamines with aging, the exogenous supply of these compounds is crucial for the elderly population. In fact, it has been observed that the enrichment of the diet with polyamines during this stage can increase the concentration of these compounds in the blood and, hence, help reduce the risk of age-associated pathologies (Soda et al., 2009a; Soda et al., 2013).

6.3.1 Mechanism of Action of Polyamines in Aging

Several age-associated pathologies, including cancer, neurodegeneration, and cardiovascular diseases, are directly connected to the intracellular accumulation of toxic debris, and its removal by autophagy constitutes a well-documented pathway for protection against aging and disease (Choi et al., 2013; Frake et al., 2015). Many of the antiaging properties of polyamines, in particular spermidine, have been causally linked to their capacity to stimulate cytoprotective autophagy (Yin et al., 2016; Madeo et al., 2018).

The induction of autophagy by polyamines is independent of certain well-characterized pathways, such as sirtuins and mTOR (Morselli et al., 2011). Morselli et al. (2011) reported that spermidine could induce short-term autophagy regulating cytoplasmic (de)acetylations without transcription of new proteins. More recently, it has been reported that spermidine induces autophagy through the inhibition of several acetyltransferases, including that of E1A-associated protein p300, which is one of the main negative regulators of autophagy (Mariño et al., 2014; Pietrocola et al., 2015). In fact, the potency of spermidine has been quantified to be equivalent to that of rapamycin, an FDA-approved immunosuppressant with protective and autophagy-stimulatory properties (Harrison et al., 2009; Du Toit et al., 2018).

Moreover, a new mechanism of polyamines' regulation of autophagy in memory immune cells has been described (Puleston et al., 2019; Zhang et al., 2019). Autophagy levels are specifically reduced in mature lymphocytes, leading to compromised memory cell responses in old individuals (Phadwal et al., 2012). Zhang et al. (2019) demonstrated that spermidine induces autophagy *in vivo* and rejuvenates memory immune cell responses. These results reveal an unexpected autophagy regulatory mechanism, which can be harnessed to reverse immune senescence in humans (Zhang et al., 2019; Green, 2020).

Beyond the anti-inflammatory effects of autophagy itself, the antioxidant and anti-inflammatory activities of polyamines have been described as complementary mechanisms of action of polyamines in age-associated diseases (Minois, 2014a; Hussain et al., 2017). Polyamines' effect against oxidative stress has been studied both *in vitro* and *in vivo* with inflammation models. In all experiments, polyamines significantly inhibited the production of pro-inflammatory mediators, such as nitric oxide, prostaglandin E2, and cytokines. Moreover, polyamines also reduced the accumulation of intracellular reactive oxygen species (Choi & Park, 2012; Morón et al., 2013; Yang et al., 2016; Jeong et al., 2018).

Furthermore, other mechanisms have been ascribed to the action of polyamines, including the regulation of ion channels, DNA and RNA stability, regulation of DNA methylases, and protein acetylation. Soda (2020) recently reviewed the relation between polyamine metabolism and DNA methylation, as changes in DNA methylation status play an important role in lifespan and aging-associated pathologies. The authors suggested that the synthesis of polyamines acts by inhibiting aging-associated aberrant DNA methylation. In this sense, it has been shown, both *in vitro* and in experimental animals, that this beneficial effect of polyamines mainly acts by maintaining the activity of DNA-methyltransferase in a sustained manner (Soda, 2020).

6.3.2 Health Effects of Polyamines Related to Aging-Associated Pathologies

Polyamines exert various beneficial effects on aging and age-related diseases. A recent prospective population-based study over a period of 15 years reported for the first time that a diet rich in spermidine was associated with a decrease in the risk of all-cause mortality in humans (Kiechl et al., 2018). In this study, spermidine showed the strongest inverse relation with mortality among 146 nutrients investigated. This effect was dose-dependent, and the authors stated that spermidine effectively induced autophagy and could reduce the acetylation of histones, which are critical processes for cell homeostasis in aging. However, more studies are still needed to clarify the role of polyamines in lifespan and to further unravel the age-associated effects of polyamines in humans. Here, a summary of the polyamine main effects on aging-associated diseases is presented.

6.3.2.1 Neuroprotection by Polyamines

Polyamines, in particular spermidine, seem to exert neuroprotective effects according to various *in vivo* studies performed in animal models. In flies, spermidine feeding protects from age-induced memory impairment (Gupta et al., 2013) and loss of locomotor activity (Minois et al., 2014b). These effects have been explained by a rejuvenation, dependent on autophagy, which maintains synaptic flexibility and plasticity (Gupta et al., 2016). In a mouse model for multiple sclerosis, spermidine attenuates disease progression and improves visual functions through reduced demyelination of the optic nerve and spinal cord and a decreased loss of retinal ganglion cells (Guo et al., 2011; Yang et al., 2016). Similarly, spermidine promotes optic nerve regeneration and blunts retinal degeneration in a mouse model of normal-tension glaucoma (Noro et al., 2015a; Noro et al., 2015b). On the other, it has been reported that spermine may improve the recognition memory deficit, spatial learning, and memory capabilities in rodent models (Velloso et al., 2009; Kibe et al., 2014). Overall, these studies suggest a wide range of neuroprotective effects of exogenously applied polyamines with relevance to several neurodegenerative motor disorders and dementias.

6.3.2.2 Polyamines in Cardiovascular and Metabolic Syndromes

The effect of polyamines in the protection from cardiac aging and cardiovascular pathologies has been widely described both in animal and human studies. Wang et al. (2020) reported the ability of spermidine to attenuate cardiac aging through activation of mitochondrial biogenesis. Eisenberg et al. (2016) showed that spermidine extends the lifespan of old mice and exerts cardioprotective effects, reducing cardiac hypertrophy and blood pressure, preserving diastolic function, and delaying the transition to heart failure. Moreover, spermidine reversed age-induced arterial stiffness with a reduction in oxidative damage of endothelial cells and alleviated the formation of atherosclerotic plaques in mice (LaRocca et al., 2013; Michiels et al., 2016). Finally, six-week supplementation of spermine and spermidine in mice reduced age-associated changes in myocardial morphology and inhibited cellular apoptosis of the heart (Zhang et al., 2017).

In humans, an increase in dietary polyamines inversely correlates with blood pressure and the incidence of cardiovascular disease and death (Soda et al., 2012; Eisenberg et al., 2016). However, it is necessary to perform interventional studies in humans to elucidate the exact mechanism of polyamines in the prevention and incidence of cardiovascular disease.

Regarding type 2 diabetes, polyamines could function as antiglycan agents due to their chemical structure, delaying the accumulation of advanced glycation end-products, which are associated with diabetes complications (Moinard et al., 2005; Bjelakovic et al., 2010). The interaction of the free amino groups of polyamines with the highly reactive carbonyl compounds may explain this protective effect (Gugliucci & Menini, 2003). *In vitro* studies have demonstrated that spermine can protect DNA and histones from glycation in the cell nucleus (Gugliucci & Menini, 2003). Whether polyamines might be useful in the treatment of obesity and type 2 diabetes is an important topic for future research.

In mice fed with hypercaloric diets, polyamines attenuated weight gain and the comorbidities of obesity induced by hypercaloric regimens, correlating with autophagy induction in white adipose tissue (Fernández et al., 2017). Moreover, polyamines prevented adiposity, improved glucose tolerance, led to increased energy expenditure, and conferred resistance to obesity-associated complications (Bonhoure et al., 2015; Sadasivan et al., 2014; Kraus et al., 2014).

6.3.2.3 Polyamines in Muscle-Related Diseases

One of the hallmarks of aging is the decline in stem cell function, resulting in impaired tissue regeneration and immunosenescence (López-Otín et al., 2013). In old mice, spermidine reversed the age-associated defect of autophagy and mitophagy in muscle stem cells, preventing their senescence and improving muscle regeneration (García-Prat et al., 2016). Spermidine application (or spermidine combined with exercise) successfully inhibited skeletal muscle atrophy in rats, concomitant with induction of autophagy and mitochondrial improvements (Fan et al., 2017). The spermidine-mediated ultrastructural and functional improvement of mitochondria from skeletal muscle stem cells further support the potential utility of spermidine in the treatment of muscle-related disorders (García-Prat et al., 2016; Fan et al., 2017).

6.3.2.4 Polyamines' Effects on Tumorigenesis

Polyamines are essential for cell proliferation and growth and, hence, a dysregulation of their metabolism is implicated in many tumor types. Although increased polyamine concentrations caused by enhanced biosynthesis have been found in skin, breast, colon, lung, and prostate cancers, the exact role of polyamines in cancer is still unclear (Nowotarski et al., 2013).

Despite that polyamines have shown *in vitro* pro-carcinogenic properties on cultured human cancer cells, *in vivo* animal studies have not demonstrated the same effect (Gerner & Meyskens, 2004). In fact, polyamines seem to reduce tumorigenesis, as demonstrated in skin tumors (Matsumoto et al., 2011), hepatocellular carcinomas (Yue et al., 2017), or colorectal tumors (Vargas et al., 2012; Miao et al., 2016). Moreover, polyamines reduce the growth of transplantable tumors in mice treated with chemotherapies by the stimulation of immunosurveillance. Concretely, spermidine improves the antitumor efficacy of chemotherapy *in vivo* by enhancing the anticancer immune response (Pietrocola et al., 2016). The role of polyamines in the stimulation of the immune system explains why they reduce tumorigenesis *in vivo*, although it enhances the proliferation of cancer cells *in vitro*.

6.4 POLYAMINES IN SOYBEAN AND SOY PRODUCTS

Polyamines are found in foods of both animal and plant origin, although their content and distribution depend on the type of product. The occurrence of spermidine, spermine, and putrescine in foods mainly has a physiological origin (as they proceed from animal and plant tissues) (Kalač et al., 2005; Sánchez-Pérez et al., 2018; Muñoz-Esparza et al., 2021). In addition, high levels of putrescine may be achieved by the action of fermentative and/or spoilage microorganisms (Bover-Cid et al., 2001; Kozová et al., 2009). Moreover, some authors have also associated the formation of spermidine and spermine with a bacterial activity, especially in fermented products (Atiya-Ali et al., 2011; Kalač, 2014; Kobayashi et al., 2016).

In foods of plant origin, spermidine is the main polyamine, usually followed by spermine, with the exception of fruits, in which putrescine is the highest polyamine, especially in citrus fruits (Sánchez-Pérez et al., 2018; Muñoz-Esparza et al., 2021). On the other hand, foods of animal origin tend to have a higher content of spermine and, in some cases, significant levels of putrescine can be achieved (Kalač et al., 2005; Nishimura et al., 2006; Nishibori et al., 2007; Kozová et al., 2009; Bover-Cid et al., 2014).

6.4.1 Soybean and Non-Fermented Soy Products

Soybean and soy products are a good source of polyamines, although their content shows great variability, even within the same type of food. Table 6.1 summarizes the polyamine content in soybean and non-fermented soy products reported in the literature. Due to its plant origin, the predominant polyamine in soybeans was spermidine, with mean values ranging from 106 to 218 mg/kg, followed by spermine (36–82 mg/kg) and putrescine (17–41 mg/kg). For non-fermented soy products, a similar polyamine distribution profile has been reported, although in notably lower amounts (with approximately a ten-fold reduction). Regarding soy drink, the fact that it is produced by the hydration and grinding of the soybeans may help explain the lower polyamine occurrence observed. Moreover, a subsequent heating process is applied to improve the taste and flavor of soy drink and achieve its stabilization. The application of both ultra-high temperature (UHT) and ultra-high-pressure homogenization (UHPH) treatments in the manufacturing of soy drinks did not modify its polyamine content (Toro-Funes et al., 2014). In the case of tofu, obtained by the coagulation of soy drink, a very similar distribution profile of polyamines has been reported.

In soybean sprouts, putrescine was the predominant polyamine, with a mean level of 44.7 mg/kg according to data reported by Toro-Funes et al. (2015), which may be attributed to the germination process in which putrescine acts as a growth factor (Kusano et al., 2008). In soybeans, the germination process leads to an accumulation of all polyamines, finding maximum values at 48 h of germination, followed by slightly lower values after 96 h (Glória et al., 2005). In this sense, Kralj-Cigic et al. (2020) reported that germination of lentils only increased the content of putrescine while spermine and spermidine remained practically unchanged. The conditions (e.g. luminosity, temperature, humidity) and the period of germination of pulses may modify the polyamine levels achieved in the sprouts (Gloria et al., 2005; Mao-Jun et al., 2005; Ponce de Leon et al., 2013; Menéndez et al., 2019).

Overall, the occurrence of polyamines in soybean and, subsequently, its derivatives, could be affected by the cultivar, the geographical location, certain environmental factors, and the specific cultivation and/or harvesting conditions (Glória et al., 2005; Kobayashi et al., 2017; Sagara et al., 2017). In plants, apart from the involvement of polyamines in the germination process, they also play a role in the response to stress to various environmental factors, such as drought or the presence of extreme temperatures during the harvest period (Toro-Funes et al., 2015; Shao et al., 2015; Dawood & Abeed, 2020). Actually, it has been observed that polyamine levels in plants, particularly those of putrescine, increase in response to stress during cultivation (Shao et al., 2015; Menéndez et al., 2019). Likewise, some studies have shown that the application of polyamines can also compensate for the negative effects of cold or drought, thus favoring the germination, growth, or survival of plants (Kusano et al., 2007; Luna-Esquivel et al., 2014; Chen et al., 2019; Menéndez et al., 2019). In addition, fertilization can also influence the levels of polyamines. On this topic, Losák et al. (2018) reported that sulfur and nitrogen fertilization increased the levels of spermidine present in soybeans.

6.4.2 Fermented Soy Products

Nowadays, a range of fermented soybean derivatives are available worldwide (i.e. natto, sufu, tempeh, tamari, soy sauce, and miso). These products are all obtained through the fermentation of the soybean, but they differ in the specific treatment applied to the raw material (e.g. dehulled, soaking,

TABLE 6.1

Polyamine Content in Soybean and Non-Fermented Soy Products (mg/Kg)

Soybean and Soy Products	n	Putrescine			Spermidine			Spermine			References
		Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
Soybean	3	–	–	1.6–6.5	–	–	33.2–62.1	–	–	29.7–34.3	Bardócz et al. (1993)
	1	17.0	–	–	128.0	–	–	–	–	–	Ziegler et al. (1994)
	2	41.0	–	–	207.0	–	–	69.0	–	–	Okamoto et al. (1997)
	13	–	–	3.7–16.8	–	–	99.2–389.0	–	–	27.8–114.0	Gloria et al. (2005)
	4	30.9	15.5	16.3–57.0	180.0	82.7	90.8–305.0	–	–	7.2–19.1	Kalač et al. (2005)
	2	–		35.2–57.2	158.0	–	–	58.6	–	–	Nishimura et al. (2006)
	5	17.1		6.4–24.2	106.0	–	88.2–125.0	36.6	–	30.3–41.6	Nishibori et al. (2007)
	6	18.1	0.7	–	218.0	9.2	–	82.6	2.4	–	Hou et al. (2019)*
	1	3.18	0.13	–	86.04	3.17	–	5.97	0.24	–	Tan et al. (2019)
Soy drink	2	2.1		–	16.3	–	–	2.8	–	–	Nishimura et al. (2006)
	8	1.3	0.4	0.7–2.1	10.1	0.5	9.1–10.9	2.2	0.6	1.6–3.2	Toro-Funes et al. (2015)

Tofu	4	nd	–	–	0.2	–	nd–0.2	nd	–	–	Nishibori et al. (2007)
	19	2.6	1.4	nd–5	23.6	5.6	15–35.3	7.6	4.1	4.1–19.2	Byun et al. (2013)
	2	1.8	–	–	15.5	–	–	6.8	–	–	Nishimura et al. (2006)
	8	0.8	0.6	nd–1.5	20.8	6.3	3.4–30.2	4.5	3.0	nd–8.1	Toro-Funes et al. (2015)
	32	44.6	2.4	–	9.1	0.3	–	–	–	–	Yue et al. (2019)
Soy sprouts	3	44.7	3.2	41.1–47.4	11.2	0.6	10.5–1.7	0.5	0.4	0.3–0.9	Toro-Funes et al. (2015)

Notes
nd = not detected; – = not reported by authors.
*mg per Kg of dry weight.

boiling, roasting, and steaming) and in the addition of several ingredients (e.g. sesame oil, wheat, and rice). Overall, the occurrence of polyamines in fermented soy products was highly variable among them, both from a quantitative and qualitative point of view (Table 6.2). This heterogeneity is mainly due to the different occurrence of polyamines in the raw soybeans used in their manufacturing, as well as to the contribution from the different added ingredients (Toro-Funes et al., 2015; Kobayashi et al., 2017; Park et al., 2019; Yang et al., 2020; Liu et al., 2020).

Moreover, the fermentation process could, partly, influence the polyamine content, especially explaining the high putrescine values observed for some products, such as soy sauce and sufu (Tang et al., 2011; Yang et al., 2020). In this topic, it has been described that putrescine production may depend on the strains of the fermentative microorganisms, as well as on the fermentation conditions, such as temperature and period (Park et al., 2019; Tan et al., 2019; Lan et al., 2020; Yang et al., 2020). For example, Tan et al. (2019) evaluated the addition of two different starter cultures (*Aspergillus* and *Mucor*) during the douchi fermentation process. Their results showed an increase in putrescine content with respect to its initial content (raw); particularly the *Aspergillus* strains increased putrescine levels up to ten times, while in the *Mucor* strains this increase was lower (up to three times more).

During the production of these types of soy products, a traditional fermentation with naturally occurring microorganisms has been historically used (Tan et al., 2019; Park et al., 2019). In this case, the fermentation process takes longer and is generally carried out in open environments where random spontaneous microorganisms could be responsible for a higher formation of amines than in soy products fermented with starter cultures (Li et al., 2019; Tan et al., 2019). Thus, some authors related the occurrence of higher levels of putrescine in fermented soy products with the presence of spoilage microorganisms with decarboxylase activity (i.e. *Enterococcus*, *Bacillus*, or *Staphylococcus*) (Li et al., 2019; Yue et al., 2019; Hou et al., 2019; Yang et al., 2020).

Despite the fact that most of the studies dealing with soy fermented products do not link the formation of spermine and spermidine to bacterial activity, Kobayashi et al. (2016) reported the capacity of different strains of *Bacillus subtilis* to form spermidine during the production of natto. These authors suggested that the selection of starter cultures with spermidine production potential could contribute to improved polyamine levels in natto, reinforcing the health benefits of this traditional Japanese fermented food (Kobayashi et al., 2016).

6.5 IMPACT OF POLYAMINE INTAKE FROM SOYBEAN FOOD ON THE ELDERLY POPULATION

It has been argued that, during aging, polyamines evolve to the status of anti-aging vitamins, and thus its dietary intake should be promoted to secure the maintenance of homeostasis (Madeo et al., 2019). Although there are no specific recommendations on the daily intake of polyamines, some authors have shown that long-term intake of foods rich in polyamines could have a positive impact on the prevention of age-associated diseases. Specifically, Soda et al. (2009b) observed in a Japanese population that the continuous intake of soy and soy derivatives, such as natto, increased the blood levels of polyamines, which could potentially have a positive impact on cardiovascular health. Likewise, Binh et al. (2011) and Soda et al. (2012) have pointed out that a higher intake of polyamines in the frame of a Mediterranean dietary pattern could promote greater longevity and provide a protective effect against cardiovascular diseases. More recently, Kiechl et al. (2018) also observed that a diet rich in spermidine, mainly from plant origin foods, was associated with a lower risk of mortality in a follow-up cohort for 20 years.

The daily intake of polyamines has been estimated in various geographical areas, showing highly variable results (Muñoz-Esparza et al., 2019). Different studies performed in the adult European population showed ranges of polyamine intake from 140 to 390 µmol/day, depending on the country (Ralph et al., 1999; Atiya Ali et al., 2011; Buyukuslu et al., 2014). For the USA, the daily intake of

TABLE 6.2
Polyamine Content in Fermented Soy Products (mg/Kg)

Fermented Soy Products	n	Putrescine Mean	Putrescine SD	Putrescine Range	Spermidine Mean	Spermidine SD	Spermidine Range	Spermine Mean	Spermine SD	Spermine Range	References
Natto	2	11.4	–	–	87.2	–	–	17.8	–	–	Nishimura et al. (2006)
	4	15.4	–	7.1–23.5	33.6	–	21.8–45.5	3.8	–	2.0–5.3	Nishibori et al. (2007)
	3	7.4	1.9	5.8–9.5	66.4	9.2	56.9–75.2	10.1	1.0	9.2–11.2	Toro-Funes et al. (2015)
Sufu	10	–	–	21.2–47.3	–	–	nd–27.1	–	–	nd–22.9	Tang et al. (2011)
	38	–	–	0.5–316.9	–	–	nd–4.0	–	–	nd–6.9	Guan et al. (2013)
	3	14.2	4.7	9.3–18.8	0.5	0.8	nd–1.4	1.8	0.8	0.9–2.2	Toro-Funes et al. (2015)
	3	–	–	13.8–36.4	–	–	0.6–6.5	–	–	nd–9.4	Yang et al. (2020)
Tempeh	2	45.3	–	–	85.6	–	–	13.6	–	–	Nishimura et al. (2006)
	3	23.2	7.0	17.5–31.1	108.9	13.7	97.3–124.0	12.7	8.3	6.1–21.8	Toro-Funes et al. (2015)
Tamari	3	15.3	2.0	13.1–17.1	34.8	4.6	29.45–38.02	4.4	2.10	2.8–6.8	Toro-Funes et al. (2015)
Douchi	30	–	–	nd–276.0	–	–	nd–74.92	–	–	nd	Yang et al. (2014)
	6	–	–	4.47–33.36	–	–	7.59–18.0	–	–	nd	Tan et al. (2019)
Soy sauce	10	26.8	–	–	12.9	–	–	nd	–	–	Nishimura et al. (2006)
	6	61.4	–	29.8– 136.4	11.9	–	6.3–16.7	2.0	–	0.2–3.9	Nishibori et al. (2007)
	3	7.2	0.4	6.9–7.6	21.9	1.7	20.0–22.9	1.9	0.3	1.5–2.1	Toro-Funes et al. (2015)
	45	22.9	60.3	0.3–229.0	3.9	3.3	nd–10.4	–	–	–	Deetae et al. (2017)
	3	31.75	0.52	–	73.86	2.83	–	nd	–	–	Li et al. (2019)

Miso	6	26.1	–	19.8 – 34.3	1.7	–	0.4–5.9	1.0	–	0–6.3	Nishibori et al. (2007)
	3	11.7	7.8	2.7–17.8	8.4	1.3	7.5–9.9	2.9	0.6	2.5–3.5	Toro-Funes et al. (2015)

Notes
nd = not detected; – = not reported by authors.

polyamines in adults aged 40–80 years old was estimated at 250 μmol. In Japan, a slightly lower average intake of polyamines was estimated for children and adults (200 μmol/day) (Nishibori et al., 2007).

In recent years, the consumption of soy and its derivatives has increased in Western countries, mainly through the use of soy drink and a variety of traditional fermented products (Guan et al., 2013; Losák et al., 2018). This consumption behavior may be due not only to the potential health benefits, but also to their use as a substitute for animal protein or, in the case of soy drink, as an alternative to cow's milk for people who are lactose intolerant, allergic to milk protein, or avoid milk for other reasons (Toro-Funes et al., 2014). However, the estimation of the polyamine intake only derived from the consumption of soy-derived products in Western countries is still challenging due to the scarcity of their consumption data. Here, a first attempt has been made to assess the contribution of polyamines per serving of some of the most popular soy products by Western population (Table 6.3). The soy-derivative product that showed the highest contribution of polyamines per serving was tempeh (129.0 μmol), mainly due to its outstanding polyamine occurrence. Soy drink, tofu, soybean sprouts, natto, and sufu provided a lower polyamine contribution (10.4–29.3 μmol), spermidine being the predominant compound. As tamari, soy sauce, and miso are usually consumed as condiments, their expected polyamine contribution was very low.

Nowadays, cow milk is frequently substituted by several plant-based beverages, soy drink being one of the most largely consumed. Then, taking into account the cow milk polyamine content as reported by Bover-Cid et al. (2014), a 60-fold intake of polyamines from soy drink is obtained in comparison with cow milk. It is also noteworthy that the typical replacement of certain animal protein foods (i.e. meat and fish) by high-protein soy derivatives (i.e. tempeh or tofu) would also provide a greater polyamine intake. For example, the consumption of one serving of tofu would provide double the polyamine intake than one of fish, while tempeh would provide a 6- and 12-times higher intake in comparison with meat and fish, respectively. On the contrary, the consumption of sufu, a matured soy-product that is often consumed as cheese, would lead to a lower intake of polyamines.

TABLE 6.3
Estimation of the Polyamine Contribution (μmol) per Serving of Different Soy Products*

	Serving Size (g)	Total Polyamines (μmol)	Putrescine (μmol)	Spermidine (μmol)	Spermine (μmol)
Soybean sprouts	50	29.3	25.4	3.8	0.1
Soy drink	250	23.7	3.6	17.5	2.7
Tofu	120	20.9	1.0	17.2	2.7
Natto	30	17.7	2.5	13.7	1.5
Sufu	60	10.4	9.7	0.2	0.5
Tempeh	120	129.0	31.5	90	7.4
Tamari	15	6.5	2.6	3.6	0.3
Soy sauce	15	3.6	1.2	2.3	0.1
Miso	15	3.0	1.9	0.9	0.2

Notes
**Content data from Toro-Funes et al. (2015) and serving sizes according to CESNID Food Composition Tables (CESNID, 2008) were used to estimate the polyamine contribution. The following equivalences were used:* soy drink as a substitute for cow's milk, tempeh and tofu as substitutes for meat and fish, sufu as aged cheese, and miso, tamari and soy sauce as condiments.

Some authors have suggested that the daily intake of polyamines should be approximately 540 μmol/day (Atiya-Ali et al., 2011). In this sense, in a hypothetical scenario with daily consumption of two glasses of soy drink and a serving of sufu, tofu, and tempeh, the intake of dietary polyamines would achieve 207.7 μmol, covering almost half of the above-mentioned recommendation. The inclusion of other foods, such as vegetables, fruits, cereals, legumes, and foods of animal origin in the daily diet could help to reach the suggested intake of polyamines.

In conclusion, polyamines are associated with the prevention of a range of age-related processes and pathologies, thus promoting life expectancy. Thus, the dietary intake of polyamines becomes of relevance for the elderly population. Considering that soybeans and soy products are a good source of dietary polyamines, their consumption, instead of animal protein foods, could help to significantly increase the intake of polyamines.

6.6 SUMMARY

Spermidine, spermine, and putrescine, known as polyamines, are involved in different aspects of human health. They are associated with the maturation and maintenance of the gastrointestinal tract, as well as with the prevention of age-associated pathologies, such as cardiovascular diseases and metabolic syndrome, and thus favoring the lifespan. Polyamines are also related to neuroprotection and to the stimulation of the antineoplastic immune response. This protective effect against aging and aging-associated pathologies is mainly related to the fact that spermidine can induce autophagy and reduce the acetylation of histones, which are critical processes for cell homeostasis in aging. In addition to endogenous synthesis, polyamines can also be exogenously supplied through food. It is known that during aging the endogenous synthesis of polyamines decreases, which is why dietary polyamines acquire greater importance for the elderly population. Polyamines can be found in all types of food, although with different levels and distribution depending on the type of product. Soybean is a plant-based food that stands out for having a high content of polyamines, and due to its origin, spermidine is the majority polyamine. Soy-derived products also show a high occurrence of polyamines, although their contents are highly variable, both from a quantitative and qualitative point of view. This heterogeneity is mainly due to the different occurrence of polyamines in the raw soybeans used in their manufacturing, as well as the contribution from the different added ingredients. Therefore, the regular consumption of both soybeans and soy products could help to increase the intake of polyamines and achieve the requirements of these compounds, especially in the elderly.

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6000 Broken Sound Pkwy., NW, Suite #300
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http://www.crcpress.com

September 17, 2021

Nelly C. Muñoz-Esparza

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Dear Nelly C. Muñoz-Esparza,

I am pleased to confirm and acknowledge, via this letter, that your chapter entitled, "Polyamines in Soybean Food Potential Benefits for the Elderly," has been accepted by Dr. John Shi for publication in the book *Phytochemicals in Soybeans: Bioactivity and Health Benefits*, a volume in his Functional Foods and Nutraceuticals series.

Congratulations!

It is expected, if book production stays on schedule, that CRC Press/Taylor and Francis will publish the book in February, 2022.

Sincerely,

Laura Piedrahita

Laura Piedrahita
Editorial Assistant
Life Sciences Division

2 | Planteamiento y Objetivos

2 Planteamiento y objetivos

Las poliaminas son unos componentes bioactivos de los alimentos relativamente poco conocidos a pesar de que sus efectos fisiológicos beneficiosos han sido bien estudiados, especialmente en las primeras etapas de la vida, en el envejecimiento y en la prevención de enfermedades crónicas no transmisibles. En esta tesis doctoral se plantea el **estudio de las poliaminas en diferentes categorías de alimentos, incluyendo la leche materna y las fórmulas infantiles, así como también los factores que influyen en su contenido**. El conocimiento del contenido y perfil de poliaminas en alimentos es un paso previo imprescindible para poder plantearse a futuro recomendaciones de enriquecimiento de la dieta con estos compuestos.

Para alcanzar este objetivo general se plantean los siguientes objetivos específicos:

OBJETIVO 1. Estudiar la composición cuali y cuantitativa de poliaminas en diferentes alimentos.

OBJETIVO 2. Evaluar el efecto de diferentes tratamientos culinarios en el contenido de poliaminas de algunos alimentos ricos en estos componentes.

OBJETIVO 3. Estudiar el contenido, perfil y evolución de las poliaminas en leche materna a lo largo de la lactancia. Comparación con fórmulas infantiles.

OBJETIVO 4. Estudiar la influencia de diferentes factores asociados a la lactancia en los contenidos de poliaminas en la leche materna.

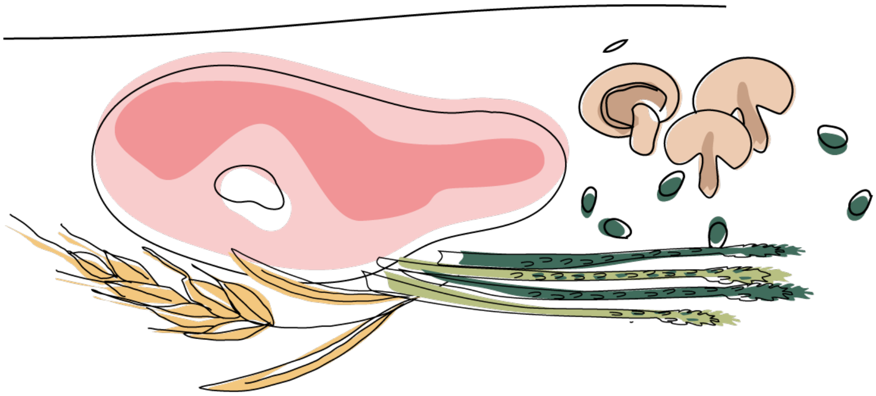
OBJETIVO 5. Evaluar la influencia del tipo de lactancia materna y de las poliaminas de la leche materna sobre los parámetros antropométricos del lactante.

3 | Resultados

3 Resultados

Este apartado se organiza en función de los objetivos planteados en la tesis doctoral. Los resultados de la tesis se recogen en un total de siete publicaciones, incluyendo seis artículos científicos y un capítulo de libro.

Cada publicación se presenta precedida por un breve resumen que sintetiza los objetivos, la metodología y los principales resultados obtenidos; y destaca las contribuciones más relevantes.



Poliaminas en alimentos

OBJETIVO 1.

Estudiar la composición cuali y cuantitativa de poliaminas en diferentes alimentos.

OBJETIVO 2.

Evaluar el efecto de diferentes tratamientos culinarios en el contenido de poliaminas de algunos alimentos ricos en estos componentes.

3.1 Estudio de la composición cuali y cuantitativa de poliaminas en diferentes alimentos y del efecto de diferentes tratamientos culinarios en su contenido.

PUBLICACIÓN 3

Occurrence of Polyamines in Foods and the Influence of Cooking Processes

Nelly C. Muñoz-Esparza, Judit Costa-Catala, Oriol Comas-Basté, Natalia Toro-Funes, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou.
Foods, **2021**. 10; 8: 1752. DOI: 10.3390/foods10081752

Factor de impacto (SJR 2020): 0.774
Categoría "Food Science": Q1 (73/332)

COMUNICACIÓN ESCRITA

Nelly C. Muñoz-Esparza, Sònia Sánchez-Pérez, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. **Poliaminas: ¿Los antioxidantes olvidados?** XIV Reunión Anual de la Sociedad española de Seguridad y Calidad Alimentarias (SESAL), 2018, Salamanca.

Planteamiento y objetivo

En los alimentos, la presencia de espermidina, espermina y putrescina es principalmente de origen fisiológico, ya que se encuentran en los tejidos animales y vegetales (Kozová et al., 2009). Sin embargo, en algunos alimentos, altos niveles de putrescina se pueden deber a la actividad aminoácido descarboxilasa de microorganismos fermentativos y/o alterantes (Bover-Cid et al., 2014). Aunque mucho menos estudiado, se ha postulado que la espermidina y la espermina también podrían tener un origen bacteriano, especialmente en productos fermentados (Atiya-Ali et al., 2011; Kalač, 2014).

Los datos disponibles en la literatura sobre el contenido de poliaminas en alimentos muestran una amplia variabilidad, con niveles de espermidina superiores a los de espermina en los alimentos de origen vegetal, mientras que en los de origen animal ocurre lo contrario. Además, la mayoría de los trabajos existentes han determinado estos compuestos en alimentos crudos y, solo unos pocos han considerado la influencia de la cocción en su contenido (Kalač, 2006; Nishimura et al., 2006; Nishibori et al., 2007). En este sentido, algunos autores han descrito que las prácticas culinarias podrían modificar el contenido de poliaminas, aunque estos datos experimentales aún son muy escasos e incluso contradictorios (Eliassen et al., 2002; Krausová et al., 2008; Kozová et al., 2009).

Teniendo en cuenta los beneficios para la salud de la ingesta de poliaminas y el potencial interés de suplementar la dieta con poliaminas, es relevante identificar las principales fuentes dietéticas de estos compuestos. Asimismo, también es necesario conocer cómo ciertos tratamientos tecnológicos o culinarios pueden afectar el contenido de poliaminas de los alimentos. Por lo tanto, el objetivo de este estudio fue evaluar la presencia de poliaminas en diferentes alimentos comercializados en España, así como el efecto de diferentes tratamientos culinarios sobre el contenido de poliaminas de algunos alimentos ricos en estos compuestos.

Diseño experimental

Para este estudio se consideraron un total de 109 alimentos diferentes comercializados en España y pertenecientes a ocho categorías: verduras y hortalizas (27 alimentos, n=292), frutas (22 alimentos, n=130), cereales y derivados (12 alimentos, n=58), legumbres (13 alimentos, n=63), frutos secos y semillas (9 alimentos, n=51), carnes y derivados (10 alimentos, n=516), pescados y mariscos (9 alimentos, n=188) y productos lácteos (7 alimentos, n=108). Los contenidos de poliaminas forman parte de la base de datos del grupo de investigación que incluye datos procedentes de diferentes estudios realizados en los últimos años. Las poliaminas se determinaron mediante cromatografía líquida de ultra alta eficacia con detección fluorimétrica (UHPLC-FL) de acuerdo con el método descrito por Latorre-Moratalla et al. (2009).

Para evaluar el efecto de diferentes tratamientos culinarios sobre los niveles de poliaminas, se seleccionaron trece alimentos con contenidos significativos de poliaminas y que habitualmente se consumen cocinados (champiñones, espárragos, judías verdes, coliflor, col, brócoli, calabacín, espinaca, calabaza, acelga, pollo, ternera y cerdo). Cada muestra se dividió de forma homogénea en cinco partes iguales (100-120 g) y se sometió a los diferentes procesos culinarios: crudo (control), hervido, plancha, microondas y *sous-vide* (al vacío).

Para el análisis estadístico de la influencia de los diferentes tratamientos culinarios en el contenido de poliaminas de los alimentos se utilizó la prueba t de Student (IBM SPSS Statistics 25.0 EE. UU.).

Resultados

En todos los alimentos se detectó la presencia de poliaminas, aunque su contenido y distribución dependió del tipo de producto. Las categorías de legumbres y lácteos fueron las que mostraron una mayor variabilidad, con un rango intercuartil de 55.4 mg/kg y 82.9 mg/kg, respectivamente. En cambio, frutas, cereales y pescados y mariscos fueron las categorías que mostraron una menor disparidad en el contenido total de poliaminas, con rangos intercuartílicos hasta diez veces más pequeños en comparación con las categorías anteriormente mencionadas.

De entre los alimentos de origen vegetal, el germen de trigo fue el que presentó los contenidos más altos de poliaminas (440 mg/kg). También destacaron por sus altos contenidos los champiñones, el pimiento verde, los guisantes, los cítricos, las habas, la soja y el tempeh, con niveles superiores a 90 mg/kg. En la gran mayoría de los alimentos vegetales, la espermidina fue la poliamina predominante, representando 90% del contenido total de poliaminas. Sin embargo, en el caso del pimiento verde, los cítricos, los brotes de soja, el plátano, la berenjena y el tomate, la putrescina fue la principal poliamina, con contenidos que representan entre el 75-96% del total de poliaminas.

En los alimentos de origen animal, los contenidos más altos de poliaminas (42-130 mg/kg) se encontraron en alimentos fermentados, tales como quesos y derivados cárnicos crudos curados. La putrescina fue la poliamina mayoritaria en estos productos, mientras que en los demás productos de origen animal la espermina constituyó entre 40% y 95% del total de poliaminas. Cabe destacar que la leche, el queso fresco y los huevos presentaron niveles extremadamente bajos de poliaminas (<1 mg/kg).

En cuanto a la influencia de los diferentes tratamientos culinarios, se observó que el hervido y la plancha fueron los métodos que más redujeron el contenido de poliaminas, con pérdidas de entre 15 y 50% dependiendo del tipo de alimento en comparación con el contenido en crudo ($p<0.05$). La acelga, la espinaca, el calabacín, la col, el cerdo y la ternera fueron los alimentos que mostraron una mayor reducción de poliaminas, especialmente de putrescina en el caso del hervido. La cocción por microondas provocó pérdidas significativas de poliaminas solamente en cuatro alimentos (calabacín, espinaca, acelga y ternera), y en porcentajes considerablemente menores en comparación con el hervido y la plancha. La cocción *sous-vide* no ocasionó pérdidas significativas de poliaminas en ninguno de los alimentos evaluados.

Aportaciones más relevantes

- Las mejores fuentes dietéticas de poliaminas, especialmente de espermidina, son el germen de trigo, los champiñones y la soja.
- La gran variabilidad observada en el contenido total de poliaminas hace necesario que, para realizar recomendaciones dietéticas de estos compuestos se deba tener en cuenta cada alimento de manera individual y no por categorías.
- Es la primera vez que se evalúa simultáneamente el efecto de cuatro tratamientos culinarios sobre el contenido de poliaminas en los alimentos.
- Los tratamientos culinarios de hervido y plancha provocaron una reducción significativa en el contenido de poliaminas en la mayoría de los alimentos evaluados, mientras que la cocción por microondas y el *sous-vide* fue altamente respetuosa con la presencia de estos compuestos.

Para futuras aplicaciones, los alimentos con altos contenidos de poliaminas podrían considerarse para la obtención de extractos de estos compuestos, ya sea para la fortificación de alimentos o como suplementos alimenticios, especialmente en las etapas de la vida en las que los requerimientos de poliaminas son mayores.

foods

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Article

Occurrence of Polyamines in Foods and the Influence of Cooking Processes

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Citation: Muñoz-Esparza, N.C.; Costa-Catala, J.; Comas-Basté, O.; Toro-Funes, N.; Latorre-Moratalla, M.L.; Veciana-Nogués, M.T.; Vidal-Carou, M.C. Occurrence of Polyamines in Foods and the Influence of Cooking Processes. *Foods* **2021**, *10*, 1752. https://doi.org/10.3390/foods10081752

Academic Editor: Maria Martuscelli

Received: 14 July 2021
Accepted: 27 July 2021
Published: 29 July 2021

Abstract: Dietary polyamines are involved in different aspects of human health and play an important role in the prevention of certain chronic conditions such as cardiovascular diseases and diabetes. Different polyamines can be found in all foods in variable amounts. Moreover, several culinary practices have been reported to modify the content and profile of these bioactive compounds in food although experimental data are still scarce and even contradictory. Therefore, the aim of this study was to evaluate the occurrence of polyamines in a large range of foods and to assess the effect of different cooking processes on the polyamine content of a few of them. The highest level of polyamines was found in wheat germ (440.6 mg/kg). Among foods of a plant origin, high levels of total polyamines over 90 mg/kg were determined in mushrooms, green peppers, peas, citrus fruit, broad beans and tempeh with spermidine being predominant (ranging from 54 to 109 mg/kg). In foods of an animal origin, the highest levels of polyamines, above all putrescine (42–130 mg/kg), were found in raw milk, hard and blue cheeses and in dry-fermented sausages. Regarding the influence of different domestic cooking processes, polyamine levels in food were reduced by up to 64% by boiling and grilling but remained practically unmodified by microwave and sous-vide cooking.

Keywords: polyamines; spermidine; spermine; putrescine; cooking processes; boiling; grilling; microwave; sous-vide

1. Introduction

Found in all living organisms, polyamines are nitrogenous low molecular weight substances characterized by the presence of two or more amino groups and are classed as spermidine (N-(3-aminopropyl)-1,4-butane diamine), spermine (N, N-bis(3-aminopropyl)-1,4-butane diamine) and putrescine (1,4-butanediamine). Their chemical structure confers notable stability to these compounds, which are capable of resisting acid and alkaline conditions and are highly soluble in hydroxyl solvents such as water and alcohol [1].

Polyamines participate in several biological processes, mainly cell proliferation and differentiation, protein synthesis, RNA transcription, the stabilization of negative charges of DNA and cell apoptosis and also possess antioxidant properties [2–4]. Multiple studies have been performed that support the involvement of polyamines in maintaining human health [5]. Due to their antioxidant and anti-inflammatory effects, polyamines play an important role in the prevention of chronic conditions such as cardiovascular diseases (i.e., hypertension, heart failure and myocardial fibrosis) and diabetes [6,7]. In addition, polyamines are associated with a protective effect against the aging process and have been described as potential lifespan-promoter compounds [8]. Spermidine can induce autophagy and reduce histone acetylation, which are critical processes for cellular homeostasis in aging [9]. Furthermore, a recent intervention study performed by Soda et al. [10] in a Japanese population showed that a long-term high intake of spermidine and spermine through the consumption of natto resulted in elevated blood spermine levels. These authors also report that an increased polyamine intake inhibits the pro-inflammatory state by decreasing the expression of LFA-1 (lymphocyte function-associated antigen) and suppressing aberrant gene methylation, which are related to the presence of age-associated chronic diseases [10]. Finally, it has been described that in certain situations that entail a rapid cell growth such as the neonatal stage and after surgery as well as in the elderly, polyamine requirements are higher [11–13].

In the human organism, polyamine levels are mainly regulated by de novo synthesis (Figure 1). Briefly, putrescine is synthesized from the amino acid ornithine by the enzymatic action of ornithine decarboxylase. Putrescine is subsequently converted by spermidine synthase into spermidine, which is finally transformed to spermine in a reaction catalyzed by spermine synthase [14,15]. There is also a cyclical process of interconversion among polyamines that controls their turnover and regulates their intracellular homeostasis (Figure 1).

On the other hand, polyamines in the organism can also have an exogenous origin, mainly proceeding from food. Dietary polyamines are absorbed in the small intestine through transcellular or paracellular pathways and are distributed to the different tissues where they can be used directly by the cell or undergo interconversion [12,16]. Another potential source of polyamines is the intestinal microbiota. However, this contribution to the global pool of polyamines in the organism is still uncertain and more information is needed on the polyamine-forming capacity of the intestinal microbiota and the possible biosynthetic pathways [16,17].

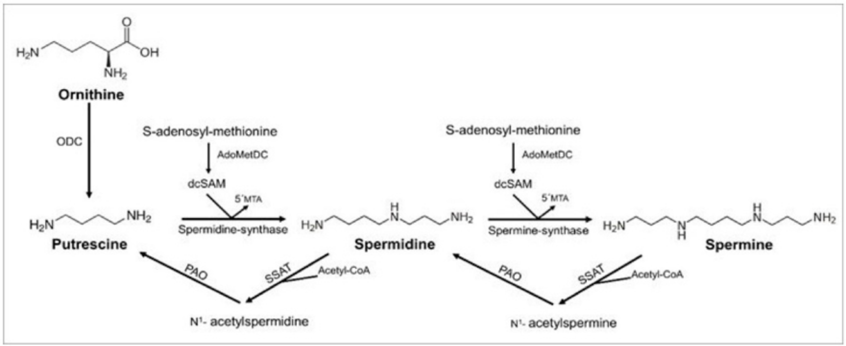

Figure 1. Synthesis and interconversion of polyamines. ODC: ornithine-decarboxylase; AdoMetDC: S-adenosyl-L-methionine-decarboxylase; dcSAM: decarboxylated S-adenosyl-methionine; 5′MTA: 5′-methylthioadenosine; SSAT: spermidine/spermine N1-acetyl-transferase; Acetyl-CoA: acetyl coenzyme-A; PAO: polyamine-oxidase. Adapted from Muñoz-Esparza et al. [15].

In foods, spermidine, spermine and putrescine occur naturally, being present in animal and plant tissues [15–18]. High levels of putrescine may arise in several foods due to the amino acid decarboxylase activity of fermentative and/or spoilage microorganisms [19,20]. Similarly, although much less described, it has been postulated that spermidine and spermine could also have a bacterial origin, especially in fermented products [1,21]. Regarding individual polyamines, spermidine levels generally tend to be higher than those of spermine in foods of a plant origin and vice versa in those of an animal origin [1,15]. Most of the available data are from raw foods and only a few authors have considered the influence of cooking practices on the polyamine content. It has been reported that a few culinary practices could potentially have a modifying effect although experimental data are still scarce and even contradictory [18,22–25].

Bearing in mind the health benefits of polyamine intake and the potential interest of supplementing the diet with polyamines, it is of relevance to identify the main dietary sources of these compounds. Likewise, it is also necessary to know how technological or culinary treatments can affect the content of these bioactive compounds. Therefore, the aim of the present study was firstly to evaluate the occurrence of polyamines in different foods marketed in Spain and secondly to assess the effect of different cooking processes on the content of polyamines in a few of these foods.

2. Materials and Methods

2.1. Polyamine Content in Foods

Putrescine, spermidine and spermine contents were determined in 109 different food products retailed in Spain in the last 5 years. Overall, a total of 1406 samples were analyzed, belonging to eight different food categories: vegetables (27 food items, $n = 292$), fruit (22 food items, $n = 130$), cereals and derivatives (12 food items, $n = 58$), legumes (13 food items, $n = 63$), nuts and seeds (9 food items, $n = 51$), meat and derivatives (10 food items, $n = 516$), fish and seafood (9 food items, $n = 188$) and dairy products (7 food items, $n = 108$). The specific list of food items included in this study and the number of samples for each one are summarized in Supplementary Tables S1 and S2.

Polyamines were determined by ion-pair ultra-high performance liquid chromatography coupled to fluorometric detection (UHPLC-FL) as described by Latorre-Moratalla et al. [26]. Briefly, 5–10 g of a food sample, previously minced and homogenized, was mixed with 10 mL of 0.6 M perchloric acid (PanReac AppliChem GmbH, Darmstadt, Germany) on a magnetic stir plate for 20 min. Subsequently, the two phases were separated by centrifugation (20,000 rpm, 4 °C, 25 min) and the supernatant was filtered and collected in a 25 mL volumetric flask. This extraction process was repeated twice and the final volume of the extract was adjusted with 0.6 M perchloric acid. All samples were filtered through a GHP 0.22 μm filter (Waters Corp., Milford, MA, USA) and stored at 4 °C until the analysis. All determinations were done in triplicate. The chromatographic determination of the polyamines was accomplished using an Acquity UPLC BEH C18 1.7 μm reverse phase column (2.1 mm × 50 mm) (Waters Corp., Milford, MA, USA), followed by an online post-column derivatization with ortho-ophthaldehyde (Sigma-Aldrich, St. Louis, MO, USA) and spectrofluorometric detection (ex: 340 nm and em: 445 nm) (Waters Corp., Milford, MA, USA). The quantification of the polyamine content of the samples was carried out with the external standard method.

2.2. Effect of Different Cooking Processes on the Food Polyamine Content

In order to assess the effect of different cooking processes on the polyamine levels, thirteen food items with significant amounts of polyamines and which are usually consumed cooked were studied (i.e., mushrooms, asparagus, green beans, cauliflower, cabbage, broccoli, zucchini, spinach, pumpkin, chard, chicken meat, beef meat and pork meat). For this purpose, each food sample was divided homogeneously into five equal parts (100–120 g) and subjected to the different culinary processes: raw (control), boiling, grilling, microwave and sous-vide. Table 1 summarizes the specific conditions applied in each cooking process.

Table 1. Specific conditions for each cooking process.

Cooking Method	Conditions	Cooking Time
Boiling	Sample was placed in 500 mL of boiling water.	15 min
Grilling	Sample was placed in the pan once it was hot (140 °C–160 °C).	7 min
Microwave	Sample was placed in a special microwave device made of silicone and cooked at 600 watts.	5 min
Sous-vide	Sample was vacuumed and sealed in a special plastic bag of polyamide and polyethylene with a thickness of 90 microns. It was subsequently immersed in water at 70 °C.	25 min

The polyamine content was determined following the analytical method described in the previous section. The water used for the boiling process was also analyzed for its polyamine content. Salt, oil or seasonings were not used in any cooking process. The results were expressed in dry matter in order to compare the effect of the different cooking methods. The moisture was determined according to the Official Method of the Association of Official Analytical Chemists, which consists of drying the samples (102 ± 2 °C) until a constant weight is reached [27].

2.3. Statistical Analysis

Polyamine contents are presented as mean values, standard deviation, minimum and maximum. A Student's *t*-test was used to determine the significance of the influence of the cooking method on the polyamine content. The statistical analysis was performed with the IBM SPSS Statistics 25.0 statistical software package (IBM Corporation, Armonk, NY, USA). Values of $p < 0.05$ were accepted as significant.

3. Results and Discussion

3.1. Polyamine Content in Foods

Figure 2 shows the distribution of the total polyamine content in different food categories. Detailed data on the polyamine content for each foodstuff are provided in Supplementary Tables S1 and S2. Polyamines were found in all the foods although with a high variability. In general, the category of legumes showed the highest polyamine content, closely followed by dairy products and meat and derivatives (Figure 2). The variability in polyamine contents is reflected in the high interquartile ranges, calculated as the difference between percentile 75 and percentile 25, being particularly high in legumes (55.4 mg/kg) and dairy products (82.9 mg/kg). In contrast, fruit, cereals and fish and seafood showed less disparity in the polyamine content with interquartile ranges up to ten-fold smaller compared with the above-mentioned food categories.

Among vegetables and fruit, mushrooms, green peppers, peas and citrus fruit stand out for their high total polyamine content with the mean values being four-fold higher than in the other products from this category (Figure 3). Spermidine was the main polyamine in most vegetables and fruit, 90% of which contained between 2.4 mg/kg and 27.4 mg/kg. Mushrooms and peas stood out for particularly high contents of this polyamine with mean values of 128.50 mg/kg and 54.4 mg/kg, respectively. On the contrary, putrescine was the main polyamine in tomatoes, eggplants, bananas, soybean sprouts, green peppers and citrus fruit, representing 75–96% of their total polyamine content. The highest levels (a mean value of 90 mg/kg) were determined in green peppers and citrus fruit with very similar contents among samples. Similar results have been reported by other authors, suggesting that the accumulation of putrescine in these food types probably has a physiological origin [1,22,28]. In other vegetables such as spinach and peas, the high occurrence of putrescine has been linked with the presence of spoilage bacteria (i.e., *Enterobacteriaceae* and *Clostridium spp.*) [1,29].

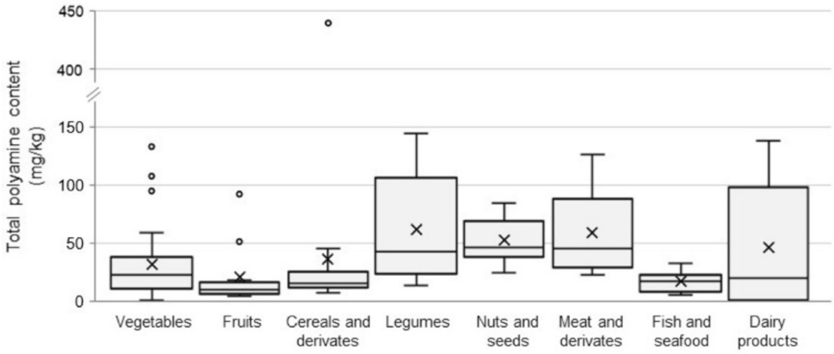

Figure 2. Distribution of the total polyamine content (mg/kg) by food category. The bottom and top of the box (interquartile range) are the percentile 25 and the percentile 75, respectively. The central line represents the median. Lines extending vertically from the boxes (whiskers) indicate variability outside the interquartile range. Outliers are plotted as circles.

In cereals and derivatives, the total polyamine levels were relatively low or moderate with mean values generally below 25 mg/kg (Figure 4). The exception was wheat germ, which had an outstandingly high polyamine content (440.6 mg/kg), far more than any other food item in the study. Among their many functions in plants, polyamines can act as growth factors, playing an important role during germination [30,31]. Thus, high levels of polyamines may be expected in all germinated foods such as those observed in wheat germ and, to a lesser extent, in soybean sprouts. Polyamines are reported to reach maximum levels after 48 h of germination and their accumulation may be influenced by conditions such as luminosity, temperature and humidity [32–35]. The predominant individual polyamine in practically all cereals and derivatives was spermidine. The exceptions were rice and barley, where the main polyamine was spermine, and corn, where putrescine prevailed, in agreement with reports by Zoumas-Morse et al. [36] and Bandeira et al. [37].

Polyamine contents in the different types of legumes, nuts or seeds were highly variable although the proportion of spermidine, spermine and putrescine was similar in practically all of them (Figure 5). Spermidine was the predominant polyamine in 86% of foods in this category with particularly high levels in certain legumes and derivatives (i.e., tempeh, soybeans, broad beans, natto, lentils and chickpeas) and seeds (sesame and sunflower seeds), reaching values of 43.0 mg/kg–108.9 mg/kg. The high amounts of putrescine in soy-fermented products (i.e., miso, sufu, soy sauce and tamari) could be related to the decarboxylase activity of both fermentative and/or spoilage bacterial strains [38]. Additionally, certain fermentation conditions such as temperature and duration may also have an impact on the accumulation of putrescine [38–40].

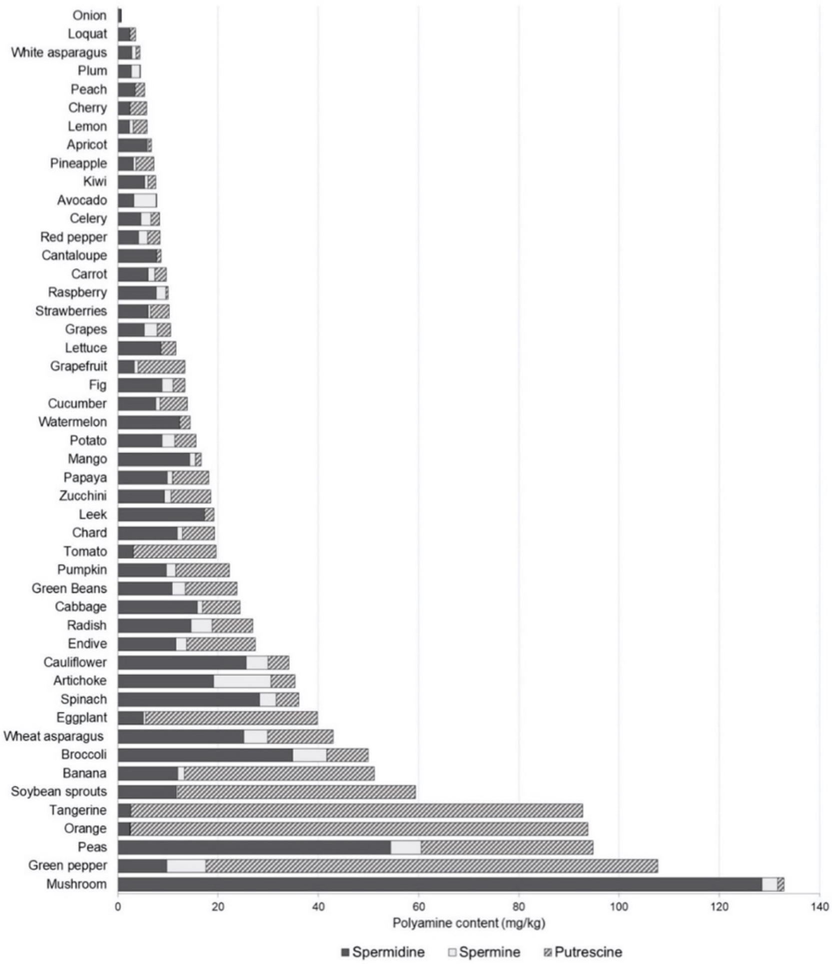

Figure 3. Polyamine profile and content (mg/kg) in vegetables and fruit.

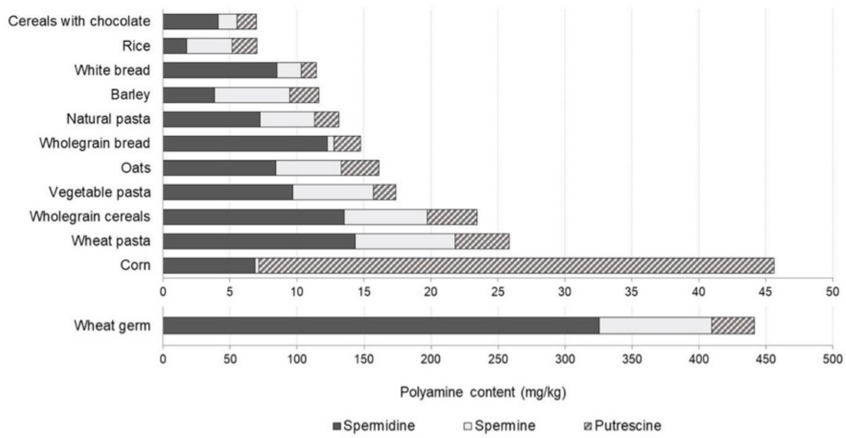

Figure 4. Polyamine profile and content (mg/kg) in cereals and derivatives.

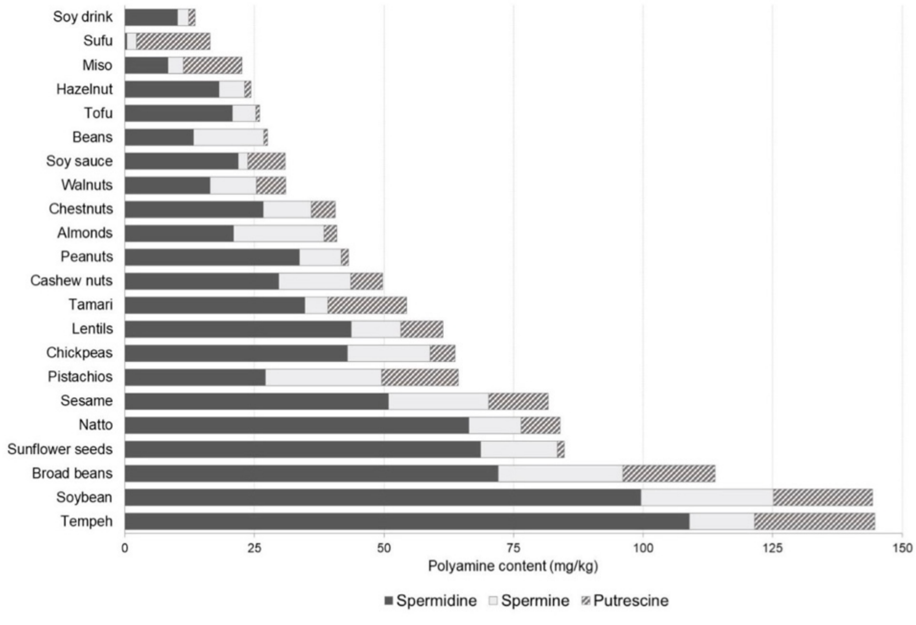

Figure 5. Polyamine profile and content (mg/kg) in legumes, nuts and seeds.

Finally, it is noteworthy that the occurrence of polyamines in all the above-mentioned plant-derived foods can be affected by the cultivar, geographical location, environmental factors and cultivation and/or harvesting conditions [25,32,41]. In this context, it has been extensively reported that polyamines play a key role in the plant response to various stressful environmental factors such as drought or the presence of extreme temperatures during the harvest period [31,42]. Specifically, it has been observed that putrescine levels in plants increase in response to stress during cultivation [35]. Likewise, several studies have shown that the exogenous application of polyamines, either pre-cultivation (i.e., soaking the seeds in water enriched with polyamines) or during cultivation through watering, can compensate for the negative effects of cold or drought, thus favoring the germination, growth or survival of plants [30,31,35,42]. These anti-stress properties of polyamines in plants could be attributed to their role in modulating morphological growth parameters, preserving the integrity of cell membranes and thus minimizing the growth inhibition caused by stress [43,44]. In addition, polyamines could increase the activity of several antioxidant enzymes present in plants, thus regulating oxidative stress caused by environmental factors [31].

In foods of an animal origin (meat, fish and dairy products), the total polyamine content was highly variable with values ranging from 0.15 mg/kg to 139 mg/kg (Figure 6). The highest levels were found in a few types of cheese (raw milk, hard and blue cheese) and dry-fermented sausages; products with an elevated content of putrescine arising from the aminogenic capacity of both fermentative microorganisms and Gram-negative spoilage bacterial strains [19,45]. Different authors have associated the use of raw meat of poor hygienic quality and/or improper production/storage conditions with a high accumulation of putrescine in fermented sausages [1,19]. Spermine was the predominant polyamine in the other animal-derived products, constituting 40% to 95% of the total polyamines in fresh meat, fresh fish, fish derivatives and cured and cooked meat products. Worth highlighting are the extremely low levels of any polyamine found in fresh milk and fresh cheese. They were also lower in yogurt compared with other fermented foods although slightly higher than those in milk. In eggs, only low levels of spermine and spermidine were determined, both in equal amounts. Despite available data on the polyamine content in milk, yogurt and eggs being very scarce, the levels reported in the literature are similar to those found in the present study [11,22,28].

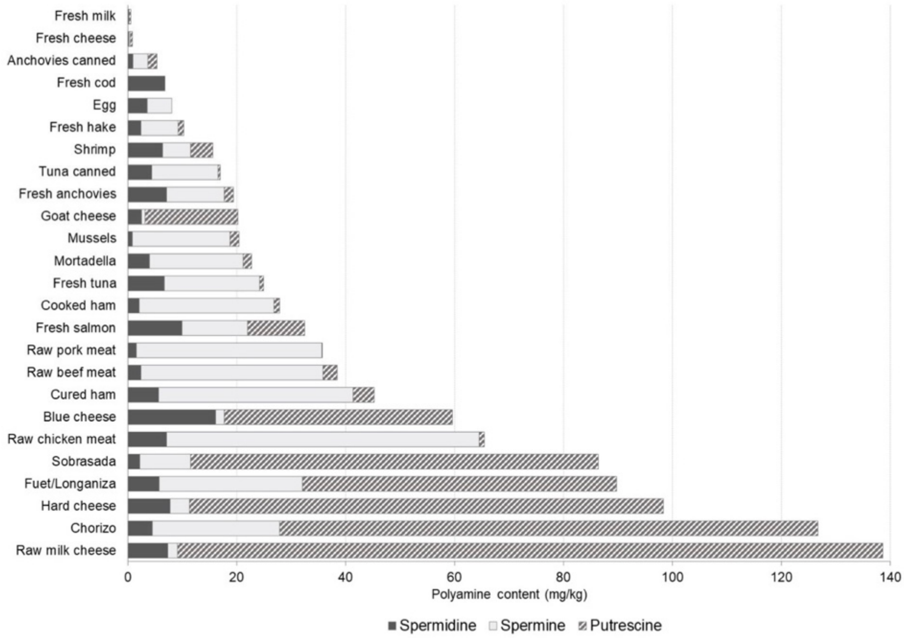

Figure 6. Polyamine profile and content (mg/kg) in meat, fish and dairy products.

3.2. *Effect of Different Cooking Processes on Food Polyamine Content*

Table 2 compares the polyamine content of thirteen food items with significant amounts of polyamines both raw and cooked by different culinary methods (i.e., boiling, grilling, microwave and sous-vide). This is the first time that the effect of these four cooking processes on the polyamine content in foods has been simultaneously assessed. In general, boiling and grilling reduced polyamine contents the most although this effect differed according to the type of food. Only cauliflower, broccoli and chicken meat did not show any polyamine loss after any of the culinary processes.

Boiling significantly decreased the polyamine content in most foods (9 out of 13) with losses ranging from 15 to 64% in comparison with raw foods depending on the polyamine. This decrease can be mainly attributed to their transfer to the boiling water, where polyamines were always recovered at a mean rate of 94%. This displacement of polyamines to water has also been reported by other authors [18,23,24,46–48]. Overall, chard, spinach, zucchini, pork and beef stood out for undergoing the highest reduction of polyamines especially putrescine (up to a 64% loss in chard). The high transfer of putrescine to boiling water can be explained by its greater solubility [15]. Moreover, polyamines are not homogenously distributed within a food product, which may account for the pronounced loss of putrescine in certain foods [46]. For example, it has been reported that asparagus accumulates higher concentrations of putrescine near the surface but not spermidine [49], which may explain the putrescine reduction in asparagus observed in the current study. Veciana-Nogués et al. [48] concluded that the putrescine content in spinach, cauliflower, chard and green beans was reduced by being transferred to the cooking water whereas boiling had no effect on other vegetables such as peppers and peas. Similarly, Eliassen et al. [22] and Bardocz et al. [50] reported no significant effect of boiling on the putrescine levels of vegetables such as carrot, broccoli, cauliflower and potato.

Table 2. Polyamine content (mean ± SD) in mg/kg of dry matter of foods subjected to different culinary processes: raw (control), boiling, grilling, microwave and sous-vide.

Food		Raw	Boiling	Grilling	Microwave	Sous-vide
Mushroom	SD	1658.9 ± 7.0	* 1274.3 ± 19.1	1495.5 ± 18.4	1646.2 ± 30.4	1658.0 ± 31.9
	SM	39.6 ± 0.2	39.6 ± 2.2	35.9 ± 1.7	38.9 ± 2.3	39.1 ± 0.6
	PU	7.0 ± 0.1	6.9 ± 0.1	6.5 ± 0.2	6.7 ± 0.1	6.3 ± 0.4
Asparagus	SD	645.8 ± 40.8	645.7 ± 13.0	* 484.9 ± 20.2	641.8 ± 44.1	638.2 ± 4.9
	SM	125.8 ± 0.3	125.4 ± 0.1	* 91.0 ± 2.5	117.2 ± 8.1	122.8 ± 7.6
	PU	160.1 ± 3.5	* 121.0 ± 10.1	145.0 ± 7.4	143.9 ± 2.5	159.3 ± 1.2
Green beans	SD	185.6 ± 0.3	* 157.6 ± 0.1	* 156.1 ± 2.7	179.0 ± 0.4	174.1 ± 5.6
	SM	88.9 ± 2.0	* 73.3 ± 1.4	* 67.7 ± 1.1	80.0 ± 1.9	89.5 ± 2.2
	PU	12.9 ± 0.4	12.6 ± 0.4	12.5 ± 0.3	12.5 ± 0.2	12.4 ± 0.1
Cauliflower	SD	327.1 ± 9.0	325.8 ± 5.3	324.4 ± 8.3	320.3 ± 23.8	324.0 ± 35.9
	SM	66.6 ± 1.7	62.7 ± 2.1	65.5 ± 3.1	63.4 ± 1.5	64.4 ± 3.0
	PU	49.7 ± 0.6	48.4 ± 0.3	48.2 ± 2.1	47.2 ± 4.8	45.7 ± 4.3
Cabbage	SD	105.1 ± 1.8	105.3 ± 0.2	* 69.6 ± 0.2	96.1 ± 3.4	105.3 ± 0.3
	SM	36.4 ± 0.3	33.7 ± 7.2	* 15.9 ± 0.2	33.0 ± 0.3	35.9 ± 0.2
	PU	2.9 ± 0.1	2.37 ± 0.2	* 1.7 ± 0.1	2.8 ± 0.1	2.7 ± 0.1
Broccoli	SD	389.1 ± 23.9	382.6 ± 29.5	396.0 ± 17.4	389.9 ± 21.6	394.9 ± 4.0
	SM	77.2 ± 6.6	69.8 ± 4.0	73.8 ± 0.1	71.2 ± 0.7	72.1 ± 1.7
	PU	91.7 ± 5.6	91.7 ± 6.5	89.5 ± 4.0	85.9 ± 5.4	88.5 ± 0.9
Zucchini	SD	344.2 ± 3.4	* 298.0 ± 2.0	* 282.0 ± 1.7	* 301.7 ± 1.8	341.7 ± 12.0
	SM	62.8 ± 3.9	* 27.4 ± 4.9	* 41.6 ± 2.7	59.3 ± 1.4	51.0 ± 1.9
	PU	160.7 ± 5.6	* 133.1 ± 6.61	* 116.7 ± 1.1	* 123.2 ± 2.6	163.5 ± 12.9
Spinach	SD	330.2 ± 0.3	* 238.5 ± 20.89	* 236.1 ± 17.0	* 278.6 ± 1.1	317 ± 4.9
	SM	42.2 ± 2.5	* 31.5 ± 1.9	* 25.9 ± 1.0	38.8 ± 1.6	39.0 ± 0.5
	PU	40.8 ± 0.6	* 22.3 ± 4.7	* 31.4 ± 2.3	40.2 ± 1.7	38.1 ± 0.3
Pumpkin	SD	80.3 ± 0.6	* 66.6 ± 4.2	* 60.4 ± 1.1	78.1 ± 0.5	76.7 ± 0.6
	SM	840.3 ± 8.4	834.0 ± 10.4	* 664.8 ± 5.4	839.5 ± 0.8	833.2 ± 2.8
	PU	19.3 ± 0.5	* 15.1 ± 1.0	17.4 ± 2.5	19.8 ± 0.6	19.5 ± 0.1
Chard	SD	239.7 ± 11.4	* 178.0 ± 0.3	234.7 ± 2.7	* 196.6 ± 1.0	215.3 ± 14.5
	SM	28.4 ± 1.8	27.1 ± 1.0	26.0 ± 0.2	25.9 ± 0.6	28.1 ± 0.5
	PU	38.6 ± 1.7	* 13.7 ± 0.2	* 26.1 ± 0.6	35.1 ± 0.3	32.8 ± 0.7
Chicken meat	SD	1.5 ± 0.1	1.0 ± 0.1	1.4 ± 0.2	1.11 ± 0.0	1.2 ± 0.1
	SM	10.0 ± 0.9	8.2 ± 0.4	8.5 ± 0.0	8.4 ± 0.3	9.9 ± 0.4
	PU	0.4 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.1	0.4 ± 0.1
Beef meat	SD	9.3 ± 0.4	8.1 ± 0.1	* 7.5 ± 0.1	* 7.6 ± 0.5	8.6 ± 0.1
	SM	130.0 ± 9.5	* 94.4 ± 3.4	115.7 ± 0.4	120.8 ± 0.9	127.2 ± 9.5
	PU	10.4 ± 0.6	* 5.9 ± 0.1	* 7.1 ± 0.1	* 7.7 ± 0.3	9.4 ± 0.6
Pork meat	SD	9.4 ± 0.5	* 5.9 ± 0.1	* 7.7 ± 0.2	8.8 ± 0.3	9.0 ± 0.2
	SM	138.1 ± 1.0	* 89.0 ± 0.3	* 118.6 ± 3.4	137.6 ± 0.1	136.9 ± 0.8
	PU	0.4 ± 0.0	0.3 ± 0.1	0.4 ± 0.0	± 0.0	0.4 ± 0.0

* Significant differences in the polyamine content with respect to their raw food ($p < 0.05$).

Grilling also resulted in notable losses of polyamines in practically the same foods as boiling. In general, more than a 20% reduction was observed in all polyamines with notably high spermine losses in cabbage (57%), spinach (39%) and zucchini (34%). The impact of grilling on the polyamine content has been scarcely studied to date and only for animal-derived foods. Available reports describe high losses of putrescine, spermidine and spermine in chicken and pork meat after grilling or roasting [18,23,46,47]. In the current study, the polyamine reduction in meat products was much lower and only observed in beef and pork. It has been hypothesized that the high temperatures reached during grilling (180 °C) may favor the so-called Maillard reaction by the interaction of the primary amino groups of polyamines with reducing sugars or, in the case of foods of an animal origin, with carbonyl compounds produced in the lipid oxidation pathway [18,51,52].

Microwave cooking caused a significant loss of polyamines only in zucchini, spinach, chard and beef but in considerably lower amounts in comparison with boiling and grilling. The affected polyamines were putrescine and/or spermidine. Microwave cooking can dehydrate food leading to the outflow of the most soluble polyamines and, accordingly, most of the lost polyamines were found in the water recovered from the cooking device. To compare the different foods, a standardized cooking time of five minutes was applied. The application of shorter times properly adapted to the nature of each food could minimize the leakage of water and hence the potential loss of polyamines.

Sous-vide is the French term used to designate the culinary method in which vacuumed foods are subjected to low temperatures for a long duration. One of the main features of sous-vide cooking is a high preservation of the organoleptic properties and compounds of raw food. Therefore, as expected, no significant loss of polyamines was observed for any food prepared with this technique and the minimal loss of water clearly prevented their leakage.

It should be noted that spinach was the only food in which amines other than polyamines were found. Specifically, a histamine content of 142 ± 6 mg/kg of dry matter was determined in raw spinach. In fact, spinach is one of the few plant foods to frequently contain histamine [20]. Comparable with their effect on putrescine, boiling and grilling of spinach caused significant histamine losses of nearly 60% and 25%, respectively. As both compounds are diamines, a similar behavior could be expected. These results are supported by a previous study, which also reported that adding salt when boiling had no effect on the high transfer of histamine from spinach to the cooking water [53].

4. Conclusions

In view of the reported benefits of polyamines for human health, including the prevention of certain chronic diseases, an increased intake of dietary polyamines is of potential importance. The great variability in the food polyamine content observed in this study indicates that the corresponding dietary recommendations should be issued considering each food product rather than general food categories. The best dietary sources of polyamines, especially spermidine, are wheat germ, soybeans and mushrooms. In future applications, these foods could be used to obtain plant extracts for food enrichment and/or polyamine supplements, which are especially recommended for certain stages of life with higher polyamine requirements.

Comparing domestic cooking processes revealed that boiling and grilling cause a significant reduction in the polyamine content in most of the tested foods, unlike microwave and sous-vide methods. Overall, the impact on polyamine levels depended not only on the type of food but also on the specific processing technique.

Supplementary Materials: The following are available online at www.mdpi.com/article/10.3390/foods10081752/s1, Table S1: Polyamine content (mg/kg) in food of a plant origin and Table S2: Polyamine content (mg/kg) in food of an animal origin.

Author Contributions: Conceptualization, N.C.M.-E., M.L.L.-M., M.T.V.-N., M.C.V.-C.; investigation, N.C.M.-E., J.C.-C., M.L.L.-M.; data analysis, N.C.M.-E., M.L.L.-M, M.T.V.-N., O.C.-B; writing—original draft preparation, N.C.M.-E., M.L.L.-M., M.T.V.-N., O.C.-B.; writing—review and editing, N.C.M.-E., O.C.-B., M.L.L.-M., M.T.V.-N., N.T.-F, M.C.V.-C.; supervision, M.C.V.-C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Nelly C. Muñoz-Esparza is a recipient of a doctoral fellowship from the University of Guadalajara, Mexico.

Conflicts of Interest: The authors declare no conflict of interest.

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Poliaminas en leche materna y fórmulas infantiles

OBJETIVO 3.

Estudiar el contenido, perfil y evolución de las poliaminas en leche materna a lo largo de la lactancia. Comparación con fórmulas infantiles.

OBJETIVO 4.

Estudiar la influencia de diferentes factores asociados a la lactancia en los contenidos de poliaminas en la leche materna.

OBJETIVO 5.

Evaluar la influencia del tipo de lactancia materna y de las poliaminas de la leche materna sobre los parámetros antropométricos del lactante.

3.2 Contenido, perfil y evolución de poliaminas en leche materna a lo largo de la lactancia. Comparación con fórmulas infantiles.

PUBLICACIÓN 4

Differences in polyamine content between human milk and infant formulas.

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou.
Foods, **2021**. 10; 11: 2866. DOI: 10.3390/foods10112866

Factor de impacto (SJR 2020): 0.774
Categoría “Food Science”: Q1 (73/332)

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COMUNICACIÓN ESCRITA

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, Sònia Sánchez-Pérez, Salvador Hernández-Macías, M. Teresa Veciana-Nogués, M. Luz Latorre-Moratalla, M. Carmen Vidal-Carou. **¿Es comparable el contenido y perfil de poliaminas en la leche materna y fórmulas infantiles?** IV Congreso de la Federación Española de Sociedades de Nutrición, Alimentación y Dietética (FESNAD), 2020, Virtual Zaragoza.

Planteamiento y objetivo

Las poliaminas juegan un papel importante en los primeros años de vida, como en la etapa neonatal y lactante, ya que promueven la maduración del tracto gastrointestinal, reduciendo así el riesgo de alergia en el lactante (Pérez-Cano et al., 2010; Dandrifosse et al., 2000; Almeida et al., 2021). La leche materna contiene estos compuestos, principalmente espermidina y espermina, que se sintetizan en la glándula mamaria durante el embarazo y la lactancia. Sin embargo, en la actualidad son todavía escasos los estudios disponibles sobre la presencia de poliaminas en leche materna (Romain et al., 1992; Pollack et al., 1992; Buts et al., 1995; Atiya-Ali et al., 2013; Plaza-Zamora et al., 2013; Atiya-Ali et al., 2014; Gómez-Gallego et al., 2017).

Las fórmulas infantiles son los productos alimenticios adecuados para reemplazar, de forma parcial o total, a la leche materna cuando la lactancia no es posible (Koletzko et al., 2005). Aunque algunos autores han descrito la presencia de poliaminas en fórmulas infantiles, estos trabajos son también muy limitados (Pollack et al., 1992; Romain et al., 1992; Buts et al., 1995; Atiya-Ali et al., 2014; Gómez-Gallego et al., 2016; Spizzirri et al., 2019). Además, la mayoría de estos trabajos solo consideran fórmulas de inicio y de continuación, y prácticamente no existen datos sobre el contenido de poliaminas en fórmulas infantiles de uso médico especial.

El objetivo de este estudio fue evaluar el contenido, perfil y evolución de las poliaminas en leche materna durante el primer semestre de lactancia. Además, también se evaluó el contenido de poliaminas de diferentes tipos de fórmulas infantiles para, finalmente, compararlo con el de la leche materna.

Diseño experimental

Se analizaron un total de 30 muestras de leche materna cedidas por el Banco de Sangre y Tejidos de Cataluña (España), correspondientes al seguimiento de seis madres durante los primeros cinco meses de lactancia materna.

Además, se seleccionaron un total de 15 fórmulas infantiles de inicio, de continuación y de uso médico especial (para prematuros y a base de proteína de soja y arroz) disponibles en el mercado español. Se analizaron tres marcas y dos lotes diferentes de cada tipo de fórmula infantil.

La determinación de putrescina, espermidina y espermina se realizó mediante UHPLC-FL de acuerdo con el método descrito por Latorre-Moratalla et al. (2009).

El análisis estadístico se realizó con el paquete de software estadístico IBM SPSS Statistics 25.0 (IBM Corporation, EE. UU.). La comparación de los contenidos de poliaminas a lo largo de la lactancia se realizó con la prueba no paramétrica de Wilcoxon para muestras pareadas (distribución no normal de las muestras según la prueba de Shapiro-Wilk). Se utilizó la prueba ANOVA (post-hoc T3 de Dunnett) para la comparación de los contenidos de poliaminas entre los diferentes tipos de fórmulas infantiles y la prueba T de Student para la comparación entre lotes de una misma marca.

Resultados

El contenido de poliaminas en la leche materna de las diferentes madres fue muy variable. Las concentraciones totales de poliaminas disminuyeron progresivamente a lo largo de la lactancia, observando concentraciones medias de hasta 1.7 veces más altas al inicio de la lactancia en comparación con las de los cinco meses (790 nmol/dL y 477 nmol/dL, respectivamente). Sin embargo, esta reducción solo fue estadísticamente significativa a los cuatro meses en comparación con los dos primeros meses ($p=0.016$).

En cuanto al perfil de distribución de las tres poliaminas, la putrescina fue siempre la poliamina minoritaria, mientras que la espermidina y la espermina estuvieron en proporciones muy similares, con una relación espermidina/espermina de 1.1. Con respecto a la evolución de cada poliamina durante el progreso de la lactancia, se observó que los niveles de espermidina y espermina tendieron a disminuir a lo largo de la lactancia ($p=0.016$). Por el contrario, los niveles de putrescina se mantuvieron prácticamente sin cambios durante el primer semestre de lactancia. Por lo que refiere a esta amina, se encontraron niveles anormalmente altos en las muestras de leche de una madre a los tres y cuatro meses de lactancia (121 nmol/dL y 183 nmol/dL, respectivamente). Además, en estas muestras también se detectó la inusual presencia de histamina (170 nmol/dL) y cadaverina (2,680 nmol/dL).

En las fórmulas infantiles, la espermidina y la putrescina se encontraron en todas las muestras, mientras que la espermina únicamente se detectó en dos fórmulas destinadas a lactantes prematuros. En todas aquellas fórmulas a base de leche de vaca (de inicio, de continuación y para prematuros), los niveles de putrescina y espermidina fueron muy similares, con valores siempre por debajo de 60 nmol/dL. En ningún caso se encontraron diferencias estadísticamente significativas entre lotes de una misma marca comercial.

En el caso de las fórmulas de uso médico especial a base de proteína vegetal, se observó una mayor variabilidad en el contenido de poliaminas en comparación con las fórmulas convencionales a base de leche de vaca, tanto entre marcas como entre lotes de una misma marca. Las fórmulas a base de arroz destacaron por sus altas concentraciones de putrescina, con valores que oscilaron entre los 188 y 312 nmol/dL, dependiendo de la marca. En cambio, la espermidina fue la poliamina principal en las fórmulas a base de soja (179-337 nmol/dL).

Al comparar la presencia de poliaminas en la leche materna con la de las fórmulas infantiles, se observaron grandes diferencias en el contenido y el perfil de distribución de las tres poliaminas. En general, los niveles medios de poliaminas totales fueron hasta 30 veces más bajos en las fórmulas infantiles que en la leche materna. A nivel de perfil, la espermidina y la espermina fueron las poliaminas mayoritarias en la leche materna, mientras que la putrescina fue más relevante en las fórmulas para lactantes.

Aportaciones más relevantes

- El contenido de poliaminas tiende a disminuir con el progreso de la lactancia materna, especialmente los de espermidina y espermina, con valor medios 1.7 veces menores a los cinco meses con respecto al primer mes de lactancia.
- Una posible contaminación bacteriana por la presencia de mastitis podría explicar la acumulación de concentraciones más altas de putrescina en leche materna, así como la presencia de otras aminas (histamina y cadaverina) que, a priori, no deberían encontrarse.
- Las concentraciones totales de poliaminas fueron hasta 30 veces más bajas en las fórmulas infantiles en comparación con la leche materna.

- La espermidina y la espermina fueron las poliaminas predominantes en la leche materna, mientras que la presencia de putrescina fue más relevante en las fórmulas infantiles.

Dada la importancia de las poliaminas en las primeras etapas de la vida, es importante que las fórmulas infantiles mejoren su contenido de poliaminas, tanto de manera cualitativa como cuantitativa, con el fin de que se asemejen lo más posible a la composición de la leche materna.

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Differences in Polyamine Content between Human Milk and Infant Formulas

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Abstract: Human milk is the gold standard for nutrition during the first months of life, but when breastfeeding is not possible, it may be replaced by infant formulas, either partially or totally. Polyamines, which play an important role in intestinal maturation and the development of the immune system, are found both in human milk and infant formulas, the first exogenous source of these compounds for the newborn. The aim of this study was to evaluate the occurrence and evolution of polyamines in human milk during the first semester of lactation and to compare the polyamine content with that of infant formulas. In total, 30 samples of human milk provided by six mothers during the first five months of lactation as well as 15 different types of infant formulas were analyzed using UHPLC-FL. Polyamines were detected in all human milk samples but with great variation among mothers. Spermidine and spermine levels tended to decrease during the lactation period, while putrescine remained practically unchanged. Considerable differences were observed in the polyamine contents and profiles between human milk and infant formulas, with concentrations being up to 30 times lower in the latter. The predominant polyamines in human milk were spermidine and spermine, and putrescine in infant formulas.

Keywords: polyamines; putrescine; spermidine; spermine; human milk; breastfeeding; infant formulas

Citation: Muñoz-Esparza, N.C.; Comas-Basté, O.; Latorre-Moratalla, M.L.; Veciana-Nogués, M.T.; Vidal-Carou, M.C. Differences in Polyamine Content between Human Milk and Infant Formulas. *Foods* **2021**, *10*, 2866. https://doi.org/10.3390/foods10112866

Academic Editor: Jayani Chandrapala

Received: 11 October 2021
Accepted: 16 November 2021
Published: 19 November 2021

1. Introduction

Human milk is the gold standard for human nutrition for at least the first six months of life since it satisfies all the requirements for infants to achieve optimal growth and development [1–3]. In addition to nutrients, this complex and highly variable biofluid contains nucleotides, hormones, growth factors, immunoglobulins, oligosaccharides, cytokines, and bacteria, which participate in the development of the immune system and provide protection against infectious diseases [2,4,5]. Additionally, human milk is relatively rich in polyamines, including putrescine, spermidine, and spermine, which are synthesized in the mammary gland during pregnancy and lactation and are reported to play a role in the hormonal regulation of lactogenic processes [6].

The few studies in the literature focusing on polyamines in human milk report highly variable concentrations [6–13], which may be determined by the mother–child dyad (i.e., the ethnic origin, age, nutritional status, and dietary patterns of the mother and the type of birth) [6,11,12,14]. The lactation phase and factors related to the breastfeeding process itself (foremilk vs. hindmilk and the time of the day), as well as infection in the mammary gland, are also influential [13–16].

When breastfeeding is not possible during the first year of life, human milk can be replaced partially or totally by infant formulas [17], whose compositional standards are established by the Nutrition Committee of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pedi-atrics (AAP). The aim is to achieve formulas that match human milk as closely as possible and cover the nutritional requirements of the infant for optimal growth [18,19]. Infant formulas are classified into two groups: those that are based on cow's milk, including first formulas (those that satisfy the infant's nutritional requirements during the first semester of life; EU 609/2013) and follow-on formulas (aimed at infants of about 4–6 months of age who have commenced complementary feeding; EU 609/2013), and formulas for special medical use (aimed at infants with digestion, absorption, or intolerance problems, or those who do not consume animal products for religious or other reasons) [18,20,21]. The latter group includes formulas for premature infants and formulas modified in carbohydrates, proteins, and/or fats; examples include lactose-free, soy-based, rice-based, hydrolyzed protein, and elemental formulas.

The occurrence of polyamines in infant formulas has been reported, although data are scarce and, in some cases, outdated. Moreover, most of the studies are focused on first and follow-on infant formulas [7–9,12,22,23], with only two studies analyzing preterm formulas [8,12] and one study analyzing soy-based formulas [7]. Due to recent changes in the formulation of these products, the available data on polyamine content may not reflect the current reality.

Polyamines participate in several biological processes, mainly cell growth and differentiation and protein synthesis [24,25]. Their role in the first years of life, in both the neonatal and infant stages, is important, as they promote the maturation of the gastrointestinal tract and help to maintain the integrity of the intestinal mucosa [26–28]. In this way, these compounds reduce intestinal mucosal permeability and the passage of antigenic macromolecules from the lumen to the blood circulation, thus reducing the risk of allergy in the infant [7,29,30]. Additionally, polyamines are involved in the development of the immune system and modulate the inflammatory response [28,29,31].

Due to the importance of polyamines in the first stages of life, the aim of this study was to evaluate the occurrence, profile, and evolution of polyamines in human milk during the first five months of breastfeeding. Moreover, the polyamine contents of different types of infant formulas retailed in Spain were determined and compared to that of human milk.

2. Materials and Methods

2.1. Samples

2.1.1. Human Milk

In total, 30 samples of human milk provided by the Blood and Tissue Bank of Catalonia, Spain, were analyzed. These samples were taken from six mothers during the first five months of breastfeeding and correspond to a pool of the milk produced over a whole day. All mothers were from the same geographical region (Catalonia, Spain) and had full-term babies by natural birth. All samples were stored at −80 °C until the day of their analysis.

2.1.2. Infant Formulas

In total, 15 different types of infant formulas available on the Spanish market as powdered products were selected. The formulas included were first, follow-on, preterm, and others designed for special use based on plant protein (rice and soy). For each kind of infant formula, three brands and two different batches were analyzed. The formulas were reconstituted according to the instructions on the label of each product on the same day as the analysis.

2.2. Polyamine Analysis

The polyamines were extracted from human milk and infant formulas as described by Muñoz-Esparza et al. [13]. Briefly, 1 mL of homogenized human milk or previously reconstituted infant formula was acidified with 70% perchloric acid and mixed for 20 min. Subsequently, samples were centrifuged (15,000 rpm, 4 °C, 15 min) and the supernatant was recovered and filtered through a 0.22 μm GHP filter (Waters Corp., Milford, MA, USA). Samples were stored at 4 °C until their analysis.

Putrescine, spermidine, and spermine were determined by ion-pair ultra-high-performance liquid chromatography coupled with fluorometric detection (UHPLC-FL), as described by Latorre-Moratalla et al. [32]. The chromatographic separation of polyamines was accomplished with an Acquity UPLC BEH C18 1.7 μm reverse phase column (2.1 mm × 50 mm) (Waters Corp., Milford, MA, USA), followed by online post-column derivatization with ortho-ophthaldehyde and fluorometric detection (ex: 310 nm and em: 445 nm). The quantification of polyamines in human milk and infant formula samples was carried out using the external standard method through a linear calibration curve of fluorometric response obtained from a range of standard solutions between 0.05 and 5 mg/L.

2.3. Statistical Analysis

The statistical analysis was performed with the IBM SPSS Statistics 25.0 statistical software package (IBM Corporation, Armonk, NY, USA). When analyzed by Shapiro–Wilk tests, the human milk samples did not follow a normal distribution, so the polyamine contents throughout the breastfeeding process were compared using the nonparametric Friedman test with Wilcoxon post hoc for paired samples. The one-way analysis of variance test, employing T3 de Dunnett, was used to compare the polyamine content among infant formulas, and the differences among batches were assessed with the Student T test. The level of significance was a p value ≤ 0.05.

3. Results and Discussion

3.1. Polyamines in Human Milk

Spermine, spermidine, and putrescine were detected in all human milk samples collected from different Spanish nursing mothers. Figure 1 shows the distribution of the total polyamine levels found in human milk during the first five months of lactation. The total polyamine content varied greatly among mothers, with interquartile ranges oscillating from 544 nmol/dL to 699 nmol/dL. As depicted in Figure 1, the mean total polyamine content progressively decreased as lactation progressed, with levels at the beginning being 1.7-fold higher than those at 5 months (790 nmol/dL and 477 nmol/dL, respectively). However, according to the post hoc Wilcoxon test, the reduction in the total polyamine content was only statistically significant at month four in comparison with months one and two ($p = 0.016$). Other studies have also reported higher polyamine contents in human milk in the first months of breastfeeding, with values 1.3- to 3.5-fold higher, depending on the study, when compared to the subsequent months [7,8,12,13]. As polyamines are involved in cellular growth and differentiation, it has been hypothesized that their higher concentration at the beginning of lactation could be related to the rapid growth of the infant in this period [11,12].

Regarding the distribution profile of the three polyamines, putrescine was always the minor compound, while spermidine and spermine were detected in very similar proportions (a ratio of 1.1) (Figure 2). Putrescine has been extensively described as the minor polyamine in human milk, but consensus is lacking as to which is the most abundant, with reported spermidine/spermine ratios ranging from 0.9 to 2.5 [6–13]. Figure 2 also shows the evolution of each polyamine during the lactation period. Overall, spermidine and spermine levels showed a decreasing tendency, although their reduction only became statistically significant at month 4 ($p < 0.05$). On the contrary, putrescine levels remained practically unchanged during the first five months of breastfeeding.

On the other hand, abnormally high levels of putrescine were found in samples from one mother at three and four months of breastfeeding (121 nmol/dL and 183 nmol/dL, respectively), as well as an unusual occurrence of other biogenic amines, histamine (169.6 ± 5.7 nmol/dL), and cadaverine (2679.6 ± 78.9 nmol/dL). A possible explanation for the high presence of these amines could be that this mother suffered from mastitis, an inflammatory disease of the mammary gland that involves bacteria with potential aminogenic capacity. These findings are supported by the results of the work performed by Perez et al. [16], which showed higher concentrations of putrescine together with the presence of histamine, tyramine, and cadaverine in mastitis-infected milk in comparison with that of healthy mothers. It is worth highlighting that putrescine, in addition to a physiological origin, can be formed by microbial activity, as can histamine, tyramine, and cadaverine [33]. On the contrary, the sources of spermidine and spermine are generally physiological rather than bacterial [25,34]. Despite the abnormally high levels of putrescine in these samples, the overall polyamine profile was not affected due to the strong prevalence of spermine and spermidine.

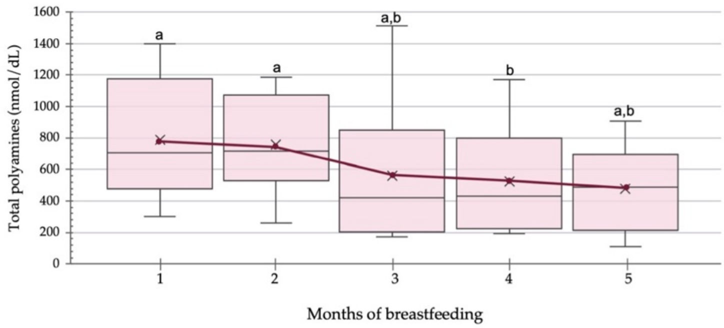

Figure 1. Distribution of total polyamine levels (nmol/dL) in human milk samples (n = 6) during the first five months of breastfeeding. The bottom and top of each box (interquartile range) are the 25th and 75th percentiles, respectively. The central line represents the median and X represents the mean. Lines extending vertically from the boxes (whiskers) indicate variability outside the interquartile range. The red line represents the evolution of mean polyamine content during the first semester of breastfeeding. The Friedman test with Wilcoxon post hoc were used to compare the total polyamine contents during the breastfeeding process. Different letters indicate statistically significant differences between breastfeeding months (1 vs. 4 months, p = 0.016 and 2 vs. 4 months, p = 0.016).

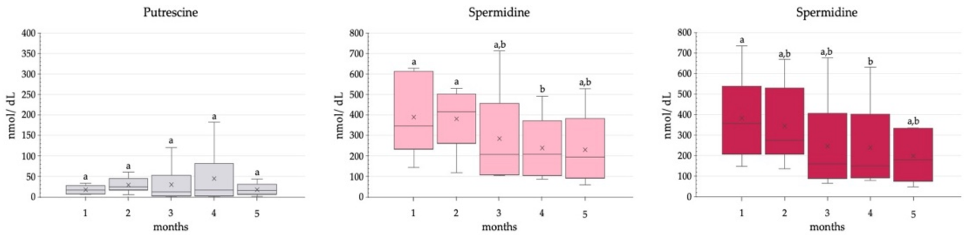

Figure 2. Polyamine levels (nmol/dL) in human milk (n = 6) during the first five months of breastfeeding. The Friedman test with Wilcoxon post-hoc were used to compare the total polyamine contents during this period. Different letters indicate statistically significant differences between breastfeeding months. For spermidine: 1 vs. 4 months, p = 0.016 and 2 vs. 4 months, p = 0.031. For spermine: 1 vs. 4 months p = 0.016.

The large individual variation in polyamine levels in human milk reported here is in accordance with the literature [6,12,14]. This high variability can be attributed mainly to the particular characteristics of each mother–child dyad, such as the ethnic origin, age, nutritional status, and dietary patterns of the mothers and the types of birth (whether natural delivery or cesarean section and term or preterm) [6,10–13]. Geographic location can also influence the polyamine content of human milk, as reported by Gómez-Gallego et al. [6], who found significantly higher polyamine levels in samples from mothers in Spain compared to Finland, South Africa, and China, which they attributed mainly to differences in dietary patterns [6]. Moreover, in the current study, the mean polyamine content in breast milk from Spanish mothers was notably higher than that recently found by Muñoz-Esparza et al. [13] in Mexican mothers, which could be explained by differences in genetics and/or diet associated with each geographic region. This supposition needs to be confirmed by further studies with a higher number of participants than are involved here.

Regarding the influence of diet, Atiya-Ali et al. [12] found a relationship between the maternal intake of dietary polyamines and their levels in preterm milk. Thus, the higher content of spermidine in human milk was significantly associated with a greater intake of vegetables and that of putrescine with fruits, especially oranges. These authors also observed an increase in polyamine contents in breast milk of obese mothers in response to a nutritional intervention with higher consumption of vegetables and fruits [10]. According to Muñoz-Esparza et al. [35], the major polyamine in most vegetables and fruits is spermidine, whereas putrescine predominates in citrus, which supports the findings of Atiya-Ali et al. [10,12]. Therefore, if the influence of diet on polyamine levels in human milk is confirmed, supplementing the maternal diet with polyamine-rich foods would be a simple and effective way of boosting the polyamine content in human milk. The best dietary sources of polyamines include mushrooms, soybeans, wheat germ, broad beans, green peppers, and citrus fruits [35].

The need for polyamines increases in periods marked by rapid cell growth, such as the first years of life or after surgery [12,36,37] and, therefore, probably also during fetal and infant growth and development. Accordingly, the diet of pregnant or lactating mothers could be adjusted to increase the supply of exogenous polyamines.

Another factor that could influence the polyamine contents in human milk is the time of sample collection, i.e., whether it was during the day or night and/or at the beginning or end of the feed [11,13,15]. In a cohort of 83 Mexican mothers, Muñoz-Esparza et al. [13] found significantly higher concentrations of all three polyamines in human milk obtained at the end of the feed (hindmilk) than at the beginning (foremilk). Unfortunately, in the current study, this comparison could not be made because the samples were obtained from a human milk bank and correspond to the total volume provided by each mother.

3.2. Polyamines in Infant Formulas

Spermidine was found in all analyzed infant formulas and putrescine in 86% of them. In contrast, spermine was only detected in two premature infant formulas. Table 1 summarizes the polyamine content of 15 commercial brands of infant formulas belonging to five different categories (first, follow-on, preterm, rice-based, and soy-based). In general, the levels of putrescine and spermidine were very similar among all the first, follow-on, and preterm formulas, with values always lower than 60 nmol/dL, except for one preterm formula, which contained spermidine levels of up to 230 nmol/dL ($p < 0.05$). The low content of polyamines in cow's milk may account for the low values in these infant formulas [34,35]. No statistically significant differences were found among the batches of any of the analyzed brands of infant formulas made from cow's milk.

To date, few studies have analyzed the polyamine content in infant formulas [7–9,12,22,23], only two of which have included preterm formulas [8,12]. Overall, the polyamine data for infant formulas in the literature are highly variable in terms of both content and profile. The results of the current study for first and follow-on formulas coincide with those of Pollack et al. [8], Buts et al. [9], and Atiya-Ali et al. [12]. However, much higher values have been reported by other authors, with levels reaching 964 nmol/dL, 923 nmol/dL, and 712 nmol/dL for putrescine, spermidine, and spermine, respectively [23]. A study by Gómez-Gallego et al. [22] indicated that the polyamine content in infant formulas depends mainly on the raw milk composition but also on the manufacturing process. They also suggest that the activity of polyamine oxidase, an enzyme found in raw milk, may be responsible for changes in polyamine concentrations, as it seems resistant to the skimming, pasteurization, concentration, and drying processes used in formula production [22]. Thus far, no other study has related the activity of polyamine oxidase with the variability of polyamine content in infant formulas, and further work is required to elucidate if the differences among products are the result of polyamine interconversion reactions as well as enzymatic degradation.

Table 1. Polyamine content (nmol/dL) in different types of infant formulas.

Infant Formulas	Batch	Putrescine	Spermidine	Spermine
		Mean ± SD	Mean ± SD	Mean ± SD
First formula				
A1	1	Nd	10.7 ± 0.5	Nd
	2	Nd	20.7 ± 1.0	Nd
A2	1	40.3 ± 0.8	26.5 ± 0.5	Nd
	2	33.5 ± 0.8	18.6 ± 2.0	Nd
A3	1	36.3 ± 1.6	45.1 ± 1.5	Nd
	2	37.4 ± 1.6	42.3 ± 1.4	Nd
Follow-on formula				
B1	1	40.3 ± 0.8	32.7 ± 2.4	Nd
	2	42.5 ± 0.8	39.2 ± 1.0	Nd
B2	1	35.7 ± 0.8	32.0 ± 1.5	Nd
	2	34.6 ± 0.8	32.7 ± 0.5	Nd
B3	1	59.6 ± 0.8 #	47.2 ± 4.8	Nd
	2	57.3 ± 0.8 #	56.8 ± 4.3	Nd
Preterm formula				
C1	1	47.1 ± 0.8	29.3 ± 0.5	62.0 ± 1.1
	2	38.0 ± 0.8	24.8 ± 1.0	61.7 ± 2.8
C2	1	Nd	226.9 ± 3.4 #	63.7 ± 7.7
	2	Nd	229.6 ± 7.8 #	61.5 ± 3.8
C3	1	39.1 ± 0.8	33.4 ± 0.5	Nd
	2	39.1 ± 0.8	33.4 ± 0.5	Nd
Rice-based formula				
D1	1	188.9 ± 12.0 †	18.6 ± 2.0	Nd
	2	191.7 ± 6.4 †	13.8 ± 2.9	Nd
D2	1	199.7 ± 1.6 †	43.7 ± 3.4	Nd
	2	188.3 ± 4.8 †	52.7 ± 0.5	Nd
D3	1	306.3 ± 28.9 †	53.7 ± 6.8 *	Nd
	2	311.9 ± 24.1 †	19.6 ± 1.5 *	Nd
Soy-based formula				
E1	1	70.3 ± 1.6	337.4 ± 2.9 *†	Nd
	2	77.7 ± 0.8	278.5 ± 0.5 *†	Nd
E2	1	43.1 ± 1.6	179.0 ± 1.0 *†	Nd
	2	60.7 ± 4.0	225.8 ± 1.9 *†	Nd
E3	1	74.9 ± 1.6	303.6 ± 2.9 *†	Nd
	2	70.3 ± 3.2	258.2 ± 4.9 *†	Nd

Nd: not detected. One-way ANOVA employing T3 Dunnett was used to compare the polyamine content in infant formulas. Different symbols indicate statistical significance. # $p < 0.05$ differences among brands in putrescine in B3 follow-on formulas and spermidine in C2 preterm formulas. † $p < 0.05$ differences in putrescine in rice-based formulas and spermidine in soy-based formulas among all infant formulas. The Student *t* test was used to compare the polyamine content between batches. * $p < 0.05$ differences in spermidine in rice-based formulas (D3) and soy-based formulas (E1, E2, E3).

Table 1 also shows the polyamine contents of infant formulas for special medical use prepared from plant proteins (rice and soy), which are a bit more variable compared to conventional cow's milk formulas, not only among brands but also batches. Significant differences among brands and batches are displayed in Table 1. Rice-based formulas stand out for high putrescine levels, which range from 188 to 312 nmol/dL and are significantly higher than in soy-based and cow's milk formulas ($p < 0.05$). In contrast, spermidine predominated in soy-based formulas (179–337 nmol/dL) ($p < 0.05$). Spermine was not detected in any plant-based infant formulas, which can be attributed to its lower presence in products of plant origins.

The only prior study on polyamines in soy-based formulas, performed by Romain et al. (1992) [7], obtained very similar results for putrescine (74 nmol/dL) and spermidine (256 nmol/dL) but also found low levels of spermine (44 nmol/dL). No previous data on polyamines in rice-based infant formula are available in the literature.

In plant protein-based infant formulas, the polyamine content and profile are also clearly related to the raw materials, with putrescine and spermidine being predominant in rice and soybean, respectively [35,38]. Thus, the differences in polyamine content among brands and batches can be attributed not only to differences in the manufacturing processes but also to the characteristics of the raw materials (i.e., rice or soybean). The levels of polyamines in plant foods and, therefore, in derived products such as infant formulas, can be influenced by several factors, including cultivation, harvesting, and environmental conditions (e.g., droughts) [25,39–41].

Regarding the polyamine profiles, a high variation was observed when comparing the samples of human milk and the different types of infant formulas (Figure 3). In conventional infant formulas, the proportion of putrescine was far higher than in human milk (where spermidine and spermine predominated), with spermine being found only in two preterm formulas (hence its low proportion overall). Differences were particularly striking among human milk and plant protein-based formulas, with those based on rice and soy being characterized by a hegemonic predominance of putrescine and spermidine, respectively.

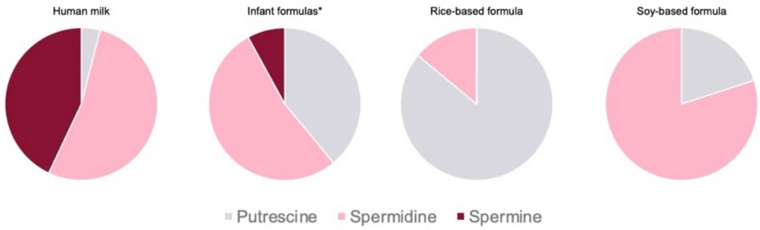

Figure 3. Polyamine distribution in human milk and infant formulas. * First, follow-on and preterm infant formulas.

In conclusion, polyamines were detected in all human milk samples during the first five months of lactation, with spermidine and spermine being the predominant compounds. Considerable differences were observed in polyamine content and profile among human milk and infant formulas. In fact, polyamine concentrations were up to 30 times lower in infant formulas, with putrescine being the predominant polyamine. Bearing in mind the importance of polyamines in the early stages of life, the results of the current study indicate that the polyamine content of infant formulas should be improved, both qualitatively and quantitatively, to more closely match the composition of human milk.

Author Contributions: Conceptualization, N.C.M.-E., M.L.L.-M., M.T.V.-N. and M.C.V.-C.; investigation, N.C.M.-E., M.L.L.-M. and O.C.-B.; data analysis, N.C.M.-E., M.L.L.-M., M.T.V.-N. and O.C.-B.; writing—original draft preparation, N.C.M.-E., M.L.L.-M., M.T.V.-N. and O.C.-B.; writing—review and editing, N.C.M.-E., O.C.-B., M.L.L.-M., M.T.V.-N. and M.C.V.-C.; supervision, M.C.V.-C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki. This study did not involve any human or animal testing. The transfer of the human milk samples was approved by the Ethics Committee for Drug Research and Research Project Committee of the Universitary Vall d'Hebron Hospital (PR(CS)203/2019) and by the Scientific Committee and the Scientific Directorate of the Biobank of the Blood and Tissue Bank. The Bioethics Commission of the University of Barcelona (IRB00003099) approved this study.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Acknowledgments: Nelly C. Muñoz-Esparza is a recipient of a doctoral fellowship from the University of Guadalajara, Mexico.

Conflicts of Interest: The authors declare no conflict of interest.

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3.3 Influencia de diferentes factores asociados a la lactancia en los contenidos de poliaminas en la leche materna.

PUBLICACIÓN 5

Influence of breastfeeding factors on polyamine content in human milk.

Nelly C. Muñoz-Esparza, Edgar M. Vásquez-Garibay, Elizabeth Guzmán-Mercado, Alfredo Larrosa-Haro, Oriol Comas-Basté, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou.
Nutrients, **2021**. 13, 3016. DOI: 10.3390/nu13093016

Factor de impacto (SJR 2020): 1.418
Categoría "Nutrition and Dietetics": Q1 (14/124)

COMUNICACIÓN ORAL

Nelly C. Muñoz-Esparza. **Polyamines profile and content in breast milk**. VII Spanish Nutrition Society Young Researchers´ Meeting, 2020, Virtual, Zaragoza.

COMUNICACIÓN ESCRITA

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, Elizabeth Guzmán-Mercado, Alfredo Larrosa-Haro, Edgar M. Vásquez-Garibay, M. Teresa Veciana-Nogués, M. Luz Latorre-Moratalla, M. Carmen Vidal-Carou. **Contenidos y evolución de poliaminas en leche materna durante el primer semestre de lactancia**. XIX Congreso Latinoamericano de Nutrición (SLAN), 2021, Virtual, Paraguay.

Planteamiento y objetivo

Se ha sugerido que la presencia de poliaminas en la leche materna puede estar influenciada por diversos factores relacionados con la díada madre-hijo, tales como el origen étnico, la genética, la edad, la ingesta dietética y/o el estado nutricio de la madre, así como el tipo de parto (p.ej. natural o cesárea y/o término o pretérmino) (Plaza-Zamora et al., 2013; Atiya-Ali et al., 2013, 2014; Gómez-Gallego et al., 2017). Además, factores relacionados con la propia lactancia, como el mes, la hora del día, el seno elegido y/o la presencia de infección (p.ej. mastitis) también podrían influir en los contenidos de poliaminas de la leche materna (Pollack et al., 1992; Romain et al., 1992; Löser, 2000;

Perez et al., 2016). Sin embargo, los datos experimentales que apoyan estas hipótesis son aún muy escasos o inexistentes. Según nuestro conocimiento, hasta la fecha únicamente se había estudiado la influencia del periodo de la lactancia, del tipo de parto y de la ingesta dietética de poliaminas, en la concentración de estos compuestos en la leche materna (Pollack et al., 1992; Romain et al., 1992; Buts et al., 1995; Plaza-Zamora et al., 2013; Atiya Ali et al., 2013, 2014; Gómez-Gallego et al., 2017).

El objetivo de este estudio fue evaluar la influencia de diferentes factores de la lactancia en el contenido de poliaminas de la leche materna. Específicamente, se estudió la evolución de los contenidos de putrescina, espermidina y espermina en la leche materna durante el primer semestre de lactancia, comparando además las concentraciones de estos compuestos entre la leche inicial y final de cada toma. También se evaluó el efecto del tipo de lactancia (lactancia materna completa o parcial) y otros factores relacionados con la díada madre-hijo (edad e índice de masa corporal de la madre (IMC), tipo de parto y peso al nacer del lactante).

Diseño experimental

Se realizó un estudio de cohorte no aleatorizado con madres residentes en el área metropolitana de Guadalajara, que dieron a luz en el Nuevo Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" (México). Se siguió una cohorte de 83 madres de entre 18 y 34 años durante cuatro meses, todas con un lactante sano, nacido a término y con un peso adecuado para la edad gestacional. De estas, un subgrupo de 33 madres se siguió durante todo el primer semestre de lactancia. Respecto al tipo de lactancia, 60 madres dieron lactancia materna completa y 23 lactancia parcial.

Las muestras de leche materna se recolectaron utilizando un extractor de leche previamente esterilizado. En cada punto de muestreo (2, 4 y 6 meses), se recolectaron dos muestras de leche de aproximadamente 5-10 mL. La primera muestra se obtuvo antes de que el lactante fuera amamantado, correspondiendo a la leche inicial de la toma, y la segunda muestra se recogió inmediatamente después de que el lactante había sido amamantado durante 10 minutos, correspondiendo a la leche final de la toma.

El análisis de poliaminas de las muestras de leche materna se realizó en el Campus de la Alimentación de la Universidad de Barcelona (Santa Coloma de Gramenet, España). Las tres poliaminas se determinaron mediante UHPLC-FL de acuerdo con el método descrito por Latorre-Moratalla et al. (2009).

El análisis estadístico de los datos se realizó mediante el software estadístico IBM SPSS Statistics 25.0 (IBM Corporation, EE. UU.). La comparación de los contenidos de poliaminas a lo largo de la lactancia, así como dentro de una misma toma (leche inicial versus final), se realizó con la prueba no paramétrica de Wilcoxon para muestras pareadas (distribución no normal de las muestras según las pruebas de Kolmogorov-Smirnov y de Shapiro-Wilk). El efecto del tipo de lactancia se evaluó mediante la prueba U de Mann-Whitney. Las asociaciones entre el contenido de poliaminas y las características de la díada madre-hijo se evaluaron a través del análisis de regresión lineal múltiple.

Resultados

El contenido total de poliaminas en la leche materna osciló entre 45 nmol/dL y 2,841 nmol/dL, aunque el 95% de las muestras mostró concentraciones por debajo de 1,575 nmol/dL. Se observó una elevada variabilidad en el contenido total de poliaminas, independientemente del mes de lactancia y del tipo de leche (leche inicial o final de la toma).

En todos los puntos de muestreo, el contenido total de poliaminas fue significativamente mayor en la leche obtenida al final de la toma que al inicio ($p<0.001$). En cuanto a la evolución de las poliaminas a lo largo de la lactancia, y teniendo en cuenta el subgrupo de 33 madres que completaron los seis meses de lactancia, se observó una disminución significativa en las concentraciones totales de poliaminas. Concretamente, en el caso de la leche inicial, los niveles de poliaminas fueron significativamente menores a los cuatro y seis meses con respecto a los dos meses ($p=0.009$ y $p=0.031$, respectivamente). Para la leche del final de la toma, esta reducción solo fue significativa a los seis meses de lactancia ($p=0.011$).

La putrescina fue la poliamina minoritaria en todas las muestras, con un contenido medio cercano a 8% del total de poliaminas. Las concentraciones medias de espermidina y espermina fueron muy similares entre ellas, independientemente de la fase o el mes de lactancia (proporción media de 1.1). Como sucedía con el contenido total de poliaminas, los niveles individuales de putrescina, espermidina y espermina también se mostraron significativamente más altos en la leche del final de la toma que en la inicial ($p<0.01$). En cuanto a la evolución a lo largo de la lactancia ($n=33$), las concentraciones medias de putrescina se mantuvieron constantes, mientras que las de espermidina y espermina tendieron a disminuir ($p<0.05$).

En cuanto al tipo de lactancia materna, desde el punto de vista cualitativo, el perfil de distribución de poliaminas en la leche materna no difirió entre las madres que daban lactancia materna completa o parcial. Cuantitativamente, a pesar de que se observó una tendencia de un contenido de poliaminas ligeramente mayor en la leche de madres que siguieron una lactancia parcial, solo se encontraron diferencias estadísticamente significativas para la espermina a los cuatro meses.

De acuerdo con el modelo de regresión lineal múltiple, no se encontraron asociaciones significativas entre el contenido de poliaminas en la leche materna con la edad y el IMC de la madre, ni con el peso al nacer o el sexo del lactante. Con respecto al tipo de parto, se observó una tendencia de menores concentraciones de poliaminas en las muestras de leche de madres que tuvieron cesárea en comparación con las de parto natural. Sin embargo, debido al bajo número de madres con cesárea, no fue posible realizar un análisis estadístico.

Aportaciones más relevantes

- Las concentraciones de poliaminas en la leche materna aumentaron significativamente en la leche del final de la toma respecto a la inicial, especialmente los de espermidina y espermina. Es la primera vez que se evalúa la influencia de este factor en el contenido de poliaminas de la leche materna.
- Los contenidos de poliaminas disminuyeron significativamente a lo largo de la lactancia, siendo alrededor de 30% menores a los seis meses en comparación con los dos meses.
- Se encontraron niveles ligeramente más altos de poliaminas en la leche de madres que dieron lactancia materna parcial en comparación a las de lactancia completa, aunque las diferencias no fueron significativas.

Teniendo en cuenta que existe cierta influencia por parte de diferentes factores de la lactancia en el contenido de poliaminas de la leche materna, sería importante disponer de más información de cómo el proceso de lactancia, o las características de la díada madre-hijo pueden modificar el contenido de estos compuestos. En particular, la influencia de la ingesta dietética de poliaminas de la madre merece ser estudiada en más detalle, ya que enriquecer la dieta con poliaminas podría ser una estrategia efectiva para incrementar el contenido de poliaminas de la leche materna.

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Influence of Breastfeeding Factors on Polyamine Content in Human Milk

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Citation: Muñoz-Esparza, N.C.; Vásquez-Garibay, E.M.; Guzmán-Mercado, E.; Larrosa-Haro, A.; Comas-Basté, O.; Latorre-Moratalla, M.L.; Veciana-Nogués, M.T.; Vidal-Carou, M.C. Influence of Breastfeeding Factors on Polyamine Content in Human Milk. *Nutrients* **2021**, *13*, 3016. https://doi.org/10.3390/nu13093016

Academic Editor: Martine Armand

Received: 14 August 2021
Accepted: 18 August 2021
Published: 29 August 2021

Abstract: The polyamine content of human breast milk, which is the first exogenous source of polyamines for the newborn, can be affected by several factors associated with the mother, the infant, or breastfeeding itself. The aim of this study was to evaluate the influence of different breastfeeding factors on the polyamines found in human milk. For this study, a cohort of 83 mothers was considered for up to 4 months, and a subgroup of 33 mothers were followed during the first six months of breastfeeding. Two breast milk samples were collected at each sampling point (foremilk and hindmilk) and the polyamine content was determined by UHPLC-FL. Polyamine levels varied considerably between the mothers and tended to decrease over time. Putrescine was the minor polyamine, whereas spermidine and spermine contents were very similar. The concentrations of the three polyamines were significantly higher in hindmilk than foremilk ($p < 0.001$). Spermidine and spermine levels decreased significantly through the lactation progress ($p < 0.05$). Finally, slightly higher levels of polyamines were observed in the milk of mothers providing partial, rather than full, breastfeeding, although the differences were not significant. The polyamine content in human milk was found to change during a single feed (foremilk versus hindmilk) and as lactation progressed, mainly in response to the specific circumstances of the newborn.

Keywords: polyamines; putrescine; spermidine; spermine; human milk; full breastfeeding; partial breastfeeding

1. Introduction

In humans, the intracellular levels of polyamines (i.e., putrescine, spermidine and spermine) are primarily regulated by de novo synthesis, although these bioactive compounds may also have an exogenous origin, mainly from food [1,2]. Breast milk supplies the infant with the first exogenous source of polyamines. Synthesized in the mammary gland during pregnancy and lactation, polyamines are involved in several physiological processes, notably cell growth and differentiation, protein synthesis, RNA transcription, and the regulation of the immune response [3–6]. Although the required daily intake of polyamines has not been established, their ingestion from human milk is known to be important during the neonatal and infant stages of rapid cell growth [5,7,8].

Human milk polyamines are mostly absorbed in the small intestine by transcellular or paracellular pathways and are subsequently distributed to the different tissues through the systemic circulation [9]. Nevertheless, some of these dietary polyamines remain in the intestines, where they participate in intestinal maturation and improve the integrity of the intestinal barrier [9,10]. Several studies in animal models have shown that polyamines administered orally during the postnatal period induce early maturation of the intestine and act in the repair of the intestinal mucosa [3,10–12]. In particular, spermine and spermidine produce morphological changes in the intestinal epithelium and improve mucosal permeability by enhancing the protein expression and enzymatic activity of disaccharidases and alkaline phosphatases [12,13]. At the same time, polyamines play a key role in the development of the immune system. It has been reported that they promote the maturation of intestinal immune cells, increasing the levels of immunoglobulin A in the villi and crypts of enterocytes [10,13–15]. The enhancement of intestinal maturation in newborns is consequently associated with a lower intestinal permeability to antigenic macromolecules, thus reducing the risk of developing food allergies [13,16]. Accordingly, Peulen et al. found that a higher spermine intake during the first month of breastfeeding was significantly associated with a reduced incidence of food allergies in children at the age of five [16]. On the other hand, it has also been described that the metabolism of polyamines is involved in adipogenesis [9,17]. In this sense, some authors have shown that the exogenous administration of spermidine or spermine in mice with induced obesity decreased body weight, fat mass, and visceral fat, and stimulated thermogenesis [18–20].

Despite the potential health benefits of polyamines in human milk, to date only a few studies have addressed this topic, and they have been based on a limited sample size [3,5,6,21–25]. The highly variable levels of polyamines in human milk reported in the literature could be explained by sample heterogeneity (i.e., they were taken at different phases of lactation) [3,21,22]. Moreover, it has been suggested that the presence of polyamines in breast milk may be influenced by factors intrinsic to the mother, infant, or the act of breastfeeding itself (Figure 1) [5,6]. However, experimental data supporting these hypotheses are still very scarce or nonexistent. Thus, only two studies, carried out by Romain et al. and Pollack et al. in 1992, describe a progressive decrease of polyamines over the course of lactation [21,22], and more recently two studies have found higher polyamine contents in the milk of mothers of pre-term infants compared to the mothers of full-term infants [5,23]. In addition, the influence of maternal diet on the levels of polyamines in human milk has also been addressed by Atiya-Ali et al. [5]; they found that a higher intake of polyamines was associated with increased contents of these compounds in breast milk.

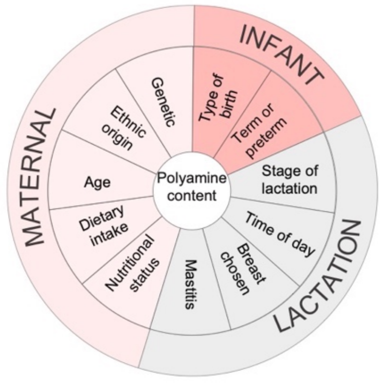

Figure 1. Factors influencing the polyamine content of human milk [6,23,26,27].

The aim of this study was to evaluate the influence of different breastfeeding factors on the content of polyamines in human milk. Specifically, the evolution of putrescine, spermidine, and spermine in human breast milk was studied during the first six months of breastfeeding, and levels in foremilk and hindmilk were compared. The effect of the type of lactation (full or partial breastfeeding) and other factors related with the mother–child dyad (age and body mass index of the mother, type of birth, and infant's birth weight) were also assessed.

2. Materials and Methods

2.1. Study Design and Subjects

A non-randomized cohort study was carried out with mothers living in the metropolitan area of Guadalajara, who gave birth at the Nuevo Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" (Mexico) [28]. For this study, a cohort of 83 mothers aged between 18 and 34 years were followed for 4 months, all with a healthy full-term baby with an adequate weight for the gestational age. From this group, a subgroup of 33 mothers were followed during the first six months of breastfeeding. The inclusion and exclusion criteria and the fieldwork strategy are described in detail by Vasquez-Garibay et al. [28]. Briefly, the exclusion criteria were: mothers with a history of chronic, genetic, or congenital diseases; addiction to alcohol, tobacco, or drugs; newborns with congenital malformations and/or genetic diseases.

Full breastfeeding was promoted during the enrollment phase. Overall, 60 mothers provided full breastfeeding (optionally including oral supplements of hydration and/or vitamins/inorganic nutrients) and 23 partial breastfeeding (i.e., the infants were fed with different proportions of breast milk and infant formula).

2.2. Human Milk Sample Collection

Breast milk samples were collected using a breast pump that was previously sterilized. At each sampling point, two milk samples of approximately 5–10 mL were collected. The first sample was obtained before the infant was breastfed, corresponding to foremilk (i.e., milk available at the beginning of the feed). The second sample was collected immediately after the infant had been breastfed for 10 min, corresponding to hindmilk (i.e., milk at the end of the feed). All samples were obtained from 9 am to 1 pm, and after collection they were homogenized and stored at −80°C until their analysis.

2.3. Analysis of Polyamines in Human Milk

The analysis of polyamines in human milk samples was performed at the Food and Nutrition Campus of the University of Barcelona (Santa Coloma de Gramenet, Spain). Putrescine, spermidine, and spermine were determined by ion-pair ultra-high-performance liquid chromatography coupled to fluorometric detection (UHPLC-FL) as described by Latorre-Moratalla et al. [29]. In brief, 1 mL of homogenized human milk was acidified with 70% perchloric acid and mixed for 20 min. Subsequently, samples were centrifuged (15,000 rpm, 4 °C, 15 min) and the supernatant was recovered and filtered through a 0.22 μm GHP filter (Waters Corp., Milford, MA, USA). Samples were stored at 4 °C until their analysis. Chromatographic separation of polyamines was accomplished using an Acquity UPLC BEH C18 1.7 μm reverse-phase column (2.1 mm × 50 mm) (Waters Corp., Milford, MA, USA), followed by online post-column derivatization with ortho-ophthaldehyde and fluorometric detection (ex: 310 nm and em: 445 nm). The quantification of polyamines in the human milk samples was carried out using the external standard method.

2.4. Statistical Analysis

The statistical analysis of data was performed with the IBM SPSS Statistics 25.0 statistical software package (IBM Corporation, Armonk, NY, USA). The data did not follow a normal distribution when analyzed by Kolmogorov–Smirnov and Shapiro–Wilk tests. Thus, the non-parametric Wilcoxon test for paired samples was used to compare the polyamine contents between foremilk and hindmilk and along the lactation process. The comparison between breastfeeding groups was performed with the Mann–Whitney U test for independent samples. In addition, multiple linear regression analysis was performed to evaluate the associations between the polyamine contents in human milk and the characteristics of the mother–child dyad (age and body mass index of the mother, type of birth, weight at birth, and sex of the infant). Values of $p < 0.05$ were accepted as significant.

3. Results

Table 1 shows the sociodemographic characteristics of the mother–child dyad, both for the total cohort followed for the first 4 months of lactation ($n = 83$) and for the subgroup of mothers that were followed during the first six months of lactation ($n = 33$).

Table 1. Sociodemographic characteristics of the mother–child dyad.

Mother	Total Cohort (*n* = 83)	Subgroup (*n* = 33)
Age (years)	23.5 ± 4.5	23.0 ± 4.6
BMI (mg/kg^2) *	25.0 ± 5.7	24.9 ± 6.5
Education level		
Incomplete junior high school or lower	18 (22%)	6 (18%)
Complete junior high school	30 (36%)	12 (36%)
Complete high school or higher	35 (42%)	15 (46%)
Occupation		
Housewife	69 (83%)	31 (94%)
Employee/merchant	8 (10%)	1 (3%)
Student	3 (3.5%)	1 (3%)
Unemployed	3 (3.5%)	-
Marital status		
Married	20 (24%)	8 (24%)
Free union	50 (60%)	20 (61%)
Single/separated	13 (16%)	5 (15%)
Infant		
Birth weight	3210.3 ± 340.1	3195.9 ± 333.4
Sex		
Female	29 (35%)	12 (36%)
Male	54 (65%)	21 (64%)
Delivery type		
Natural birth	79 (95%)	31 (94%)
Cesarean section	4 (5%)	2 (6%)

Data are presented as mean ± SD and as frequencies and percentages. * BMI: body mass index at two months postpartum.

Polyamines were found in all human milk samples (Figure 2). Total polyamine contents in human milk ranged from 45 nmol/dL to 2841 nmol/dL, although 95% of samples showed levels below 1575 nmol/dL. The variability in total polyamine contents was observed regardless of the month or the phase (foremilk or hindmilk) of breastfeeding, the coefficients of variation always being higher than 50%. Figure 2 shows the total polyamine contents in foremilk and hindmilk at two and four months of breastfeeding ($n = 83$, Figure 2A) and during the first six months of breastfeeding ($n = 33$, Figure 2B). Total polyamine contents were significantly higher in hindmilk than foremilk in all sampling points ($p < 0.001$). Regarding the evolution of polyamines throughout the breastfeeding progress (Figure 2B), a significant decrease was observed in total polyamine levels in foremilk at four and six months with respect to those at two months ($p = 0.009$ and $p = 0.031$, respectively), and in hindmilk between two and six months of lactation ($p = 0.011$).

Figure 3 shows the mean contents of putrescine, spermidine, and spermine in foremilk and hindmilk at two and four months of breastfeeding ($n = 83$, Figure 3A) and during the first six months of breastfeeding ($n = 33$, Figure 3B). Putrescine was always the minor polyamine, with mean contents close to 8% of the total polyamines. Mean concentrations of spermidine and spermine were very similar, with ratios of 1.1 regardless of the phase or month of lactation. As can be seen in Figure 3A,B, the levels of the three polyamines were always higher in hindmilk than foremilk, the increases ranging from 1.3- to 2.0-fold depending on the polyamine and the sampling time. According to the Wilcoxon test, these differences between foremilk and hindmilk were statistically significant ($p < 0.01$).

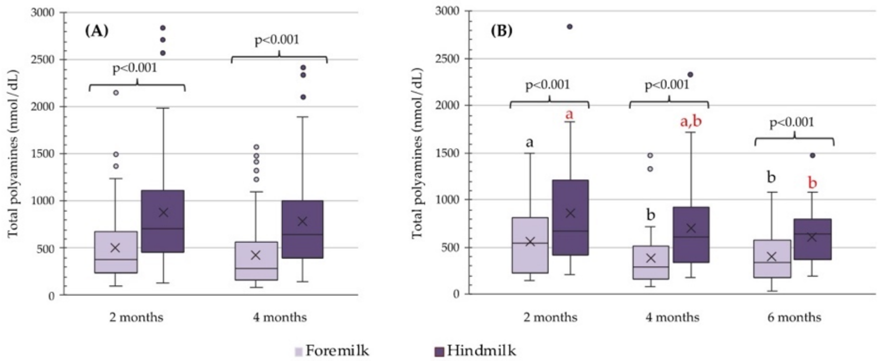

Figure 2. Total polyamine contents (nmol/dL) in foremilk and hindmilk at two and four months of breastfeeding (n = 83) (**A**) and during the first six months of breastfeeding (n = 33) (**B**). The bottom and top of the box (interquartile range) are the 25th and 75th percentile, respectively. The central line represents the median and X represents the mean. Lines extending vertically from the boxes (whiskers) indicate variability outside the interquartile range. Outliers are plotted as circles. Wilcoxon test was used to compare the polyamine contents between foremilk and hindmilk (**A**,**B**) and along the breastfeeding process (**B**). Different letters in black indicate statistically significant differences among lactation months for foremilk samples and letters in red indicate differences in hindmilk samples, being $p = 0.009$ for foremilk 2 vs. 4 months, $p = 0.031$ for foremilk 2 vs. 6 months, and $p = 0.011$ for hindmilk 2 vs. 6 months.

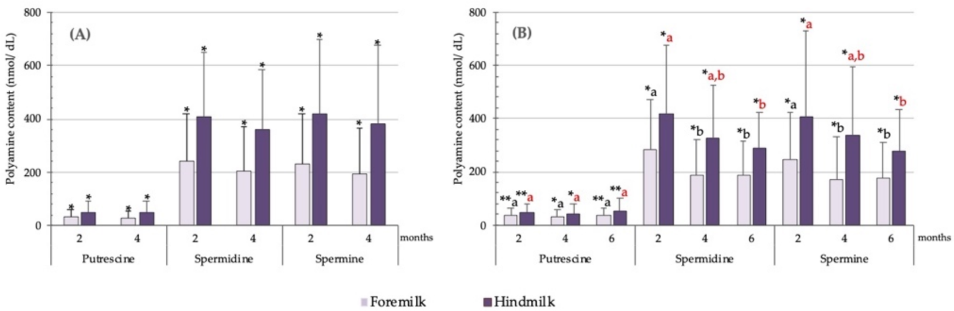

Figure 3. Putrescine, spermidine, and spermine contents (nmol/dL) in foremilk and hindmilk at two and four months of breastfeeding (n = 83) (**A**) and during the first six months of breastfeeding (n = 33) (**B**). Wilcoxon test was used to compare the polyamine contents between foremilk and hindmilk (**A**,**B**) and along the breastfeeding process (**B**). Asterisks indicate differences between foremilk and hindmilk (* $p < 0.001$ and ** $p < 0.01$). Different letters in black indicate statistically significant differences between lactation months for foremilk samples and letters in red indicate differences in hindmilk samples. For spermidine, $p = 0.010$ for foremilk 2 vs. 4 months, $p = 0.010$ for foremilk 2 vs. 6 months, and $p = 0.006$ for hindmilk 2 vs. 6 months. For spermine, $p = 0.009$ for foremilk 2 vs. 4 months, $p = 0.049$ for foremilk 2 vs. 6 months, and $p = 0.015$ for hindmilk 2 vs. 6 months.

During the first six months of breastfeeding, the mean putrescine concentrations remained constant, whereas those of spermidine and spermine tended to decrease (Figure 3B). Specifically, the Wilcoxon test revealed a statistically significant decrease between months two and four in both spermidine and spermine levels, as well as between two and six months in spermidine and spermine levels ($p < 0.05$).

Figure 4 shows the contents of the three polyamines according to the type of breastfeeding (full or partial). From a qualitative point of view, the polyamine distribution profile in breast milk did not differ between mothers providing full or partial breastfeeding. A general trend towards higher polyamine levels was associated with partial breastfeeding, although statistically significant differences were only found for spermine at month four. Foremilk and hindmilk samples showed the same trend, although higher contents of the three polyamines were always found in hindmilk, in agreement with the results obtained from the total pool of samples.

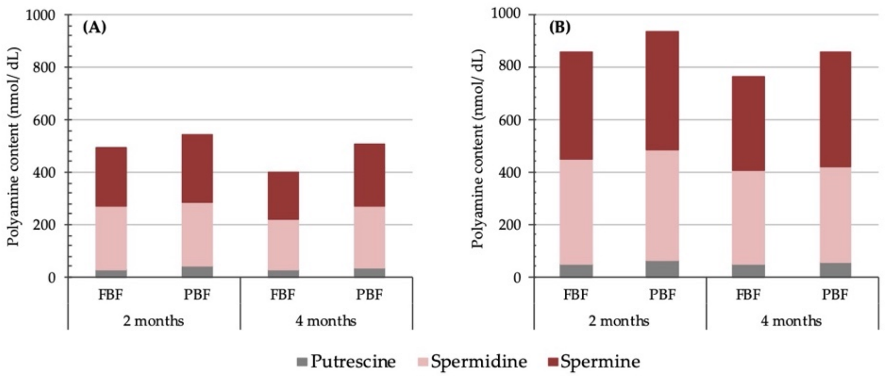

Figure 4. Polyamine levels (nmol/dL) in foremilk (**A**) and hindmilk (**B**) according to the type of breastfeeding (FBF: full breastfeeding and PBF: partial breastfeeding) at two and four months of lactation. FBF group $n = 60$ and PBF group $n = 23$.

With regard to the characteristics of the mother–child dyad, according to the multiple linear regression model, no significant associations were found between the content of polyamines in human milk with the age and BMI of the mother and with the weight at birth and sex of the infant. Regarding the type of birth, a trend of lower concentrations of polyamines was observed in the milk samples of mothers who gave birth by cesarean section instead of a natural delivery at two months postpartum. However, due to the low number of mothers who delivered by caesarean section, it was not possible to perform a statistical analysis.

4. Discussion

It is known that the nutritional composition of breast milk varies considerably and is constantly modified over the course of lactation, mainly in response to the changing requirements of the infant [30–33]. Although the human milk samples in the current study yielded highly variable polyamine contents, the mean data match those of other reports in the literature (ranging from 150 to 819 nmol/dL) [21–24]. The wide range of polyamine levels found in human milk in different studies may be attributed to cohort heterogeneity [3,6,21–24], or to the inter-individuality of each mother–child dyad. Thus, factors such as genetics, ethnic origin, nutritional status, and dietary intake of the mother have been postulated to have an impact on the polyamine content of breast milk [5,6,23,24]. For example, Gómez-Gallego et al. [6] suggested that the geographical region (linked to differences in genetics and dietary patterns) plays a key role, after finding a higher polyamine content in breast milk from mothers in Spain and Finland compared to China and South Africa [27]. However, information about how polyamine intake by the mother can affect breast milk content remains scarce. The study performed by Atiya-Ali et al. [5]

showed a positive association between the dietary intake of putrescine, spermidine, and spermine, mainly coming from fruits, with the polyamine content of breast milk. It would be interesting to carry out further studies to better establish the connection between dietary polyamines and their content in human milk.

In accordance with previous reports that describe a progressive decrease in polyamine concentration in human milk during lactation [21–24], in this study we observed a decline during the first six months. Thus, spermidine decreased significantly by 34% and spermine by 27% between the second and sixth month of breastfeeding. In contrast, putrescine remained practically unchanged during this period. The high growth and differentiation rate of cells during the first months of life may account for the larger amounts of polyamines in milk during the early months of breastfeeding [23]. On the other hand, an increase in the catalytic activity of polyamine oxidase in human milk over the course of lactation could help explain the reduction in polyamine levels after the second month [34].

Regarding the distribution profile of the three polyamines, the results show the predominance of spermidine and spermine, both detected in similar proportions, while the levels of putrescine were always lower, regardless of the sample type. All previously published studies in this field similarly report that putrescine is the least abundant polyamine in human milk [3,6,21–24], although discrepancies arise about which is the major polyamine, spermidine [5,21,23,24] or spermine [3,6,22]. In any case, a high content of spermine and spermidine in breast milk in the first postnatal months has been linked with a lower risk of developing food allergies in infancy and childhood [10,13,16]. These health-related effects are due to the contribution of spermine and spermidine to the postnatal maturation of the small intestine and the immune system [3,10–13].

The amount of polyamines in breast milk may vary not only according to the breastfeeding stage, but also during a single feed [5,23]. To our knowledge, the current study is the first to evaluate potential differences in the polyamine concentration between foremilk and hindmilk over the course of lactation. The results of this work showed that polyamine levels were significantly higher (up to two-fold) in hindmilk, especially those of spermidine and spermine, regardless of the breastfeeding month. Regarding the general composition of human milk, it is well established that hindmilk has a higher energy density and greater concentrations of fat and vitamins A and E [30,32,35,36]. Moreover, the fact that hindmilk remains in the mammary gland for longer in the presence of active endo- and exopeptidases (i.e., enzymes responsible for breaking down the amino acids of milk peptides) could lead to a higher content of free amino acids [35,36]. Specifically, Sadelhoff et al. [36] reported that hindmilk contains more arginine, which is the precursor amino acid of ornithine, a key substrate for the endogenous synthesis of polyamines [37,38]. The higher content of polyamines in hindmilk reinforces the importance of full feeds for infants if they are to benefit from all the nutrients provided by breast milk.

According to the World Health Organization, exclusive breastfeeding is recommended for infants during the first six months of life, followed by breast milk combined with foods for up to two years [39]. However, there is a growing tendency towards the partial breastfeeding of newborns [40]. The type of breastfeeding could also affect the composition of human milk, although it has been scarcely investigated so far. Jia et al. [41] reported that the lactose and protein content were significantly higher in the milk of mothers that partially breastfed, compared with those providing full breastfeeding during the first four months postpartum. In the current study, slightly higher levels of polyamines were observed in the milk of mothers providing partial rather than full breastfeeding, although significant differences were only found for one polyamine at four months. As the participants were always encouraged to practice full breastfeeding, only a few mothers partially breastfed (n = 23), which may limit the drawing of any solid conclusions.

According to Gómez-Gallego et al. [6], the type of birth, whether natural or by cesarean section, seems to affect the concentration of polyamines in human milk. These authors reported that mothers who delivered their baby by cesarean section produced milk with a lower polyamine content [6]. In our study, although only 5% of the mothers underwent caesarean section, a trend towards lower levels of polyamines in milk was also observed. However, due to the low number of samples, it is not possible to draw conclusions about the influence of the type of delivery on the polyamine levels of human milk. Further studies are needed, not only to confirm these outcomes, but also to analyze why polyamine levels may vary according to the birth typology. Finally, no significant associations were found between other factors related to the mother–child dyad (age and BMI of the mother, birth weight, and sex of the infant) and the polyamine levels in human milk. Although the available information regarding the influence of these factors in the levels of polyamines in human milk is still scarce, Atiya-Ali et al. [24] reported lower contents of polyamines in the milk of mothers with obesity compared to those with normal weight.

5. Conclusions

The polyamine content of breast milk from Mexican mothers varied considerably, and generally decreased during the course of lactation. This study reports for the first time that the amount of polyamines in human milk can change during a single feed, with the levels being significantly higher in hindmilk than in foremilk, especially those of spermidine and spermine. A general trend towards higher levels of polyamines in milk was observed in mothers who provided partial rather than full breastfeeding, although only spermine was statistically higher. Overall, these results indicate that polyamines in human milk may change, both during a single feed (foremilk versus hindmilk) and throughout lactation. The various health-related effects attributed to polyamines call for further studies to properly elucidate their role in infant development. More information is also needed on how polyamines in human milk are affected by different factors related to lactation, the mother, and the infant. In particular, the influence of the mother's polyamine intake deserves more detailed study, as a polyamine-enriched diet could be an effective strategy to increase the polyamine content of breast milk.

Author Contributions: Conceptualization, N.C.M.-E., M.L.L.-M., M.T.V.-N., M.C.V.-C.; investigation, N.C.M.-E., M.L.L.-M., O.C.-B., E.M.V.-G., E.G.-M., A.L.-H.; data analysis, N.C.M.-E., M.L.L.-M., M.T.V.-N., O.C.-B.; writing—original draft preparation, N.C.M.-E., M.L.L.-M., M.T.V.-N., O.C.-B.; writing—review and editing, N.C.M.-E., O.C.-B., M.L.L.-M., M.T.V.-N., E.M.V.-G., M.C.V.-C.; supervision, M.C.V.-C. All authors have read and agreed to the published version of the manuscript.

Funding: This work received financial support from the National Council of Science and Technology of Mexico (234158). Nelly C. Muñoz-Esparza is a recipient of a doctoral fellowship from the University of Guadalajara, Mexico.

Institutional Review Board Statement: The present study was conducted according to the guidelines laid down in the Declaration of Helsinki. This study did not involve any human or animal testing. The Committee of Biosecurity, Bioethics and Research of the Center of Health Sciences of the University of Guadalajara, (CI-01314) and the Bioethics Commission of the University of Barcelona (IRB00003099) approved the study protocol.

Informed Consent Statement: Informed consent was obtained from all mothers involved in the study prior to enrollment.

Conflicts of Interest: The authors declare no conflict of interest.

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3.4 Influencia del tipo de lactancia materna y de las poliaminas de la leche materna sobre los parámetros antropométricos del lactante.

PUBLICACIÓN 6

Appetite-regulating hormones and anthropometric indicators of infants according to the type of feeding.

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Food Science & Nutrition, **2020.** 8: 993-1000. DOI: 10.1002/fsn3.1381

Factor de impacto (SJR 2020): 0.614
Categoría "Food Science": Q2 (103/332)

PUBLICACIÓN 7

Influence of the type of breastfeeding and human milk polyamines on the anthropometric parameters of the infant.

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En revision en la revista Frontiers in Nutrition

Factor de impacto (SJR 2020): 1.229
Categoría "Nutrition and Dietetics": Q1 (21/124)

Planteamiento y objetivo

El Instituto de Nutrición Humana de la Universidad de Guadalajara (México) realizó un estudio para evaluar si las concentraciones séricas de las hormonas reguladoras del apetito y la composición corporal difieren en función del tipo de alimentación del lactante. Este trabajo, que se publicó en 2020, se realizó en el Nuevo Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" y siguió durante el primer cuatrimestre postparto una cohorte no aleatorizada de 169 díadas madre-hijo. Se consideraron tres subgrupos en función del tipo de alimentación del lactante: lactancia materna completa (n=74), lactancia materna parcial (n=57) y fórmula infantil (n=38).

Brevemente, los resultados de este estudio mostraron que los lactantes que recibieron lactancia materna completa presentaban indicadores antropométricos significativamente superiores y una mayor reserva de grasa en comparación con el grupo alimentado con fórmulas infantiles ($p<0.05$). Con respecto a las hormonas reguladoras del apetito, se reportó una correlación positiva entre la concentración sérica de leptina y la mayoría de los indicadores antropométricos, especialmente en los lactantes que recibieron lactancia materna, mientras que la grelina mostró una correlación negativa.

A partir de los resultados de este estudio, y teniendo en cuenta que las elecciones alimentarias durante los primeros meses de vida son determinantes del crecimiento infantil, así como la relevancia de las poliaminas de la leche materna en los procesos de crecimiento celular, y su posible participación en la regulación de la adipogénesis (Ramos-Molina et al., 2019), se planteó estudiar el papel de las poliaminas en el crecimiento y composición corporal del lactante. Se encuentra ampliamente descrito que el crecimiento y desarrollo del lactante durante el primer año de vida es acelerado, triplicando su peso y aumentando en 50% su longitud. Por este motivo, algunos autores han sugerido que los requerimientos de poliaminas podrían estar aumentados durante este período (Bardócz et al., 1995; Gómez Gallego et al., 2008; Atiya-Ali et al., 2014). Además, se ha sugerido que una desregulación de la homeostasis de las poliaminas podría tener un impacto importante sobre el metabolismo energético y la acumulación de grasa corporal (Büyükuslu & Öztürk, 2018). Sin embargo, hasta el momento no existen estudios que evalúen en qué sentido pueden influir las poliaminas de la leche materna en el crecimiento y la composición corporal del lactante. Por tanto, el objetivo de este trabajo fue estudiar la influencia del tipo de lactancia materna y la ingesta de poliaminas de la leche materna sobre los parámetros antropométricos del lactante.

Diseño experimental

Para este estudio se consideró un subgrupo de 78 lactantes sanos nacidos a término, con un adecuado peso para la edad gestacional y que recibieron lactancia materna completa (n=55) o parcial (n=23) durante el primer cuatrimestre de vida. No se incluyeron los recién nacidos con malformaciones congénitas y/o enfermedades genéticas, y se excluyeron aquellos con enfermedad subaguda o crónica.

A los dos y cuatro meses de edad se realizaron las siguientes mediciones antropométricas: peso, longitud, circunferencia cefálica (CC), circunferencia media del brazo (CMB), pliegue cutáneo tricipital (PCT) y pliegue cutáneo subescapular (PCSE). También se estimó el Z-*score* de los índices peso/talla, peso/edad, talla/edad e IMC/edad, asi como de la CC, CMB, PCT y PCSE, con el software WHO Anthro 3.2.2.

La ingesta de poliaminas por parte del lactante se estimó considerando un consumo diario de 800 ml de leche materna y el contenido de poliaminas en la leche de cada una de las madres (Publicación 5). Para los lactantes alimentados con lactancia materna parcial, se consideró un consumo de 400 ml de leche materna y 400 ml de fórmula infantil. Los contenidos de poliaminas utilizados fueron los reportados para la leche materna de madres que daban lactancia parcial (Publicación 5) y para las fórmulas infantiles (Publicación 4).

El análisis estadístico de los datos se realizó con el paquete de software estadístico IBM SPSS Statistics 25.0 (IBM Corporation, EE. UU.). La comparación de los indicadores antropométricos y de la ingesta de poliaminas entre grupos de lactancia materna se realizó con la prueba U de Mann-Whitney para muestras no paramétricas (distribución no normal de las muestras según las pruebas de Kolmogorov-Smirnov y de Shapiro-Wilk). Las asociaciones entre el contenido de poliaminas en leche materna e ingesta con los indicadores antropométricos fueron evaluadas mediante correlación de Spearman.

Resultados

Los lactantes que recibieron lactancia materna completa mostraron un mayor peso, IMC, CMB, PCT y PCSE, así como mejores valores de los Z-*score* de los índices peso/edad y peso/longitud en comparación con los que recibieron lactancia materna parcial, tanto a los dos y cuatro meses ($p < 0.05$).

En cuanto a la ingesta de poliaminas, los lactantes alimentados con lactancia materna completa mostraron una ingesta de hasta un 53% más alta en comparación con los lactantes que recibieron lactancia parcial, tanto a los dos como a los cuatro meses de edad ($p < 0.05$). Únicamente la ingesta de putrescina fue significativamente mayor en el grupo de lactancia materna parcial ($p < 0.05$).

Con respecto a la influencia de las poliaminas de la leche materna sobre los indicadores antropométricos del lactante, sólo dos de los quince parámetros evaluados mostraron una débil asociación con las poliaminas, a los dos y/o cuatro meses de edad. Específicamente, el PCT y la CMB mostraron una correlación inversa tanto con el contenido como con la ingesta de putrescina y/o espermina, para el total de la cohorte, así como también para el grupo de lactancia materna completa ($p < 0.05$).

Aportaciones más relevantes

- El crecimiento y composición corporal de los lactantes difiere de acuerdo con el tipo de lactancia, siendo los alimentados con lactancia materna completa los que presentaron mejores indicadores antropométricos.
- Los lactantes que recibieron lactancia materna completa presentaron una mayor ingesta de poliaminas en comparación con los alimentados con lactancia parcial, a excepción de la ingesta de putrescina, la cuál fue significativamente mayor en este último grupo.

- La mayoría de los indicadores antropométricos del lactante no mostraron una asociación significativa con el contenido de poliaminas de la leche materna ni con su ingesta.
- Los indicadores antropométricos del brazo de los lactantes, PCT y CMB, mostraron una correlación débil e indirecta con el contenido de poliaminas de la leche materna y con su ingesta.

Con el fin de esclarecer el posible papel de las poliaminas en el crecimiento y composición corporal del lactante, sería conveniente diseñar nuevos estudios que permitan medir la composición corporal de una manera más precisa (p.ej. DEXA) e incluyan también una población de lactantes con un estado nutricional fuera de la normalidad.

Received: 8 July 2019 | Revised: 14 October 2019 | Accepted: 5 November 2019
DOI: 10.1002/fsn3.1381

ORIGINAL RESEARCH

Food Science & Nutrition Open Access WILEY

Appetite-regulating hormones and anthropometric indicators of infants according to the type of feeding

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Funding information
National Council of Science and Technology of Mexico.

Abstract

It has been accepted that satiety- and appetite-stimulating hormones play a role in the regulation of food intake and body composition during and after the lactation stage. Therefore, the purpose was to demonstrate that serum appetite-regulating hormones in infants differ according to anthropometric indicators and type of feeding. In a nonrandom cohort study, 169 mother–newborn dyads whose pregnancy and birth were attended at the Hospital Civil de Guadalajara were enrolled. According to the type of feeding, infants were classified as full breastfeeding (FBF), partial breastfeeding (PBF), and infants receiving human milk substitutes (HMS). Serum concentrations of ghrelin (pg/ml), leptin (ng/ml), peptide YY (pg/ml), and glucagon-like peptide-1 (GLP-1) (pM) were measured. Anthropometric measurements including weight, length, cephalic, arm circumference, tricipital, and subscapular skinfolds were obtained. Weight/age, weight/height, height/age, and BMI *Z*-score indexes were estimated. We performed one-way ANOVA, unpaired Student's *t* test, post hoc Tukey test, and Pearson correlation tests. The ANOVA comparison of the three feeding types showed significant differences in most anthropometric indicators (*z*-scores), especially between infants receiving FBF versus HMS and particularly on indicators of adiposity; no differences were observed in length and cephalic circumference *z*-scores at 8th and 16th weeks. Further, significant correlations were found between most of the adiposity indicators with ghrelin, leptin, and GLP-1, especially in infants who received FBF. There were differences in anthropometric and body composition parameters among infants receiving FBF, PBF, and HMS. There were significant correlations between body composition indicators with ghrelin, leptin, and GLP-1 mainly in infants receiving FBF.

KEYWORDS
anthropometric indicators, appetite-regulating hormones, infants, type of feeding

1 | INTRODUCTION

Being overweight or obese are the most frequent nutritional problems in schoolchildren, adolescents, and adults in Mexico (Hernández-Ávila et al., 2016). This condition has disturbed most sectors of society because of its adverse effects on health and its magnitude, which demands that immediate action be taken to halt its progress (US Preventive Services Task Force et al., 2017). We all come into the world with our own genetic profile; however, there is a critical period, the first one thousand days of life, in which neonates, infants, and toddlers are particularly sensitive to interaction with the environment (Blumfield, 2015; Langley-Evans, 2015). In this context, breastfeeding and then perceptual nutrition after the sixth month play a fundamental role (Mochizuki, Hariya, Honma, & Goda, 2017).

It has also been noted that the protective role of breastfeeding against the development of obesity could be partially explained by the presence of appetite-regulating hormones (ARHs) in breastfed infants (Li, Magadia, Fein, & Grummer-Strawn, 2012; Petridou et al.., 2005; Savino et al., 2008). However, the role of the system in regulating appetite in states of hunger/starvation and in the pathogenesis of overeating/obesity remains to be fully elucidated in humans (Farr, Li, & Mantzoros, 2016).

It is accepted that satiety- and appetite-stimulating hormones play a role in the regulation of body composition by signaling satiety and energy reserves through hypothalamic receptors, during and after the lactation stage (Marić et al., 2014; Münzberg & Morrison, 2015). Satiety-regulating hormones such as leptin, glucagon-like peptide (GLP-1), and peptide YY decrease food intake, promote satiety, decrease the desire to eat, and increase the metabolic rate (Breij, Mulder, van Vark-van der Zee, & Hokken-Koelega, 2017; Schueler, Alexander, Hart, Austin, & Larson-Meyer, 2013). Therefore, the purpose of the study was to demonstrate that the serum concentration of leptin, ghrelin, glucagon-like peptide-1 (GLP-1), and peptide YY in infants differs according to the type of feeding and their body composition.

Key messages

- There are differences in anthropometric and body composition indicators among infants receiving full breastfeeding, partial breastfeeding, and human milk substitutes at 8 and 16 weeks of postnatal age.
- There are marked differences in serum concentration of appetite-regulating hormones in infants, especially in the highest concentrations of hormones related to increased food intake and growth.
- There is a direct and often significant trend of linear correlations of most indicators of fat reserve with ghrelin, leptin, and GLP-1, especially in infants who received full breastfeeding

2 | METHODS

2.1 | Design

This was a comparative and correlational analysis of a nonrandom cohort study. We identified mother–newborn dyads who were admitted to the Physiological Puerperium Ward in a shared room at the Nuevo Hospital Civil de Guadalajara. The criteria of inclusion, exclusion, and the estimation of the sample size are described elsewhere (Vasquez-Garibay et al., 2019).

2.2 | Dependent variables

Serum appetite-regulating hormones: total ghrelin (pg/ml); leptin (ng/ml); peptide YY (pg/ml); and glucagon-like peptide-1 (GLP-1) (pM). Anthropometric indicators: weight (g), length (cm), cephalic circumference (cm), arm circumference (cm), tricipital and subscapular skinfolds (mm), and *z*-scores of weight/age, weight/height, length/age, cephalic circumference/age, and BMI.

2.3 | Independent variables

Full breastfeeding (FBF); partial breastfeeding (PBF); and human milk substitutes (HMS) based on cow's milk.

2.4 | Measuring instruments and techniques

After standardization of two observers (EGM, NME), the following anthropometric measurements were made (Frisancho, 1990):

2.4.1 | Weight

Infants were placed naked and without a diaper on the scale, taking care that the whole body remained inside the tray and was distributed evenly over the center of the tray. A weighing scale model 314 (SECA) was used to measure weight; the precision was 10 g.

2.4.2 | Length

The measurement was obtained by two observers with an infant bed model 416 (Seca). The infant was placed in the supine position, with the body aligned straight on the longitudinal axis of the infantometer so that the shoulders and hip remained in contact with the horizontal plane and the arms were on the sides of the trunk. The crown of the head touched the fixed base of the infantometer and was placed on the plane of Frankfort, that is, aligned perpendicular to the horizontal plane. One of the observers held both the head and the base of the infantometer. The other observer, with one hand, stretched the infant's legs, watching for the knees to be deflected, and with the other hand moved the movable base of the infantometer, so that a slight pressure (only slightly compressing the skin) was exerted on the heel of the infant free from any object. The foot remained at an angle of 90°. The measurement had an accuracy of 0.1 cm.

2.4.3 | Cephalic circumference

This measurement was made with a 6-mm-wide metal tape (Rosscraft®, USA). The tape was applied firmly around the head in the supraciliary region, so that the tape ran along the most prominent part of the frontal area and occipital protuberance.

2.4.4 | Mid-upper arm circumference (MUAC)

The measurement was performed on the left arm. An observer bent and held the arm at a 90° angle to the forearm and marked half the distance from the acromion to the olecranon as a midpoint. Subsequently, the measurement was performed with the arm extended in the middle of the arm previously marked, using a metal tape model 201 of 6 mm wide. A tricipital skinfold (TSF) measurement was taken on the midpoint of the inner, rear surface of the previously marked arm; a subscapular skinfold (SSF) measurement was taken at the lower edge of the scapula. Both measurements were performed on the left side using a Lange skinfold caliper. The weight/age, height/age, weight/height, and BMI indices and cephalic circumference were estimated in the *Z*-score using the WHO growth standard (WHO 2006).

The collection of blood samples and the assays for the determination of hormonal biomarkers are described elsewhere (Vasquez-Garibay et al., 2019).

2.5 | Fieldwork criteria and strategies

Once the mothers had signed the informed consent form, demographic, socioeconomic, and educational dietary variables were collected; the mothers were then contacted after a period of one month to ask them about the type of feeding they had chosen for their infants. Anthropometric measurements were performed during each of the 8 and 16 weeks appointments; at 16 weeks, a blood sample was taken from the infants. There were no significant differences in the general characteristics of the mother/infant dyads between study participants and mothers, who were not located by telephone at 4 weeks postpartum or those who declined to participate in the study.

2.6 | Statistical analysis

The comparison of variances of the anthropometric data between the groups was performed with ANOVA for one factor and Tukey *post hoc* tests. The linear relationship between measurements and anthropometric indexes and the ARHs was performed with Pearson correlations. The level of significance considered for all statistical tests was <0.05. Calculations of the anthropometric indices were estimated by the WHO Anthro version 3.2.2. The statistical analysis was carried out with the SPSS 21 software.

3 | RESULTS

The total sample at 8 and 16 weeks postpartum was 169 dyads: FBF (74), PBF (57), and HMS (38). The age of the infants in the three types of feeding was 8 ± 1 weeks in the first visit and 16 ± 1 weeks in the second visit. Tables 1–3 show the crude data and *z*-scores of the anthropometric indicators of infants at 8 and 16 weeks of postnatal age. The ANOVA tests for the comparison of the three feeding types showed significant differences between them in most

TABLE 1 Length and cephalic circumference and their *z*-scores of 169 infants at 8 and 16 weeks of postnatal age according to the type of feeding: full breastfeeding (FBF), partial breastfeeding (PBF), and human milk substitutes (HMS). Comparison with one-way ANOVA; Tukey *post hoc* test (significant values with *post hoc* tests are presented as footnotes)

Postnatal age	Anthropometric measurements and indices	FBF (*n* = 74)		PBF (*n* = 57)		HMS (*n* = 38)		
		x	*SD*	*x*	*SD*	*x*	*SD*	*p*
8 weeks	Length (cm)	57.0	1.6	57.1	1.6	56.1	1.9	**.012**
	Length/age (z)	−0.62	0.8	−0.61	0.8	−0.77	0.9	.577
	Cephalic circumference (cm)	38.7	1.1	38.5	0.9	38.2	1.1	**.021**
	Cephalic circumference (z)	−0.24	0.8	−0.35	0.7	−0.38	0.7	.581
16 weeks	Length (cm)	62.2	2.0	62.1	1.6	61.7	2.2	.445
	Length/age (z)	−0.62	0.9	−0.62	0.7	−0.74	0.9	.727
	Cephalic circumference (cm)	40.9	1.2	40.8	0.9	40.5	1.3	.214
	Cephalic circumference (z)	−0.38	0.9	−0.39	0.7	−0.55	0.8	.526

Note: Significant post hoc tests at 8 weeks. Length: FBF versus HMS, ***p* = .024**. PBF versus HMS, ***p* = .017**. Cephalic circumference: C: FBF versus PBF, ***p* = .015**.

TABLE 2 Anthropometric measurements and indices of 169 infants at 8 and 16 weeks of postnatal age according to the type of feeding: full breastfeeding (FBF), partial breastfeeding (PBF), and human milk substitutes (HMS). The comparison among groups was made with one-way ANOVA; significant p values with Tukey *post hoc* tests are presented as footnotes

Postnatal age	Anthropometric measurements and indices	FBF (*n* = 74)		PBF (*n* = 57)		HMS (*n* = 38)		
		x	*SD*	*x*	*SD*	*x*	*SD*	*p*
8 weeks	Weight (g)	5,316	576	5,019	494	4,770	583	**<.001**
	Weight/age (z)	−0.33	0.8	−0.7	0.6	−0.93	0.8	**.001**
	Weight/length (z)	0.47	0.9	−0.24	0.9	−0.19	1.0	**<.001**
	Body mass index	16.3	1.3	15.4	1.2	15.1	1.2	**<.001**
	Body mass index (z)	0.01	0.9	−0.61	0.8	−0.67	0.9	**<.001**
16 weeks	Weight (g)	6,642	722	6,333	589	6,179	855	**<.001**
	Weight/age (z)	−0.31	0.9	−0.64	0.7	−0.82	0.9	**.008**
	Weight/length (z)	0.19	1.0	−0.32	0.8	−0.37	1.0	**.003**
	Body mass index	17.1	1.5	16.4	1.1	16.2	1.6	**<.001**
	Body mass index (z)	0.05	1.0	−0.44	0.7	−0.54	1.1	**.002**

Note: Significant post hoc test at 8 weeks. Weight: FBF versus PBF, ***p* = .008;** FBF versus HMS, ***p* < .001**. Weight/age: FBF versus PBF, ***p* = .041**, FBF versus HMS, ***p* = .001**. Weight/length: FBF versus PBF, ***p* < .001**. FBF versus HMS, ***p* = .004**. Body mass index: FBF versus PBF, ***p* < .001;** FBF versus HMS, ***p* < .001**. Z-BMI: FBF versus PBF, ***p* = .001**. FBF versus HMS, ***p* = .001**. Significant post hoc tests at 16 weeks. Weight: FBF versus HMS, ***p* < .001**. Weigh/age: FBF versus HMS, ***p* < .001.** FBF versus PBF, *p* = .031. Body mass index: FBF versus HMS, ***p* < .001**. FBF versus PBF, ***p* = .007**. Z-BMI: FBF versus HMS, ***p* = .006**. FBF versus PBF, ***p* = .012**.

TABLE 3 Arm anthropometric measurements and *z*-scores and subscapular skinfold of 169 infants at 8 and 16 weeks of postnatal age according to the type of feeding: full breastfeeding (FBF), partial breastfeeding (PBF), and human milk substitutes (HMS). Comparison among groups with one-way ANOVA; significant values with Tukey *post hoc* tests are presented as footnotes

Postnatal age	Anthropometric measurements and indices	FBF (*n* = 74)		PBF (*n* = 57)		HMS (*n* = 38)		
		x	*SD*	*x*	*SD*	*x*	*SD*	*p*
8 weeks	Medium upper arm circumference (cm)	12.0	0.88	11.7	0.50	11.4	0.80	**<.001**
	Medium upper arm circumference (z)	−0.63	1.11	−1.02	0.62	−1.40	1.00	**<.001**
	Triceps skinfold (mm)	8.8	1.67	7.8	1.40	8.1	1.56	**.001**
	Triceps skinfold (z)	1.80	1.46	0.95	1.27	1.14	1.42	**.002**
	Subscapular skinfold (mm)	8.4	1.59	7.5	1.59	7.8	1.52	**.002**
16 weeks	Medium upper arm circumference (cm)	13.0	0.96	12.6	0.6	12.4	1.1	**<.001**
	Medium upper arm circumference (z)	−0.62	0.92	−1.02	0.55	−1.09	1.00	**.005**
	Triceps skinfold (mm)	9.5	1.8	8.5	1.3	8.9	1.7	**.002**
	Triceps skinfold (z)	−0.13	1.15	−0.70	0.89	−0.34	0.99	**.008**
	Subscapular skinfold (mm)	8.6	1.9	7.8	1.5	8.0	1.9	**.05**
	Subscapular skinfold (z)	0.57	1.26	0.12	1.07	0.27	1.19	**.09**

Note: Significant post hoc test at 8 weeks. Medium upper arm circumference: FBF versus PBF, ***p* = .034**. FBF versus HMS, ***p* = .001**. Medium upper arm circumference (z): FBF versus PBF, ***p* = .034**. FBF versus HMS, ***p* = .001**. Triceps skinfold: FBF versus PBF, ***p* = .001**. FBF versus HMS, ***p* = .033**. Triceps skinfold (z): FBF versus PBF, ***p* = .002**, FBF versus HMS, ***p* = .048**. Subscapular skinfold: FBF versus PBF, ***p* = .002**. Significant post hoc tests at sixteen weeks. Medium upper arm circumference: FBF versus HMS, ***p* = .001**. FBF versus PBF, ***p* = .016**. Medium upper arm circumference (z): FBF versus HMS, ***p* = .025**. FBF versus PBF, ***p* = .015**. Triceps skinfold: FBF versus PBF, ***p* = .036**. FBF versus MHS, ***p* = .002**. Triceps skinfold (z): FBF versus PBF, ***p* = .006**. Subscapular skinfold: FBF versus PBF, ***p* = .048**.

anthropometric indicators and their *z*-scores except for *z*-scores of length and cephalic circumference at 8 weeks of postnatal age and length and cephalic circumference (both in cm and *z*-score) at 16 weeks of postnatal age. Crude anthropometric values and *z*-scores of the indices showed significant differences between 8 and 16 weeks mainly between the FBF versus HMS and FBF versus PBF. In most measurements and indices, infants with FBF had z-score values greater than those of the other two groups.

Table 4 shows that ghrelin correlated inversely and significantly with SSF measurement in infants who received FBF, while leptin correlated directly and significantly with the five anthropometric indicators, especially weight/age, BMI, and MUAC. In addition, with FBF there was also a direct and significant correlation of GLP-1 with four of the five anthropometric indicators, especially with MUAC. In those who received PBF, the leptin correlations with the anthropometric indicators were equally significant; there was no correlation of anthropometric indicators with ghrelin and with GLP-1. In infants receiving HMS, the correlation profile of anthropometric indicators with leptin was similar although lesser significant than with FBF and PBF; however, with this type of feeding, there was no correlation with ghrelin or with GLP-1. The peptide YY did not correlate with any anthropometric indicator in the three types of feeding.

4 | DISCUSSION

Ziegler (2006) has demonstrated that during the first 6–8 weeks of life, there is little difference in growth (gain in weight and length) between breastfed and formula-fed infants, and that there are no consistent differences in adiposity during the first 4–5 months of life. Giannì et al. (2014) found that formula-fed infants showed a different body composition through the first 4 months of life compared to breastfed infants, with higher fat-free mass content. In addition, Gale et al. (2012) showed in a systematic review that in formula-fed infants fat-free mass was higher and fat mass was lower at 3–4 months than in breastfed infants. On the other hand, Bell, Wagner, Feldman, Shypailo, and Belfort (2017) have shown that formula-fed infants gained weight more rapidly, which was out of proportion to linear growth, than did predominantly breastfed infants. These differences were attributable to greater accretion of lean mass, rather than fat mass; they concluded that any later obesity risk associated with infant feeding did not appear to be explained by differential adiposity gains in infancy.

Our data show that for infants at 8 and 16 weeks of life, most of the anthropometric indicators showed significant differences between the three types of feeding: FBF, PBF, and HMS. In addition, at these ages, the weight/age, weight/length, BMI indexes, MUAC, and skinfold indicators were significantly higher in infants receiving FBF than in those receiving HMS. Weight/age, BMI, and skinfolds were also found to be higher in infants receiving FBF versus PBF; FBF is likely to better protect infants with a greater increase in energy reserves during the first 6 months of life than infants fed a HMS. However, linear (cm) and cephalic (cm) growth only showed differences between these two types of feeding at 8 weeks of age. The infants who received PBF were a group that drew our particular attention because of their different anthropometric behavior. They were more affected in their anthropometric indicators than infants who received FBF but generally performed better in terms of growth and energy reserves than infants who received HMS (WHO, 2016).

Traditionally, PBF has been divided into three broad groups (Labbok & Krasovec, 1990): infants who receive <20% of a HMS (high breastfeeding); between 20% and 80% (medium), and those who receive <20% of human milk (low breastfeeding). From the point of view of nutritional requirements, it is difficult to give an adequate interpretation with this range of groups, especially infants receiving between 20% and 80% of human milk. This group of infants could be in a situation of nutritional vulnerability because the mother would not know exactly how much milk she produced and how much she should supplement with an HMS to avoid a potential risk of underfeeding or overfeeding her infant. It is clear that for an analysis of anthropometric and body composition indicators and the concentration of ARHs, a more detailed analysis of this type of breastfeeding would be required (Breij et al., 2017; Rao & Kanade, 1992; WHO, 2016; Yan, Liu, Zhu, Huang, & Wang, 2014).

In relation to ARHs, similarities and important differences were also observed between infants receiving FBF and those receiving PBF and HMS. In the case of ghrelin, a potent orexigenic, its concentration in infants appears to be more related to the need to be fed and nourished properly. The higher concentration of GLP-1 and peptide YY is the result of regulatory mechanisms related both to body composition and to the infant's own growth needs (Vasquez-Garibay et al., 2019).

Some of the observed results could be related to the physiological functions and mechanisms of action of these ARHs both in the gastrointestinal tract and in the CNS. It is known that the peripheral melanocortin 4 receptor (MC4R), which has an essential role in energy regulation, is implicated in the regulation of peptide YY and GLP-1 (Breij et al., 2017; Choudhury, Tan, & Bloom, 2016). Peptide YY is a short peptide (36 amino acids) secreted by the neuroendocrine cells of the ileum and colon in response to feeding. It inhibits gastric motility; consequently, it increases the efficiency of digestion and nutrient absorption after a meal and increases the absorption of water and electrolytes in the colon. It seems obvious that the concentration of peptide YY, in particular, would have individual and important regulatory mechanisms in the infant who is in a crucial stage of accelerated growth (Breij et al., 2017; Perälä et al., 2013). Breij et al. (2017) have reported that breastfed infants have higher Peptide YY concentrations, which could be a link to the protective role against obesity in exclusive breastfeeding.

The peptide hormone GLP-1 is 30 amino acids long, and its main source is the L-cell of the intestine. This peptide is derived from the transcription of a gene called proglucagon whose physiological function is based on reducing blood glucose concentration through increased secretion of insulin and suppression of glucagon secretion by the pancreas (Meier et al., 2004; Schueler et al., 2013). Among its other functions, GLP-1 inhibits gastric acid secretion and gastric emptying, and it suppresses food intake through the sensation of satiety. In the CNS, it increases the acquisition and strength of conditioned aversions to taste, anxiety, nausea, or visceral discomfort. In the presence of GLP-1, the pleasurable value of food as well as the motivation (reward) for eating, and the amount and frequency of food consumption decrease (Graaf et al., 2016; Skibicka, 2013).

These assumptions become more relevant because when the correlations between anthropometric indicators and HARs are

TABLE 4 Correlation coefficients among the serum concentration of ghrelin, leptin, and glucagon-like peptide (GLP-1) with anthropometric measurements and *z*-score indices in 157 4-month-old infants classified by the type of feeding: full breastfeeding, partial breastfeeding, and feeding with human milk substitutes

Anthropometric measurements and *z*-scores	Ghrelin (pg/ml)		Leptin (ng/ml)		GLP–1 (pM/ml)	
	r	*p*	*r*	*p*	*r*	*p*
Full breastfeeding (*n* = 69[a])						
Weight/age (z)	–.208	.093	.400	**.001**	.266	**.033**
Body mass index (z)	.165	.173	.461	**<.001**	.242	.054
Medium upper arm circumference (z)	–.216	.086	.455	**.001**	.288	**.022**
Triceps skinfold (mm)	–.197	.113	.256	**.045**	.191	.131
Subscapular skinfold (mm)	–.297	**.016**	.312	**.014**	.253	**.044**
Partial breastfeeding (*n* = 53[b])						
Weight/age (z)	–.107	.460	.343	**.013**	.076	.591
Body mass index (z)	.039	.789	.466	**.001**	–.061	.667
Medium upper arm circumference (z)	–.006	.967	.461	**.001**	.068	.631
Triceps skinfold (mm)	.237	.097	.409	**.003**	–.252	.068
Subscapular skinfold (mm)	.046	.751	.462	**.001**	.042	.766
Human milk substitutes (*n* = 35[c])						
Weight/age (z)	–.150	.397	.394	**.026**	–.097	.590
Body mass index (z)	–.162	.359	.429	**.014**	–.236	.186
Medium upper arm circumference (z)	–.022	.900	.348	.051	–.020	.913
Triceps skinfold (mm)	–.022	.900	.348	.051	–.020	.913
Subscapular skinfold (mm)	–.113	.523	.239	.188	.014	.937

Note: Bold indicates statistical significant value ($p < .05$) .
Values excluded due to technical problems in the sample handling or in the laboratory assay
[a]n = 5.
[b]n = 4.
[c]n = 3.

explored, a directly differentiated character is observed. For example, cephalic circumference as an indicator of brain growth is inversely and significantly related to ghrelin, while it correlates directly and significantly with leptin. Perhaps because there is a great need for brain growth in infants, there is a need for a higher concentration of ghrelin; this may be due to its role as an orexigenic hormone acting at key hypothalamic and midbrain circuits involved in feeding control to ensure adequate nutrient intake (Fidanci et al., 2010; Méquinion et al., 2013). However, direct and higher concentrations of leptin could be an indicator of the assurance of energy reserves that would promote brain growth. In contrast, lower overall growth and lower energy reserves to ensure growth would show lower leptin concentrations as a potential indicator of nutrient failure, food shortage, or chronic malnutrition resulting in the need for an allocation of energy reserves to ensure brain growth in particular (Kayardi, Icagasioglu, Yilmaz, & Candan, 2006; Stein, Vasquez-Garibay, Kratzsch, Romero-Velarde, & Jahreis, 2006; Yilmaz et al., 2005). The direct relationship of GLP-1 with all the indicators that express energy reserves would have a similar interpretation to leptin, a situation that would be expected considering that both are anorexigenic hormones.

In contrast, it was evident that peptide YY, despite being an anorexigenic hormone, was not associated with any anthropometric indicators. This finding suggests that adiposity is not a factor that directly influences the peptide YY concentration and its potential function, and that the regulating mechanism of this hormonal biomarker could be influenced by appetite regulation of the infant. This is most probably related to signaling mechanisms of the gastrointestinal tract and their effect on the CNS. This argument is supported by the fact that in infants who received PBF and HMS only leptin correlated with energy reserve or adiposity indicators.

In addition, infants who received PBF also showed an inverse and significant relationship between ghrelin and cephalic circumference, which supports the need for these infants to boost their physiological need to eat (hunger) together with the need for hyperplastic brain growth. The CNS is a vital organ in the growth and development of human beings, and it surely has a direct relationship with growth hormones (insulin, ghrelin, growth hormone, and insulin-like growth factor-1 among others) (Gray, Meijer, & Barrett, 2014; Hara et al., 2014).

The main strength of this study was that it was a cohort of the mother–infant dyad identified in the immediate postnatal period, followed longitudinally along 4 months, and without the researcher's intervention on the type of feeding that mothers selected for their infants. One limitation of the study was that the number of infants fed HMS was lower than those who received FBF and PBF.

In conclusion, the main contribution of the study was the demonstration of the differences in anthropometric and body composition indicators among infants receiving FBF, PBF, and HMS at 8 and 16 weeks of postnatal age. In addition, there were marked differences in serum concentration of appetite-regulating hormones in infants, especially in the highest concentrations of hormones related to increased food intake and growth, and lower concentrations of leptin, the hormone related to increase in the energy reserve. Finally, we observed the direct and often significant trend of linear correlations of most indicators of fat reserve with ghrelin, leptin, and GLP-1, especially in infants who received FBF.

ACKNOWLEDGEMENT

E.M.V.G., A.L.H., F.N.V., and E.R.V. designed research; E.G.M., N.M.E., and S.G.A., conducted research; E.M.V.G., A.L.H., and E.G.M. analyzed data; E.M.V.G. had primary responsibility for final content; all authors read and approved the final manuscript.

Source of financial support: National Council of Science and Technology of Mexico (234158)

CONFLICT OF INTEREST

All authors involved in these work disclose any potential sources of conflict of interest related to patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company.

ETHICAL APPROVAL

The recommendations of the Declaration of Helsinki were followed in its last Amendment during the 64th Annual Assembly organized by the World Medical Association, 2013.

Ethical review: This study does not involve any human or animal testing and was approved by the Committees of Bioethics and Research of the Hospital Civil Hospital of Guadalajara, and the Committees of Biosecurity, Bioethical and Research of the University of Guadalajara, Center of Health Sciences (CI-01314).

Informed Consent: Written informed consent was obtained from the parents of the participating dyads.

Human testing (measurement of serum concentration of appetite-regulating hormones) was necessary for our study.

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How to cite this article: Vásquez-Garibay E, Larrosa-Haro A, Guzmán-Mercado E, et al. Appetite-regulating hormones and anthropometric indicators of infants according to the type of feeding. *Food Sci Nutr*. 2020;8:993–1000. https://doi.org/10.1002/fsn3.1381

Influence of the type of breastfeeding and human milk polyamines on the anthropometric parameters of the infant

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Keywords: full breast feeding, partial breastfeeding, infant growth, body composition, polyamines, spermidine, spermine, adipogenesis.

Abstract

Feeding choices in the early months of life are key determinants of growth during infancy. Human milk is the main exogenous source of polyamines in the infant. These compounds participate in cell proliferation and differentiation, and it has also been suggested that polyamine metabolism plays a role in adipogenesis. Thus, the aim of this work was to study if there is any influence of the type of breastfeeding and the polyamine intake from human milk on the anthropometric parameters of the infant. A cohort of 78 full-term healthy newborns was followed up until four months of age; 55 were fully and 23 partially breastfed. Anthropometric measurements were taken at two and four months, when human milk samples were also collected for analysis of polyamine content by UHPLC-FL. Fully breastfed infants had a better anthropometric profile than those partially breastfed ($p < 0.05$). In addition, partially breastfed infants showed significantly lower polyamine intake compared to fully breastfed infants. Among all the anthropometric indicators evaluated, only two (triceps skinfold and mean upper arm circumference) of the fifteen parameters showed a weak and inverse a correlation with the content of polyamines in human milk and their intake ($p<0.05$). Infant growth and body composition differ according to the type of breastfeeding received. Based on the weak and inconsistent associations between polyamines and anthropometric indicators, it is not possible to conclude the influence of polyamines in the infant growth and body composition.

1 Introduction

Besides determining infant growth, the feeding choices in the first months of life have a long-term health outcome, especially in the prevention of childhood obesity (1–4). It has been suggested that the protective effect of breastfeeding against the development of obesity could be related with the unique composition of human milk, which provides the energy and nutrients required by the infant, together with a range of bioactive compounds (e.g. hormones, immunoglobulins, growth factors and polyamines) (5–8). It has been widely described that growth and body composition patterns of infants who are exclusively breastfed are different from those who receive infant formulas (9–14). Although much less studied, differences in the growth and body composition have also been reported between infants fed with full/exclusive breastfeeding and those receiving partial breastfeeding (2,4,15). However, the specific mechanisms of the anti-obesity effect of breastfeeding remain unclear (3,15).

In the infant, human milk is the main exogenous source of polyamines in the organism (i.e. putrescine, spermidine and spermine), in addition to de novo synthesis (16–18). Polyamines are involved in several biological processes, mainly cell proliferation and differentiation, and protein synthesis; in the early stages of life they also contribute to intestinal maturation and the development of the immune system (17–19). More recently, it has been suggested that polyamine metabolism could also play a role in adipogenesis. Thus, the dysregulation of polyamine homeostasis could have an important impact on energy metabolism and the accumulation of body fat (20–22).

It has been suggested that polyamine requirements are high in the first months of life due to the accelerated growth and development of the infant (the weight is triplicated and length increases by 50%) (23–25). However, to date, no studies have evaluated the role of human milk polyamines in infant growth and body composition. Bearing in mind that feeding choices during the first months of life impact the growth and body composition of the infant, as well as the importance of polyamines for the newborn and their hypothetical involvement in adipogenesis, the aim of this work was to study whether there is any influence of the type of breastfeeding and the polyamine intake from human milk on the anthropometric parameters of the infant.

2 Material and methods

2.1. Study design and subjects

A non-randomized cohort study was conducted in healthy infants born at the Nuevo Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" (Mexico) (26). The current study was carried out with a subgroup of 78 full-term healthy newborns, all with an appropriate weight for gestational age, until they were four months old. Among them, 55 infants were fully breastfed (optionally including oral hydration supplements and/or vitamins/inorganic nutrients) and 23 received partial breastfeeding (i.e., the infant received human milk and at least one bottle of infant formula/human milk substitutes). The inclusion and exclusion criteria, as well as the fieldwork strategy, are described in detail by Vásquez-Garibay et al. (26).

2.2. Anthropometric measurements

Anthropometric measurements of weight, length, head circumference, mean upper arm circumference (MUAC), triceps skinfold (TSF) and subscapular skinfold (SSF) were performed at two and four months of age according to the guidelines described by Frisancho (27). The techniques and instruments used to perform the aforementioned measurements are described by Vásquez-Garibay et al. (26). The Z-score value for weight/length, weight/age, length/age and body mass index (BMI)/age indices and the cephalic circumference, MUAC, TSF and SSF were estimated using the software WHO Anthro 3.2.2 (WHO, Geneva, Switzerland).

2.3. Analysis of polyamines in human milk

Human milk samples (5-10 mL) were collected on the same day as infant anthropometric measurements were taken. After collection, the milk samples were stored at -80°C until the day of their analysis.

Sample preparation and chromatographic determination of polyamines in human milk were performed in the Food and Nutrition Campus of the University of Barcelona, according to the methods described in Muñoz-Esparza et al. (28) and Latorre-Moratalla (29). Briefly, after sample acidification with perchloric acid, putrescine, spermidine and spermine were separated and quantified by ion-pair ultra high-performance liquid chromatography coupled to an online derivatization with ortho-ophthaldehyde and subsequent fluorometric detection (UHPLC-FL).

2.4. Estimation of polyamine intake

The intake of polyamines by the infant was estimated considering a daily consumption of 800 ml of human milk. For partially breastfed infants, a consumption of 400 ml of human milk and 400 ml of infant formula was considered. The intake of polyamines in the latter scenario was estimated taking into account the content of polyamines in the human milk of mothers practicing partial breastfeeding and the mean content of polyamines in infant formulas reported by Muñoz-Esparza et al. (30).

2.5. Statistical analysis

The statistical analysis of data was performed with the IBM SPSS Statistics 25.0 software package (IBM Corporation, Armonk, NY, USA). The non-parametric Mann-Whitney U test was used to compare the two breastfeeding groups due to the lack of normal data distribution according to the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Wilcoxon test was used to compare the polyamine content of human milk between two and four months. In addition, Spearman correlations were performed to evaluate the associations between polyamine contents in human milk and polyamine intake with the anthropometric parameters. The level of significance was a p value ≤ 0.05.

3 Results

Table 1 shows the anthropometric measurements and their indices of the infants at two and four months of age for the total cohort and according to the type of breastfeeding received. Fully breastfed infants showed better anthropometric parameters compared to partially breastfed infants, observing significance differences in the weight, BMI, MUAC, TSF and SSF, as well as higher z-score values for the indexes weight/age and weight/length, both at two and four months of age ($p < 0.05$).

Polyamine contents in human milk were extremely variable among mothers, with relative standard deviations of over 54%, regardless of the polyamine and month (Table 2). In all cases, spermidine and spermine were the main polyamines, and they were found in very similar levels. Total polyamine, spermidine and spermine contents were statistically lower at four versus two months of breastfeeding ($p < 0.05$). Moreover, slightly lower values were found in the milk of mothers practicing full breastfeeding, although the differences were statistically significant only for putrescine and spermine at two months ($p < 0.05$).

Regarding the estimation of polyamine intake, infants with full breastfeeding showed a significantly higher intake of total polyamines, spermidine and spermine, being up to 53% higher than those partially breastfed, both at two and four months ($p < 0.05$) (Table 3). In contrast, partially breastfed infants showed 51% and 25% higher intake of putrescine in comparison with those fully breastfed at two and four months, respectively ($p < 0.05$).

Among all the anthropometric indicators evaluated, only two of the fifteen parameters showed a weak correlation with the content of polyamines in human milk at two and/or four months of age. Specifically, TSF (mm) showed a weak and inverse correlation with putrescine (2 months: $r = -0.322$, $p = 0.004$; and 4 months: $r = -0.246$, $p = 0.033$) and spermine (2 months: $r = -0.309$, $p = 0.006$; and 4 months: $r = -0.259$, $p = 0.025$) concentrations. MUAC (cm) was also weak and inverse correlated with spermidine ($r = -0.302$, $p = 0.009$) and spermine ($r = -0.327$, $p = 0.004$) at four months. When stratifying the total cohort according to the type of breastfeeding, these correlations were only found with the full breastfeeding group. The TSF (mm) showed a weak inverse association with putrescine ($r = -0.276$, $p = 0.043$) at two months and with spermine ($r = -0.311$, $p = 0.023$) at four months. MUAC was inversely correlated with putrescine ($r = -0.380$, $p = 0.005$) and spermine ($r = -0.389$, $p = 0.004$) at four months.

Likewise, when the spearman correlation test was performed between anthropometric indicators and the estimated polyamine intake, weak and inverse associations were only found for the same two parameters out of the total fifteen anthropometric indicators considered. Specifically, TSF (mm) showed a weak and inverse correlation with putrescine intake at two ($r = -0.361$, $p = 0.001$) and four ($r = -0.236$, $p = 0.04$) months of age. MUAC (cm) also showed a weak and inverse association with putrescine ($r = -0.241$, $p = 0.036$) and spermine ($r = -0.253$, $p = 0.028$) at four months. When stratifying the total cohort according to the type of breastfeeding, these correlations were only found in the full breastfeeding group. Concretely, at two months TSF (mm) was inversely and weakly correlated with putrescine ($r = -0.306$, $p = 0.023$), whereas at four months MUAC (cm) showed a weak and inverse association with putrescine ($r = -0.291$, $p = 0.035$) and spermine ($r = -0.389$, $p = 0.004$) and TSF was inversely correlated with spermine ($r = -0.310$, $p = 0.024$).

4 Discussion

The worldwide prevalence of obesity has tripled in the last four decades, becoming a current public health concern (31). According to the World Health Organization, 41 million children under the age of five were overweight or obese in 2016 (31), highlighting the need to implement strategies in order to improve their prevention and/or early detection. Postnatal environmental factors, such as the type of feeding during the first months of life have important implications in the growth and body composition of the infant and influence long-term health outcomes, especially in the prevention of childhood overweight and obesity (3,4,10). In this sense, it is widely described that patterns of infant growth and body composition differ greatly according to the type of feeding (1,4,9,14). For example, fully breastfed infants have a higher accumulation of fat (both in grams and percentage) during the first 4 months of life, whereas formula-fed infants have a major accumulation of lean mass and a rapidly gain weight (1,4,9,10,32). Nowadays, there is evidence supporting that the accumulation of adipose tissue during breastfeeding is not associated with an increased risk of obesity in later stages of life (12,14,33,34). Nevertheless, most of these studies considered fully/exclusively breastfed and formula-fed infants, and only a few included partially breastfed infants (2,4,15). The results of the current work demonstrated that fully breastfed infants showed better anthropometric parameters in comparison to those partially breastfeed. Specifically, infants that received full breastfeeding had significantly higher weight, BMI, MUAC, TSF, and SSF, as well as greater Z-score values for weight/age and weight/length. Similarly, Jia et al. (2) also reported better Z-score values for weight/age and weight/length in fully breastfed infants. Likewise, as observed in the present work, Rodríguez-Cano et al (4) found that fully breastfed infants had higher BMI, TSF, SSF and fat mass (in kg and percentage) values in comparison to those partially breastfed.

The variable content and distribution profile of polyamines found in human milk samples are in agreement with previous reports by other authors (16,24,35). Moreover, the significant decrease in polyamine concentrations at four months is similar to that reported by Pollack et al. (36), Romain et al. (37) and Muñoz-Esparza et al. (30). According to the results of the current study, the milk of mothers who partially breastfed had slightly higher polyamine contents than those fully breastfeeding, although this higher content of polyamines did not translate into a higher intake of these compounds by the infant. In fact, according to our data, the polyamine intake in partially breastfeed was 23-50% lower in comparison to fully breastfeed infants, depending on the individual polyamine and the month of lactation. In contrast, the intake of putrescine was higher in the partial breastfeeding group. Polyamine levels in infant formulas have been described to be up to 30 times lower than in human milk, which could explain the lower intake of polyamines in partially breastfed infants (30). Regarding putrescine, its higher intake can be attributed to the fact that infant formulas have putrescine contents up to two times higher than human milk (24,30,35,38). Overall, the potentially higher intake of polyamines in fully breastfed infants coincides with a higher growth and better anthropometric values than those found in partially breastfed infants.

It has been suggested that polyamine requirements are high in the first months of life due to the accelerated growth and development of the infant. In fact, higher polyamine contents have been reported in the milk of mothers who had preterm infants (24,25). In addition, it has also been described that polyamines are involved in the early stages of adipocyte differentiation (22,39). The enzyme spermidine/spermine N1-acetyltransferase (SSAT) is a key metabolic regulator in polyamine homeostasis, and is strongly involved in adipogenesis. SSAT catalyzes the transfer of acetyl groups from acetyl-CoA to spermidine or spermine, allowing polyamine interconversion (20,40). Thus, a dysregulation of polyamine homeostasis could have an important impact on the accumulation of body fat (20,40,41). Some studies in animal models have shown that overexpression of the SSAT enzyme in mice caused a decrease in white adipose tissue (20,40,41). Likewise, it has also been reported that the administration of spermidine or spermine reduced body weight and fat mass, in a dose-dependent manner (42–44). However, these results cannot be extrapolated to the possible role of polyamines in the accumulation of adiposity in healthy infants because there were all carried out in animal models with induced obesity. Therefore, taking into account the higher requirement of polyamines in the first months of life and the participation of polyamines in adipogenesis, it was also proposed to study if there was an association between the content of polyamines in human milk and the intake of these compounds with the anthropometric parameters of the infant. The results of this work indicated that most of the anthropometric indicators evaluated did not show significant correlations with the polyamine contents of human milk or with the polyamine intake. All the infants included in the study had an adequate nutritional status for age, with anthropometric parameters within normal limits (± 2 SD), which could explain the lack of association. Specifically, TSF and MUAC were the only indicators that showed an inverse and weak, but yet significant, association with the content of putrescine and spermine in human milk and with their intake, both in the total cohort and in the group of full breastfeeding. Although these two anthropometric parameters (TSF and MUAC) are related with adiposity and fat reserves of the infant, the weak and inconsistent associations did not allow to draw solid conclusions about the role of polyamines in infant growth and body composition. In this sense, it would be necessary to develop further studies that consider infants with anthropometric indicators outside the limits of normality in order to demonstrate the potential role of polyamines in infant growth and body composition. In addition, it would be desirable to include other techniques for measuring body composition in a more precise way, such as DEXA (Dual Energy X-ray Absorptiometry) or ADP (Air displacement plethysmography).

5 Conclusion

The results of the current study confirm that infant growth and body composition differ according to the type of breastfeeding received, with a better anthropometric profile found in fully breastfed infants. As expected, partially breastfed infants showed lower polyamine intake compared to fully breastfed infants. However, a clear association could not be established between the levels of polyamines in human milk and most of the anthropometric indicators. Therefore, more studies are needed not only to confirm the potential role of polyamines in infant growth and body composition, but also to determine if a higher intake of polyamines through human milk results in higher blood polyamine concentrations in the infant.

6 Ethics Statement

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki in its last Amendment during the 64th Annual Assembly organized by the World Medical Association, 2013. This study was approved by the Committees of Biosecurity, Bioethics and Research at the University of Guadalajara, Center of Health Sciences (CI-01314) and the Bioethics Commission of the University of Barcelona (IRB00003099). All the mothers of the participating infants signed the informed consent sheet.

7 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8 Author Contributions

N.C.M.-E., E.M.V.-G, A.L-H, M.L.L.-M. and M.C.V.-C. conceptualization and design of the study; N.C.M.-E., E.G.-M., E.M.V.-G and A.L-H were involved in the data collection; N.C.M.-E., M.L.L.-M., M.T.V.-N. and O.C.-B analyzed the samples and interpreted the data; N.C.M.-E., E.M.V.-G, M.L.L.-M., M.T.V.-N., O.C.-B, M.C.V.-C. were involved in the writing original draft manuscript; N.C.M.-E., M.L.L.-M., M.T.V.-N., O.C.-B, M.C.V.-C critically reviewed the manuscript. All authors have read and approved the final version of the manuscript.

9 Funding

This study received financial support from the National Council of Science and Technology of Mexico (234158). N.C.M.-E. is a recipient of a doctoral fellowship from the University of Guadalajara, Mexico.

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Table 1. Anthropometric measurements and indices (Mean ± SD) of the infants at two and four months of age according to the type of breastfeeding.

Anthropometric measurements and indices	2 months				4 months			
	Total cohort (n=78)	Full Breastfeeding (n=55)	Partial Breastfeeding (n=23)	p*	Total cohort (n=78)	Full Breastfeeding (n=55)	Partial Breastfeeding (n=23)	p*
Weight (g)	5309 ± 592	5404 ± 617	5084 ± 462	**0.016**	6639 ± 727	6708 ± 758	6476 ± 632	0.071
Length (cm)	57.22 ± 1.64	57.22 ± 1.63	57.23 ± 1.69	0.367	62.34 ± 1.91	62.25 ± 2.00	62.57 ± 1.67	0.200
Weight /Age (z)	-0.35 ± 0.80	-0.22 ± 0.83	-0.65 ± 0.65	**0.012**	-0.30 ± 0.93	-0.21 ± 0.99	-0.52 ± 0.74	**0.039**
Length /Age (z)	-0.55 ± 0.78	-0.55 ± 0.76	-0.53 ± 0.86	0.447	-0.54 ± 0.81	-0.58 ± 0.86	-0.45 ± 0.69	0.225
Weight /Length (z)	0.26 ± 0.95	0.45 ± 0.90	-0.20 ± 0.90	**0.004**	0.11 ± 1.02	0.27 ± 1.05	-0.27 ± 0.87	**0.017**
BMI (kg/m^2)	16.18 ± 1.36	16.47± 1.37	15.51 ± 1.10	**0.002**	17.06 ± 1.49	17.28 ± 1.53	16.53 ± 1.25	**0.025**
BMI (z)	-0.05 ± 0.90	0.13± 0.90	-0.50 ± 0.73	**0.001**	-0.01 ± 1.02	0.14 ± 1.06	-0.36 ± 0.85	**0.020**
Cephalic C. (cm)	38.70 ± 1.10	38.77 ± 1.17	38.56 ± 0.89	0.298	40.89 ± 1.12	40.89 ± 1.23	40.90 ± 0.88	0.357
Cephalic C. (z)	-0.26 ± 0.82	-0.24 ± 0.87	-0.35 ± 0.61	0.252	-0.38 ± 0.87	-0.38 ± 0.97	-0.38 ± 0.58	0.445
MUAC (cm)	11.96 ± 0.90	12.07 ± 0.97	11.71 ± 0.67	0.061	13.01 ± 0.93	13.11 ± 1.03	12.78 ± 0.59	0.056
MUAC (z)	n/a	n/a	n/a	-	-0.64 ± 0.89	-0.55 ± 0.99	-0.87 ± 0.55	**0.029**
TSF (mm)	8.62 ± 1.68	8.96 ± 1.77	7.83 ± 1.12	**0.002**	9.25 ± 1.85	9.46 ± 1.99	8.74 ± 1.39	**0.040**
TSF (z)	n/a	n/a	n/a	-	-0.29 ± 1.2	-0.17 ± 1.28	-0.57 ± 0.95	**0.037**
SSF (mm)	8.26 ± 1.68	8.61 ± 1.65	7.44 ± 1.50	**0.002**	8.33 ± 1.89	8.60 ± 1.95	7.69 ± 1.60	**0.022**
SSF (z)	n/a	n/a	n/a	-	0.42 ± 1.28	0.59 ± 1.31	0.01 ± 1.12	**0.024**

*Significant differences between breastfeeding groups according to the Mann-Whitney U test. (z): Z-score; BMI: Body Mass Index; MUAC: Mean Upper Arm Circumference; TSF: Triceps Skinfold; SSF: Subscapular Skinfold. Cephalic Circumference: Cephalic C.; n/a: not applicable as it is not possible to estimate the Z-score.

Table 2. Polyamine content in human milk (nmol/dL) given at two and four months in the total cohort and according to the type of breastfeeding (Mean ± SD, median, minimum and maximum).

	Total Cohort (n=78)	Full Breastfeeding (n=55)	Partial Breastfeeding (n=23)	P*
2 months				
Total polyamines	668.37 ± 358.05 550.54 (213.37 – 1632.05)	639.98 ± 377.85 510.39 (213.37 – 1632.05)	737.50 ± 300.90 697.30 (265.71 – 1493.82)	0.088
Putrescine	41.89 ± 30.89 34.03 (3.40 – 147.48)	37.24 ± 32.28 22.69 (3.40 – 147.48)	53.02 ± 24.46 51.05 (17.02 – 113.44)	**0.004**
Spermidine	318.61 ± 170.21 275.39 (92.94 – 905.34)	312.33 ± 182.03 254.73 (92.94 – 905.34)	333.91 ± 139.77 309.81 (120.49 – 688.47)	0.257
Spermine	308.32 ± 177.97 252.05 (79.08 – 822.87)	290.97 ± 185.99 228.58 (79.08 – 822.87)	350.57 ± 152.22 333.60 (111.20 – 691.91)	**0.050**
4 months				
Total polyamines	554.70 ± 338.27 480.91 (136.31 – 1598.20)	524.85 ± 310.49 500.13 (136.31 – 1486.37)	632.05 ± 399.07 470.77 (156.80 – 1598.20)	0.431
Putrescine	38.15 ± 27.10 34.03 (1.13 – 153.15)	35.67 ± 26.14 28.36 (1.13 – 153.15)	44.58 ± 29.08 34.04 (5.11 – 119.12)	0.098
Spermidine	259.18 ± 154.47 234.08 (58.52 – 733.22)	252.08 ± 148.81 237.08 (58.52 – 733.22)	277.58 ± 170.54 218.59 (58.52 – 705.68)	0.678
Spermine	257.37 ± 178.89 217.46 (46.96 – 869.83)	237.09 ± 153.54 224.87 (46.96 – 743.80)	309.90 ± 228.03 212.52 (64.25 – 869.83)	0.299

The Wilcoxon test was used to compare polyamine content at two and four months: p=0.013 in total polyamines, p= 0.016 in spermidine and p= 0.008 in spermine. *Significant differences between breastfeeding groups according to the Mann-Whitney U test.

Table 3. Estimation of polyamine intake according to the type of breastfeeding of the infant.

	Total Cohort (n=78)	Full Breastfeeding[a] (n=55)	Partial Breastfeeding[b] (n=23)	P*
2 months				
Total polyamines	4554 ± 2743	5080 ± 3011	3252 ± 1204	
	3797	3975	3091	**0.016**
	(1365 – 13056)	(1707 – 13056)	(1365 – 6277)	
Putrescine	319 ± 226	294 ± 258	379 ± 98	
	272	182	371	**0.002**
	(27 – 1180)	(27 – 1180)	(235 –621)	
Spermidine	2199 ± 1343	2499 ± 1456	1471 ± 559	
	1790	2038	1374	**0.003**
	(617 – 7243)	(744 – 7243)	(617 – 2889)	
Spermine	2058 ± 1358	2328 ± 1488	1402 ± 609	
	1700	1829	1334	**0.008**
	(445 – 6583)	(633 – 6583)	(445 –2768)	
4 months				
Total polyamines	3774 ± 2363	4199 ± 2484	2720 ± 1646	
	3474	4001	2158	**0.011**
	(302 – 11891)	(1090 – 11891)	(302 – 6695)	
Putrescine	300 ± 188	286 ± 209	338 ± 120	
	272	227	303	**0.024**
	(27 – 1225)	(27 – 1225)	(167 –643)	
Spermidine	1781 ± 1133	2017 ± 1191	1197 ± 706	
	1680	1900	989	**0.002**
	(135 – 5866)	(468 – 5866)	(135 – 2958)	
Spermine	1714 ± 1182	1897 ± 1228	1240 ± 912	
	1463	1799	850	**0.018**
	(257 – 5950)	(376 – 5950)	(257 – 3479)	

*Significant differences between breastfeeding groups according to the Mann-Whitney U test; [a]Daily consumption of 800 ml of human milk; [b]Daily consumption of 400 ml of human milk and 400 ml of infant formula.

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Influence of the type of breastfeeding and human milk polyamines on the anthropometric parameters of the infant

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Original Research, Front. Nutr. - Nutrition and Metabolism

Received on: 15 Nov 2021, **Edited by:** Abraham Wall-Medrano

Manuscript ID: 815477

Keywords: full breast feeding, partial breastfeeding, Infant growth, Body Composition, Polyamines, Spermidine, ...

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4 Discusión

Poliaminas en alimentos

En vista de los diversos efectos beneficiosos de la ingesta de poliaminas para la salud humana, especialmente en las primeras etapas de la vida y durante el envejecimiento, y del potencial interés de suplementar la dieta con estos compuestos, es importante conocer la composición cuali y cuantitativa de poliaminas en los alimentos. En el marco de esta tesis doctoral, se estudió la presencia de poliaminas en diferentes alimentos comercializados en España, así como el efecto de diferentes tratamientos culinarios sobre el contenido de poliaminas de algunos alimentos ricos en estos compuestos.

El contenido de poliaminas de los diferentes alimentos analizados (n=109) fue muy variable, dependiendo básicamente del tipo de alimento considerado (Publicación 3). En los alimentos de origen vegetal, la espermidina fue la poliamina predominante, mientras que los alimentos de origen animal presentaron una mayor proporción de espermina. Esta distribución coincide plenamente con los datos experimentales publicados hasta el momento (Eliassen et al., 2002; Nishimura et al., 2006; Nishibori et al., 2007; Cipolla et al., 2007; Kalač, 2014). El origen de estas dos poliaminas en los alimentos es generalmente fisiológico, ya que se encuentran de forma natural en los tejidos vegetales y animales (Kozová et al., 2009). La putrescina también puede estar presente de forma endógena, aunque niveles elevados de esta amina normalmente se deben a la actividad de bacterias que se desarrollan en el alimento (Bover-Cid et al., 2014). Esto último puede explicar los altos niveles de putrescina encontrados principalmente en alimentos fermentados (Kozová et al., 2009; Kalač, 2014). Por último, según han sugerido algunos autores, también parece importante tener en cuenta la contribución de la actividad bacteriana en la acumulación de espermina y espermidina, a pesar de que aún son necesarios más trabajos que sustenten este origen (Atiya-Ali et al., 2011; Byun et al., 2013).

En alimentos de origen vegetal, los altos contenidos de poliaminas se pueden atribuir, en parte, al papel de estos compuestos como factores de crecimiento, especialmente durante el proceso de germinación (Kusano et al., 2007; Chen et al., 2019). Así, el germen de trigo y los brotes de soja, que consisten en semillas germinadas, mostraron los mayores niveles totales de poliaminas (con valores medios de hasta 440 mg/kg). Algunos autores han descrito que los niveles máximos de poliaminas se alcanzan a las 48h de germinación, y que su acumulación puede verse influenciada por diversas condiciones, tales como la luminosidad, la temperatura y la humedad (Glória et al., 2005; Xu et al., 2005; Ponce De León et al., 2013; Menéndez et al., 2019).

Además de los alimentos germinados, destacaron por sus altos contenidos en poliaminas el champiñón, el pimiento verde, los guisantes, los cítricos, las habas, la soja y el tempeh. Todos estos alimentos fueron ricos en espermidina, a excepción de los cítricos y el pimiento verde, que se caracterizaron por una elevada presencia de putrescina. La mayoría de los estudios realizados con anterioridad también han destacado estos mismos alimentos como fuentes dietéticas relevantes de poliaminas (Eliassen et al., 2002; Nishimura et al., 2006; Nishibori et al., 2007; Cipolla et al., 2007; Kalač, 2014). El hecho que otros autores también hayan reportado altas concentraciones de putrescina en pimiento verde y cítricos sugiere un origen fisiológico de esta poliamina en estos alimentos (Eliassen et al., 2002; Nishibori et al., 2007; Kalač, 2014).

La variabilidad en el contenido de poliaminas en todos los alimentos de origen vegetal puede verse afectada por diversos factores agronómicos, tales como la variedad de cultivo, la ubicación geográfica, los factores ambientales y las condiciones específicas de cultivo y/o cosecha (Glória et al., 2005; Kobayashi et al., 2017; Sagara et al., 2017). Se ha descrito que las poliaminas juegan un papel clave en la respuesta de las plantas al estrés ocasionado por diversos factores ambientales como la sequía o la presencia de temperaturas extremas (Chen et al., 2019; Dawood & Abeed, 2020). Concretamente, Menéndez et al. (2019) han reportado que los niveles de putrescina en plantas de legumbres aumentan en respuesta al estrés (p.ej. sequía) durante el período de cultivo

(Menéndez et al., 2019). Similarmente, Shao et al. (2015) observaron que los niveles de espermidina durante el cultivo de alfalfa aumentaron en respuesta al estrés inducido por las altas temperaturas. Asimismo, algunos estudios han demostrado que la aplicación exógena de poliaminas ya sea pre-cultivo (remojando las semillas en agua enriquecida con poliaminas) o durante el cultivo (mediante el riego) puede compensar los efectos negativos del frío y/o la sequía, favoreciendo así la germinación, el crecimiento y/o la supervivencia de las plantas (Kusano et al., 2007; Chen et al., 2019; Menéndez et al., 2019; Dawood & Abeed, 2020). Estas propiedades anti-estrés de las poliaminas en las plantas podrían atribuirse a su papel en la modulación de los parámetros morfológicos de crecimiento, preservando la integridad de las membranas celulares y minimizando así la inhibición del crecimiento provocada por el estrés (Khajuria et al., 2018; Gull et al., 2019). Además, las poliaminas también podrían incrementar la actividad de algunas enzimas antioxidantes presentes en las plantas, regulando así el estrés oxidativo causado por factores ambientales (Chen et al., 2019).

Otro factor para tener en cuenta para interpretar los diferentes contenidos de poliaminas es su posible origen bacteriano en algunos alimentos vegetales, principalmente en el caso de la putrescina. Por ejemplo, en nuestro estudio, los alimentos fermentados de la soja (p.ej. miso, sufu, salsa de soja y tamari) mostraron contenidos relevantes de putrescina (con rangos de 7 a 15 mg/kg), en este caso relacionados con la actividad descarboxilasa de cepas bacterianas fermentativas y/o alterantes presentes en estos productos (Yang et al., 2020). Además, las condiciones de fermentación, como la temperatura y la duración, tienen un impacto en la acumulación de putrescina en este tipo de alimentos (Park et al., 2019; Lan et al., 2020; Yang et al., 2020).

En los alimentos de origen animal, los niveles más altos de poliaminas se encontraron en quesos de leche cruda y curados (129 mg/kg y 87 mg/kg, respectivamente) y en derivados cárnicos crudos curados (con rangos de entre 58-99 mg/kg). En estos productos la poliamina predominante fue, en todos los casos, la putrescina, debido principalmente a la capacidad aminogénica de los microorganismos responsables de la fermentación

(Bover-Cid et al., 2014; Latorre-Moratalla et al., 2017). En estos alimentos, y como consecuencia de esta actividad bacteriana, también se suelen acumular niveles destacados de otras aminas biógenas, tales como tiramina, cadaverina y/o histamina (Bover-Cid et al., 2014; Latorre-Moratalla et al., 2017). Además, ciertas especies bacterianas gram-negativas asociadas a procesos alterantes de los alimentos también han sido descritas como responsables de la formación de putrescina y otras aminas en este tipo de productos. Por ejemplo, diferentes autores han asociado el uso de carne cruda de mala calidad higiénica y/o condiciones inadecuadas de producción/almacenamiento con una alta acumulación de putrescina en embutidos fermentados (Kalač, 2006; Bover-Cid et al., 2014).

En el resto de los alimentos de origen animal, como por ejemplo la carne fresca, el pescado fresco y los productos cárnicos curados o cocidos, se encontraron niveles totales de poliaminas por debajo de los 40 mg/kg, siendo siempre la espermina la poliamina mayoritaria. Cabe destacar que el yogur, la leche fresca, el queso fresco y el huevo presentaron niveles muy bajos de poliaminas (<5 mg/kg). En el caso del yogur, a pesar de ser un alimento fermentado, las concentraciones de poliaminas fueron realmente bajas. En general, los datos disponibles sobre el contenido de poliaminas en alimentos de origen animal son del orden de los reportados en el presente estudio (Eliassen et al., 2002; Nishimura et al., 2006; Cipolla et al., 2007; Nishibori et al., 2007).

La mayoría de los trabajos realizados hasta la fecha reportan únicamente el contenido de poliaminas en alimentos crudos. Sin embargo, algunos autores han descrito que ciertos tratamientos culinarios podrían modificar la presencia de estos compuestos. En este contexto, parece relevante conocer la influencia de los tratamientos más frecuentemente aplicados en el ámbito doméstico y/o gastronómico sobre las poliaminas de los alimentos, datos de especial interés para estimar la ingesta real de estos compuestos. Esta tesis doctoral evaluó por primera vez y de manera comparativa el efecto del hervido, la plancha, el microondas y el *sous-vide* sobre el contenido de putrescina, espermidina y espermina en un amplio número de alimentos tanto de origen vegetal como animal (Publicación 3).

De entre todos los tratamientos culinarios ensayados, el hervido fue el que comportó las pérdidas más importantes de poliaminas, que oscilaron entre 15% y 64% dependiendo del alimento. El hervido afectó a 9 de los 13 productos analizados, siendo la acelga, las espinacas, el calabacín, la col, el cerdo y la ternera los que sufrieron las mayores pérdidas de poliaminas. Esta reducción se puede atribuir, fundamentalmente, a la transferencia de las poliaminas al agua de cocción, con porcentajes de recuperación de estos compuestos en el agua de alrededor de 94%. El paso de las poliaminas al agua de cocción también ha sido reportado por otros autores para diferentes tipos de alimentos hervidos (Shalaby, 2000; Paulsen et al., 2006; Krausová et al., 2007; Krausová et al., 2008; Kozová et al., 2009; Veciana-Nogués et al., 2014). La putrescina fue la poliamina que presentó la mayor transferencia al agua de cocción, lo que podría deberse a su mayor solubilidad (Veciana-Nogués et al., 2014). Veciana-Nogués et al. (2014) concluyeron que el contenido de putrescina en espinacas, coliflor, acelgas y judías verdes se redujo por transferencia al agua de cocción, mientras que el hervido no tuvo efecto en otras verduras, como el pimiento y los guisantes. Similarmente, Eliassen et al. (2002) y Bardocz et al. (2001) tampoco reportaron un efecto significativo del hervido sobre los niveles de putrescina de vegetales como la zanahoria, el brócoli, la coliflor y la patata. Por otro lado, el hecho de que las poliaminas no se distribuyen de manera homogénea dentro del mismo alimento, podría explicar la pérdida más pronunciada de putrescina en ciertos alimentos (Paulsen et al., 2006). Por ejemplo, se ha descrito que los espárragos acumulan concentraciones más altas de putrescina cerca de la superficie, lo que puede explicar la reducción de putrescina en los espárragos observada en el actual estudio (Ziegler et al., 1994).

La plancha también provocó notables pérdidas de poliaminas en prácticamente los mismos alimentos que el hervido. Hasta la fecha, el efecto de la plancha sobre el contenido de poliaminas ha sido escasamente estudiado y solo en alimentos de origen animal. Estos estudios reportaron altas pérdidas de putrescina, espermidina y espermina en carne de pollo y cerdo cocinadas a la plancha (Paulsen et al., 2006; Krausová et al., 2007; Krausová et al., 2008; Kozová et al., 2009). En el actual estudio, la reducción de poliaminas en los productos cárnicos tras este tipo de cocinado fue mucho menor y solo se observó en la carne de ternera y de cerdo. Para explicar la pérdida de poliaminas provocada por este tratamiento culinario, algunos autores han postulado la hipótesis de que las altas temperaturas alcanzadas (180 ºC) pueden favorecer la reacción de Maillard entre los grupos amino primarios de las poliaminas y los azúcares reductores o, en el caso de los alimentos de origen animal, con los compuestos carbonílicos producidos en la vía de la oxidación de los lípidos (Kozová et al., 2009; Zamora & Hidalgo, 2011; Jiang et al., 2017).

La cocción de los alimentos en microondas provocó pérdidas significativas de poliaminas en un bajo número de alimentos (4 de 13) y en cantidades considerablemente menores a las del hervido y la plancha, siendo la putrescina y la espermidina las poliaminas más afectadas. La cocción con microondas puede deshidratar los alimentos, provocando así la salida de las poliaminas más solubles. En este estudio y con el objetivo de poder comparar, se estandarizó el tiempo de cocción de todos los alimentos a cinco minutos, siendo excesivo para alguno de ellos. Así, la aplicación de tiempos de cocción más cortos y adaptados a la naturaleza de cada alimento podrían minimizar la salida de agua y, por tanto, la potencial pérdida de poliaminas. *Sous-vide* es el término francés que se utiliza para designar el método culinario en el que los alimentos al vacío se someten a bajas temperaturas durante un período prolongado de tiempo. Una de las principales características de la cocción al vacío es una alta conservación de las propiedades organolépticas y de los compuestos de los alimentos crudos. Por lo tanto, como era de esperar, no se reportaron pérdidas significativas de poliaminas en ningún alimento preparado con esta técnica. De acuerdo con nuestro conocimiento, esta es la primera vez que se estudia el efecto de la cocción con microondas y *sous-vide* sobre el contenido de poliaminas de los alimentos.

Poliaminas en leche materna y fórmulas infantiles

Las poliaminas desempeñan importantes funciones durante la etapa neonatal y lactante, ya que participan en la maduración intestinal y en el desarrollo del sistema inmunológico, lo que, en último término, se traduce en una menor incidencia de alergias alimentarias en el lactante (Pérez-Cano et al., 2010; Almeida et al., 2021). La leche materna es la primera fuente alimenticia de poliaminas para el ser humano. Sin embargo, su contenido puede verse influenciado por múltiples factores asociados tanto al propio proceso de lactancia como a las individualidades de cada madre e hijo. A pesar de su relevancia en la salud del lactante, todavía son escasos los datos disponibles sobre el contenido de poliaminas en la leche materna y de cómo estos varían en función de diferentes variables. Así, otro de los objetivos de esta tesis doctoral fue estudiar el contenido, perfil y evolución de las poliaminas en leche materna a lo largo de la lactancia (Publicaciones 4 y 5), así como la influencia de ciertos factores asociados a la lactancia en sus contenidos (Publicación 5).

En el marco de esta tesis doctoral se estudió el contenido de poliaminas en muestras de leche de cinco madres españolas (Publicación 4) y 83 madres mexicanas (Publicación 5) durante el primer semestre de lactancia. En ambos estudios se demostró que el contenido total de poliaminas difiere ampliamente entre las leches de diferentes madres, así como en función de otras variables como el tiempo y el momento de la toma, con niveles que oscilaron entre los 45 nmol/dL y los 2,841 nmol/dL. Esta gran variabilidad también se ha observado en los datos previamente descritos en la literatura, probablemente atribuible a la heterogeneidad de las diferentes cohortes consideradas o a la interindividualidad de cada díada madre-hijo (Pollack et al., 1992; Romain et al., 1992; Buts et al., 1995; Plaza-Zamora et al., 2013; Atiya-Ali et al., 2013, 2014; Gómez-Gallego et al., 2017). Algunos autores han postulado que factores como la genética, el origen étnico, el estado nutricional y la ingesta dietética de la madre pueden tener un impacto en el contenido de poliaminas de la leche materna (Buts et al., 1995; Löser, 2000; Gómez-Gallego et al., 2017; Atiya-Ali et al., 2013; Plaza-Zamora et al., 2013). Por ejemplo, Gómez-

Gallego et al. (2017) sugirieron que la región geográfica, la cual está fuertemente vinculada con la genética y con los patrones dietéticos de la madre, juega un papel clave en la presencia de poliaminas en la leche materna, reportando un mayor contenido de poliaminas en la leche de madres españolas y finlandesas en comparación con la de madres chinas y sudafricanas. En este sentido, al comparar los contenidos de poliaminas encontrados en las muestras de leche de madres españolas (Publicación 4) y mexicanas (Publicación 5), se observó una tendencia de mayores concentraciones de poliaminas en las muestras de leche de las madres españolas (media de 790 nmol/dL a los dos meses) que en mexicanas (media de 334 nmol/dL a los dos meses). Así, las diferencias en la genética y/o en la alimentación ligadas a cada región geográfica podrían explicar estos resultados. Sin embargo, debido al menor número de madres incluidas en el grupo de las madres españolas no se han podido extraer conclusiones definitivas sobre la influencia del origen geográfico.

En cuanto a la influencia de la dieta, el estudio realizado por Atiya-Ali et al. (2014) mostró una asociación positiva entre la ingesta dietética de poliaminas y las concentraciones en la leche materna. Según estos autores, una mayor ingesta de vegetales en madres lactantes se asoció significativamente con mayores contenidos de espermidina en la leche materna, mientras que las frutas, principalmente naranja, se correlacionaron con mayores contenidos de putrescina. Estos autores también observaron cómo el contenido de poliaminas en la leche materna aumentó en madres con obesidad que estaban bajo una intervención nutricia, como reflejo de una mayor ingesta de vegetales y frutas (Atiya-Ali et al., 2013). De acuerdo con nuestros resultados sobre contenidos de poliaminas en alimentos (publicación 3), la mayoría de los vegetales y frutas se caracterizan por tener un mayor contenido de espermidina, aunque en algunas frutas, como los cítricos, la putrescina es la poliamina mayoritaria. Este hecho puede ayudar a explicar las correlaciones reportados por Atiya-Ali et al. (2013, 2014) entre el consumo de frutas y verduras y los valores individuales de poliaminas en leche materna. Sin embargo, la información disponible sobre la influencia de la ingesta de poliaminas por parte de la madre en el contenido de la leche materna sigue siendo escasa, por lo que sería interesante promover más estudios para establecer mejor esta asociación. Si se confirmara la influencia de la dieta sobre las poliaminas de la leche materna, el enriquecimiento de la dieta materna con alimentos ricos en estos compuestos sería una forma fácil y eficaz para aumentar las poliaminas de la leche materna. En este sentido, los resultados de esta tesis doctoral mostraron que las mejores fuentes dietéticas de poliaminas serían los champiñones, la soja, el germen de trigo, las habas, el pimiento verde y los cítricos, entre otros (publicación 3).

En cuanto al perfil de distribución de las tres poliaminas, los resultados de ambos estudios (publicación 4 y 5) muestran el predominio de espermidina y espermina, ambas detectadas en proporciones similares, mientras que las concentraciones de putrescina fueron siempre menores. Todos los estudios publicados previamente en esta área coinciden en que la putrescina es la poliamina menos abundante en la leche materna, mientras que existen discrepancias sobre cuál es la poliamina principal (Romain et al., 1992, Pollack et al., 1992; Buts et al., 1995; Plaza-Zamora et al., 2013; Atiya-Ali et al., 2013; Gómez-Gallego et al., 2017). En cualquier caso, un alto contenido de espermina y de espermidina en la leche materna en los primeros meses posnatales se ha relacionado con un menor riesgo de desarrollar alergias alimentarias en la infancia y en la niñez (Peulen et al., 1998; Dandrifosse et al., 2000). Estos efectos relacionados con la salud se deben a la participación de la espermina y la espermidina en la maduración posnatal del intestino delgado y en el desarrollo del sistema inmunológico (Dandrifosse et al., 2000; Biol-N'garagba et al., 2002; Peulen et al., 2004; Pérez-Cano et al., 2010).

Por otro lado, en las muestras de leche de una madre española se encontraron niveles anormalmente elevados de putrescina (hasta 183 nmol/dL), así como la inusual presencia de histamina (170 nmol/dL) y cadaverina (2680 nmol/dL) (publicación 4). Esto podría explicarse por la actividad aminogénica de las bacterias infecciosas responsables de la mastitis, un proceso inflamatorio de la glándula mamaria. Estos hallazgos están respaldados por los resultados del trabajo realizado por Pérez et al. (2016) quienes observaron mayores concentraciones de putrescina, junto con histamina, tiramina y cadaverina, en la leche de madres con mastitis en comparación con la de madres sanas. Cabe destacar que la putrescina, además de su origen fisiológico, también puede formarse por la actividad microbiana, como en el caso de la histamina, la tiramina y la cadaverina (Bover-Cid et al., 2014). Por el contrario, la presencia de espermidina y de espermina es fundamentalmente fisiológica y, por lo general, no se asocia con un origen bacteriano (Kalač, 2014). A pesar del nivel anormalmente alto de putrescina en estas muestras de leche, el hecho de que la espermina y la espermidina fueran las poliaminas predominantes hace que el perfil general de poliaminas totales no se viera afectado.

Respecto a la evolución del contenido de poliaminas a lo largo de la lactancia, los datos obtenidos para madres españolas y mexicanas (publicaciones 4 y 5) mostraron una disminución de los contenidos de poliaminas durante el primer semestre de lactancia. Así, en ambos estudios la espermidina disminuyó significativamente alrededor de 30% y la espermina de 25% entre el primer/segundo y el quinto/sexto mes de lactancia. Contrariamente, la putrescina se mantuvo prácticamente sin cambios durante este período. Los dos trabajos realizados el año 1992 por Pollack et al. y Romain et al. con muestras de madres norteamericanas y belgas, respectivamente, también describen una disminución progresiva de la concentración de poliaminas a lo largo de la lactancia. La alta tasa de crecimiento y diferenciación de las células durante los primeros meses de vida podría explicar los mayores contenidos de poliaminas en la leche materna producida al inicio de la lactancia (Plaza-Zamora et al., 2013). Por otro lado, el aumento de la actividad catalítica de la enzima PAO en la leche materna durante el progreso de la lactancia también podría explicar la reducción progresiva de los niveles de poliaminas (Bjelakovic et al., 2012).

Las concentraciones de poliaminas en las muestras de leche materna variaron, no solo según la fase de lactancia, sino también durante una misma toma. Así, los contenidos de poliaminas fueron significativamente más altos (en algunos casos hasta el doble) en la leche obtenida al final de la toma con respecto a la del inicio, especialmente los de espermidina y espermina e independientemente del mes de lactancia. Esta es la primera vez que se ha evaluado si existen diferencias entre las concentraciones de poliaminas dentro de una misma toma (Publicación 5). A pesar de que no existen datos sobre poliaminas, sí está ampliamente establecido que la leche final de la toma tiene una mayor densidad energética y mayores concentraciones de grasas y vitaminas A y E (Andreas et al., 2015; Mosca & Giannì, 2017; Nielsen et al., 2017; van Sadelhoff et al., 2018). Además, el hecho de que la leche final permanezca en la glándula mamaria durante más tiempo en presencia de endo y exopeptidasas activas (enzimas responsables de romper los péptidos de la leche) podría conllevar un mayor contenido de aminoácidos libres (Nielsen et al., 2017; van Sadelhoff et al., 2018). Concretamente, Sadelhoff et al. (2018) reportó que la leche final tiene un mayor contenido de arginina, aminoácido precursor de la ornitina, y por tanto, sustrato clave para la síntesis endógena de poliaminas (Miller-Fleming et al., 2015; Lenis et al., 2017). En definitiva, el mayor contenido de poliaminas en la leche final refuerza la importancia de que el lactante obtenga la toma completa para que se pueda beneficiar de todos los nutrientes que aporta la leche materna.

La OMS recomienda la lactancia materna exclusiva durante los primeros seis meses de vida, seguida de la lactancia materna en combinación con los alimentos hasta los dos años (OMS, 2009). Sin embargo, existe una tendencia creciente de la lactancia materna parcial durante los primeros meses de vida (Libuda et al., 2017). En este sentido, también se estudió si el tipo de lactancia materna podría afectar el contenido de poliaminas de la leche materna (publicación 5). Las concentraciones de poliaminas fueron ligeramente más altas en la leche de las madres que daban lactancia parcial en comparación con las de lactancia completa, aunque solo se encontraron diferencias significativas en el caso de la espermina a los cuatro meses de lactancia. A pesar de esta tendencia, resulta difícil extraer conclusiones sólidas ya que sólo 23 de las 83 madres participantes del estudio dieron lactancia parcial.

De acuerdo con Gómez-Gallego et al. (2017) el tipo de parto, ya sea natural o por cesárea, parece también afectar la concentración de poliaminas en la leche materna. Estos autores reportaron que las madres que tuvieron a su bebé por cesárea producían leche con un menor contenido de poliaminas. En nuestro estudio (publicación 5), solo 5% de las madres dieron a luz por cesárea, mostrando también una tendencia de concentraciones más bajas de poliaminas en su leche. Sin embargo, debido al bajo número de muestras, no es posible concluir la influencia del tipo de nacimiento en los niveles de poliaminas de la leche materna. En este ámbito, son necesarios más estudios, no solo para confirmar estos resultados, sino también para analizar por qué las concentraciones de poliaminas pueden variar según la tipología de nacimiento.

Finalmente, en cuanto a los demás factores relacionados con la díada madre-hijo (edad e IMC de la madre, peso al nacer y sexo del lactante), no se encontraron asociaciones significativas. En este sentido, la información en la literatura sobre la influencia de estos factores en los niveles de poliaminas en la leche materna sigue siendo escasa. Únicamente Atiya-Ali et al. (2013) describieron contenidos más bajos de poliaminas en la leche de madres con sobrepeso/obesidad en comparación con aquellas con un IMC normal. Además, tanto nuestros datos como los reportados por Atiya-Ali et al. (2013) no indican un efecto de la edad de la madre sobre el contenido de estos compuestos en la leche materna.

En aquellos casos en los que no se opte por la lactancia materna o que ésta no sea posible, la leche materna es sustituida por fórmulas infantiles. Por este motivo, ha sido también objeto de estudio de esta tesis el contenido y distribución de poliaminas en diferentes tipos de fórmulas infantiles (de inicio, de continuación y de uso médico especial) (Publicación 4).

Las fórmulas de inicio, de continuación y para prematuros, todas ellas elaboradas a base de leche de vaca, mostraron contenidos de poliaminas relativamente bajos. En este tipo de productos, la putrescina y la espermidina se encontraron generalmente en proporciones similares (con valores medios de 32 nmol/dL y 33 nmol/dL, respectivamente), mientras que destaca la ausencia de espermina. La baja presencia de poliaminas en la materia prima (leche de vaca) podría explicar los reducidos niveles de estos compuestos encontrados en estos preparados para lactantes (Kalač, 2014).

Hasta la fecha, son pocos los trabajos que han estudiado la presencia de poliaminas en fórmulas infantiles, algunos de ellos bastante antiguos, y con datos muy variables entre ellos (Pollack et al., 1992; Romain et al., 1992; Buts et al., 1995; Atiya-Ali et al., 2014; Gómez-Gallego et al., 2016; Spizzirri et al., 2019). Concretamente, los contenidos encontrados en el presente estudio en fórmulas de inicio, de continuación y para prematuros coinciden con aquellos descritos por Pollack et al. (1992), Buts et al. (1995) y Atiya-Ali et al. (2014). Sin embargo, otros autores describen valores más elevados de estos compuestos en sus fórmulas infantiles (Romain et al., 1992; Gómez-Gallego et al., 2016; Spizzirri et al., 2019). Por ejemplo, Spizzirri et al. (2019) han reportado recientemente niveles de hasta 964 nmol/dL, 923 nmol/dL y 712 nmol/dL para putrescina, espermidina y espermina, respectivamente. Tal como se describe en el trabajo de Gómez-Gallego et al. (2016), las diferencias en los contenidos de poliaminas en las fórmulas infantiles se explicarían principalmente por los niveles de estos compuestos en la leche cruda de origen, pero también se podrían ver influenciadas por el proceso de fabricación. Estos autores reportaron que la actividad de la enzima PAO presente en la leche cruda puede ser responsable de cambios en las concentraciones de poliaminas, ya que parece ser resistente a los procesos de desnatado, pasteurización, concentración y secado aplicados para la obtención de las fórmulas infantiles (Gómez-Gallego et al., 2016). Sin embargo, solo existe un trabajo que relaciona la actividad de la enzima PAO con la variabilidad del contenido de poliaminas en fórmulas infantiles, por lo que sería importante ampliar este conocimiento y dilucidar si las diferencias encontradas en este tipo de productos no se deben únicamente a que la enzima PAO degrada las poliaminas, sino también a su participación en la interconversión entre ellas.

Las fórmulas infantiles para uso médico especial a base de proteínas vegetales (soja y arroz), mostraron una mayor variabilidad en los contenidos de poliaminas que las fórmulas convencionales a base de leche de vaca, tanto entre marcas como entre lotes de una misma marca. Las fórmulas a base de soja destacaron por sus altos niveles de espermidina (179 - 337 nmol/dL), mientras que en las fórmulas a base de arroz la putrescina fue la poliamina mayoritaria (188 - 312 nmol/dL). La espermina no se detectó en ninguno de los dos tipos de fórmulas a base de proteína vegetal. En la literatura científica, un único estudio realizado por Romain et al. (1992), muestra datos sobre la presencia de poliaminas en fórmulas especiales a base de soja, y según el cual la espermidina sería también la poliamina mayoritaria (256 nmol/dL) seguida de la putrescina (74 nmol/dL) y la espermina (44 nmol/dL). En cuanto a las fórmulas infantiles a base de arroz, esta es la primera vez que se estudian las poliaminas en este tipo de productos.

Al igual que en el caso de las fórmulas a base de leche de vaca, en las fórmulas para uso médico especial a base de proteína vegetal, el contenido y la distribución de poliaminas estará relacionado con los contenidos de la materia prima utilizada. De hecho, tal como se ha descrito en la publicación 3 de esta tesis, así como también por otros autores, la putrescina es la poliamina mayoritaria en el arroz y la espermidina en la soja (Nishimura et al., 2006; Cipolla et al., 2007; Byun et al., 2013; Toro-Funes et al., 2015). Además, la presencia de poliaminas en los alimentos de origen vegetal está modulada por diversos factores, tales como las condiciones de cultivo, ambientales (p.ej. sequías) y/o cosecha, entre otros. Estos factores pueden potencialmente modificar el contenido final de poliaminas en el vegetal, y consecuentemente, en los productos derivados, como las fórmulas infantiles (Glória et al., 2005; Ponce De León et al., 2013; Menéndez et al., 2019).

Cabe destacar las grandes diferencias observadas en la distribución y en el contenido de poliaminas entre la leche materna (Publicación 4 y 5) y los diferentes tipos de fórmulas infantiles (publicación 5). Así, los valores medios de poliaminas en las fórmulas infantiles fueron hasta 30 veces más bajos que los de la leche materna. En cuanto al perfil, la espermidina y la espermina fueron las principales poliaminas en la leche materna, mientras que en las fórmulas infantiles lo fue la putrescina. Por lo tanto, estos resultados enfatizan la necesidad de que las fórmulas infantiles mejoren su contenido de poliaminas, tanto de manera cualitativa como cuantitativa, con el fin de que puedan asemejarse mejor a la composición de la leche materna.

Por otra parte, está ampliamente descrito que los patrones de crecimiento y composición corporal de los lactantes difieren de acuerdo con el tipo de alimentación que reciben (Giannì et al., 2014; Giugliani, 2019; Rodríguez-Cano et al., 2019). Por ejemplo, los lactantes alimentados con lactancia materna exclusiva tienen una mayor acumulación de grasa (tanto en gramos como en porcentaje) durante los primeros 4 meses de vida, mientras que los lactantes alimentados con fórmula infantil tienen una mayor acumulación de masa magra y un aumento de peso más rápido (Butte et al., 2000; Gale et al., 2012; Giannì et al., 2014; Rodríguez-Cano et al., 2019). No obstante, la mayoría de estos estudios comparan lactantes alimentados con lactancia materna exclusiva con los que reciben fórmula infantil, y solo unos pocos consideran lactantes alimentados con lactancia materna parcial (Jia et al., 2018; Park et al., 2018; Rodríguez-Cano et al., 2019). Uno de los trabajos realizados en esta tesis (Publicación 7) demostró que los lactantes que recibieron lactancia materna completa mostraban mejores parámetros antropométricos en comparación con los que recibieron lactancia materna parcial. Específicamente, los lactantes alimentados con lactancia materna completa tuvieron un peso, IMC, CMB, PCT y PCSE significativamente más altos que los alimentados de forma parcial, así como mejores valores de puntuación Z de los índices peso/edad y peso/longitud. Estos resultados coinciden con los previamente reporatados por otros estudios. Jia et al. (2018) reportaron mejores valores de puntuación Z de los índices peso/edad y peso/longitud en los lactantes que recibieron lactancia materna completa. Asimismo, Rodríguez-Cano et al. (2019) encontraron que los lactantes alimentados con lactancia materna completa tenían valores más altos de IMC, PCT, PCSE y masa grasa (en kg y porcentaje) en comparación con los de lactancia materna parcial.

Tal como se ha reportado en las publicaciones 5 y 7, la leche de las madres que dieron lactancia parcial tenía un contenido de poliaminas ligeramente superior en comparación con la de las que dieron lactancia materna completa. Sin embargo, este mayor contenido de poliaminas no se tradujo en una mayor ingesta de estos compuestos por parte de los lactantes con alimentación parcial. De hecho, estos lactantes mostraron una ingesta de poliaminas entre un 23-50% menor en comparación con el grupo de lactancia materna completa, a excepción de la putrescina que su ingesta fue mayor en el grupo de lactancia parcial. Tal como se ha descrito en un trabajo de esta tesis (publicación 4) así como también por otros autores, los niveles de poliaminas totales en las fórmulas infantiles son de hasta 30 veces más bajos que en la leche materna (Buts et al., 1995; Atiya-Ali et al., 2014; Spizzirri et al., 2019), lo que podría explicar la menor ingesta de poliaminas en los lactantes que recibieron lactancia parcial. Sin embargo, el hecho de que las fórmulas infantiles contengan niveles de putrescina hasta dos veces superiores a los de la leche materna, explicaría la mayor ingesta de putrescina por parte de los lactantes con lactancia parcial (Buts et al., 1995; Atiya-Ali et al., 2014; Spizzirri et al., 2019). Así, en este caso, la mayor ingesta de poliaminas por parte de los lactantes alimentados con lactancia completa coincidió con un mayor crecimiento y mejores valores antropométricos en comparación con los que recibieron lactancia parcial.

Como ya se ha comentado anteriormente, los requerimientos de poliaminas son más elevados durante los primeros meses de vida debido al rápido crecimiento y desarrollo del lactante. De hecho, se han reportado contenidos más altos de poliaminas en la leche de madres que tuvieron bebés prematuros (Plaza-Zamora et al., 2013; Atiya-Ali et al., 2014). También se ha descrito que las poliaminas están involucradas en las primeras etapas de la diferenciación de los adipocitos (Ishii et al., 2012; Ramos-Molina et al., 2019). Específicamente, la enzima espermidina/espermina-N1-acetiltransferasa (SSAT) es un regulador metabólico clave en la homeostasis de las poliaminas, que, a la vez, también está fuertemente implicada en la adipogénesis. Concretamente, la enzima SSAT cataliza la transferencia de grupos acetilo de acetil-CoA a espermidina o espermina, permitiendo la interconversión entre ellas (Liu et al., 2014; Büyükuslu & Öztürk, 2018). Una desregulación de esta enzima comportaría modificaciones a nivel del contenido de Acetil-CoA y por lo tanto, influiría en la acumulación de grasa corporal (Pirinen et al., 2007; Liu et al., 2014; Büyükuslu & Öztürk, 2018). Algunos estudios en modelos animales han demostrado que la sobreexpresión de la enzima SSAT en ratones provocó una disminución del tejido adiposo blanco (Pirinen et al., 2007; Liu et al., 2014; Büyükuslu & Öztürk, 2018). Diferentes estudios también han reportado que la administración de espermidina o espermina en ratones disminuye el peso corporal y la masa grasa, siendo este efecto dosis dependiente (Sadasivan et al., 2014; Fernández et al., 2017; Ma et al., 2021). Sin embargo, se ha de tener cuenta que todos estos trabajos están realizados en modelos animales con obesidad inducida, y, por lo tanto, no se pueden extrapolar sus resultados con el posible papel de las poliaminas en la acumulación de adiposidad en lactantes sanos.

En esta tesis también se estudió la posible asociación entre el contenido de poliaminas en la leche materna o la ingesta de estos compuestos con los parámetros antropométricos del lactante (Publicación 7). La mayoría de los indicadores antropométricos evaluados no mostraban correlaciones significativas ni con el contenido de poliaminas de la leche materna ni con la ingesta estimada de estos compuestos. Todos los lactantes incluidos en este estudio tenían un estado nutricional adecuado para la edad, con parámetros antropométricos dentro de los límites de normalidad (± 2 DE), lo que podría explicar, en parte, esta falta de asociación. Solo dos parámetros antropométricos, el PCT y el CMB, mostraron una asociación inversa y débil, aunque significativa, tanto con el contenido de putrescina y espermina en la leche materna como con su ingesta. A pesar de que estos dos parámetros antropométricos están relacionados con la adiposidad y las reservas de grasa del lactante, las asociaciones débiles e inconsistentes no permiten sacar conclusiones sólidas sobre el papel de las poliaminas en el crecimiento y la composición corporal del lactante. En este sentido sería necesario realizar más estudios con el fin de esclarecer la posible participación de las poliaminas en el crecimiento y composición corporal del lactante, y para determinar si un incremento en la ingesta de estos compuestos a través de la leche materna se traduce en una elevación de sus niveles en sangre.

5 | Conclusiones

5 Conclusiones

1. El contenido y perfil de distribución de poliaminas de los alimentos fue muy variable, siendo en general la espermidina la mayoritaria en los alimentos de origen vegetal y la espermina en los de origen animal. Los alimentos que destacaron por presentar los contenidos más altos de poliaminas fueron el germen de trigo, los champiñones, la soja, el pimiento verde, los guisantes, los cítricos, los quesos y los derivados cárnicos fermentados.

2. Los tratamientos culinarios pueden alterar el contenido de poliaminas de los alimentos. El hervido y la plancha fueron los tratamientos que provocaron una mayor reducción de los niveles de poliaminas, con pérdidas que alcanzaron 60% en comparación con el alimento crudo. Por el contrario, la cocción por microondas y *sous-vide* prácticamente no modificaron el contenido de estos compuestos bioactivos.

3. Todas las muestras de leche materna presentaron cantidades variables pero sustanciales de poliaminas, principalmente espermidina y espermina, y una baja proporción de putrescina. Los contenidos de poliaminas disminuyen a lo largo del progreso de la lactancia, especialmente espermidina y espermina, con concentraciones del orden de un 30% más bajas a los cinco o seis meses con respecto al inicio de la lactancia.

4. Las concentraciones de poliaminas en las diferentes fórmulas infantiles comerciales estudiadas fueron bajas, especialmente en comparación con las de la leche materna, en las que fueron hasta 30 veces más altas. En todas las fórmulas a base de leche de vaca, independientemente de la edad a la que van destinadas, se encontraron niveles similares de putrescina y espermidina, mientras que en las fórmulas a base de arroz la putrescina fue la poliamina predominante y en las de soja fue la espermidina.

5. Las concentraciones de poliaminas en la leche materna varían dentro de una misma toma, con niveles en la leche que corresponde al final de la toma que doblan los de la inicial. Igualmente, el tipo de lactancia parece tener cierta influencia sobre los contenidos de poliaminas de la leche materna, ya que se encontraron concentraciones ligeramente más altas de espermina en las muestras de leche de las madres que dieron lactancia parcial en comparación con las de lactancia completa.

6. La influencia de otros factores de la díada madre-hijo sobre la concentración de poliaminas sólo se visualizó en una cierta tendencia de menores concentraciones de poliaminas en las leches de las madres que dieron a luz por cesárea en comparación con las de parto natural. La edad y el IMC de la madre, así como el peso al nacer y sexo del lactante, no influyeron en los contenidos de poliaminas de la leche materna.

7. El crecimiento y la composición corporal de los lactantes difieren según el tipo de lactancia materna que recibe, siendo los alimentados con lactancia materna completa los que presentaron mejores indicadores antropométricos. Además, estos lactantes mostraron una mayor ingesta de poliaminas en comparación con los alimentados con lactancia materna parcial.

8. La mayoría de los parámetros antropométricos de los lactantes no mostraron una asociación significativa con los contenidos de poliaminas de la leche materna, ni con su ingesta, a excepción del pliegue cutáneo tricipital y de la circunferencia media de brazo, que mostraron una correlación débil e inversa, pero significativa, con la putrescina y la espermina.

6 | Bibliografía

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7 | Anexos

7 Anexos

7.1 Contribuciones científicas derivadas de la tesis doctoral

7.1.1 Publicaciones

Publicación 1

Nelly C. Muñoz-Esparza, M. Luz Latorre-Moratalla, Oriol Comas-Basté, Natalia Toro-Funes, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Polyamines in food. Frontiers in Nutrition, 2019. 11; 6: 108. DOI: 10.3389/fnut.2019.00108.

Publicación 2

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, Natalia Toro-Funes, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Polyamines in soybean food and their potential benefits for the elderly. Phytochemicals in Soybeans: Bioactivity and Health Benefits. *CRC Press/Taylor and Francis.* 2022. Editor: Jonh Shi.

Publicación 3

Nelly C. Muñoz-Esparza, Judit Costa-Catala, Oriol Comas-Basté, Natalia Toro-Funes, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Occurrence of Polyamines in Foods and the Influence of Cooking Processes. Foods, 2021. 10; 8: 1752. DOI: 10.3390/foods10081752

Publicación 4

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Differences in polyamine content between human milk and infant formulas. *Foods*, 2021. 10; 11: 2866. DOI: 10.3390/foods10112866

Publicación 5

Nelly C. Muñoz-Esparza, Edgar M. Vásquez-Garibay, Elizabeth Guzmán-Mercado, Alfredo Larrosa-Haro, Oriol Comas-Basté, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Influence of breastfeeding factors on polyamine content in human milk. Nutrients, 2021. 13, 3016. DOI: 10.3390/nu13093016.

Publicación 6

Edgar M. Vásquez-Garibay, Alfredo Larrosa-Haro, Elizabeth Guzmán-Mercado, Nelly C. Muñoz-Esparza, Samuel García-Arellano, Francisco Muñoz-Valle, Enrique Romero-Velarde. Appetite-regulating hormones and anthropometric indicators of infants according to the type of feeding. Food Science & Nutrition, 2020. 8: 993-1000. DOI: 10.1002/fsn3.1381

Publicación 7

Nelly C. Muñoz-Esparza, Edgar M. Vásquez-Garibay, Elizabeth Guzmán-Mercado, Alfredo Larrosa-Haro, Oriol Comas-Basté, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Influence of the type of breastfeeding and human milk polyamines on the anthropometric parameters of the infant. En revision en la revista Frontiers in Nutrition.

7.1.2 Comunicaciones orales

Comunicación oral 1 | Premio a la mejor comunicación oral

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, Sònia Sánchez-Pérez, Salvador Hernández-Macías, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Polyamines in breast milk and infant formulas. V Workshop de l'Institut de Recerca en Nutrició i Seguretat Alimentària de la Universitat de Barcelona (INSA-UB), 2019, Santa Coloma de Gramenet, España.

Comunicación oral 2

Nelly C. Muñoz-Esparza. Polyamines profile and content in breast milk. VII Spanish Nutrition Society Young Researchers´ Meeting, 2020, Virtual Zaragoza.

7.1.3 Comunicaciones escritas

Comunicación escrita 1

Nelly C. Muñoz-Esparza, Sònia Sánchez-Pérez, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Poliaminas: ¿Los antioxidantes olvidados? XIV Reunión Anual de la Sociedad española de Seguridad y Calidad Alimentarias (SESAL), 2018, Salamanca.

Comunicación escrita 2

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, Sònia Sánchez-Pérez, Salvador Hernández-Macías, M. Teresa Veciana-Nogués, M. Luz Latorre-Moratalla, M. Carmen Vidal-Carou. ¿Es comparable el contenido y perfil de poliaminas en la leche materna y fórmulas infantiles? IV Congreso de la Federación Española de Sociedades de Nutrición, Alimentación y Dietética (FESNAD), 2020, Virtual Zaragoza.

Comunicación escrita 3

Nelly C. Muñoz-Esparza**,** Oriol Comas-Basté, Elizabeth Guzmán-Mercado, Alfredo Larrosa-Haro, Edgar M. Vásquez-Garibay, M. Teresa Veciana-Nogués, M. Luz Latorre-Moratalla, M. Carmen Vidal-Carou. Contenidos y evolución de poliaminas en leche materna durante el primer semestre de lactancia. XIX Congreso Latinoamericano de Nutrición (SLAN), 2021, Virtual Paraguay.

7.1.4 Otras contribuciones científicas

Las siguientes comunicaciones escritas, aunque no se encuentran directamente vinculadas a los objetivos de esta tesis doctoral, se han producido durante el período de realización de la tesis fruto de la participación de la doctoranda en otras líneas de investigación del grupo.

Comunicación escrita 4

Sònia Sánchez-Pérez, Oriol Comas-Basté, Nelly C. Muñoz-Esparza, M. Teresa Veciana-Nogués, M. Luz Latorre-Moratalla, M. Carmen Vidal-Carou. Biogenic amines in plant-origin foods: Are they frequently underestimated in low-histamine diets? XV Reunión Anual de la Sociedad Española de Seguridad y Calidad Alimentarias (SESAL), 2019, Alicante.

Comunicación escrita 5

Salvador Hernández-Macias, Gemma Rius-Olivella, Oriol Comas-Basté, Sònia Sánchez-Pérez, Nelly C. Muñoz-Esparza, M. Teresa Veciana-Nogués, Sara Bover-Cid, M. Luz Latorre-Moratalla, M. Carmen Vidal-Carou. Estudio de la actividad histaminasa de Lactobacillus sakei y del efecto promotor de las lías del cava en su crecimiento. V Congreso Internacional de Calidad y Seguridad Alimentaria ACOFESAL, 2019, Barcelona.

Comunicación escrita 6

Sònia Sánchez-Pérez, Oriol Comas-Basté, Salvador Hernández-Macias, Nelly C. Muñoz-Esparza, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Is there correspondence between compositional values of tables and those in labels of commercial meat products? XVII Congreso de la Sociedad Española de Nutrición (SEÑ) y X Jornada de l'ACCA, 2018, Barcelona.

Comunicación escrita 7

Sònia Sánchez-Pérez, Oriol Comas-Basté, Salvador Hernández-Macias, Nelly C. Muñoz-Esparza, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Should fresh meat and meat derivatives be placed at diferent levels of the nutritional pyramid? XVII Congreso de la Sociedad Española de Nutrición (SEÑ) y X Jornada de l'ACCA, 2018, Barcelona.

Comunicación escrita 8

Sònia Sánchez-Pérez, Oriol Comas-Basté, Salvador Hernández-Macias, Nelly C. Muñoz-Esparza, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou. Histamine-free diets: Whats about legumes? XII International Mediterranean Diet Conference, 2018, Barcelona.

7.2 Evidencia de las comunicaciones orales y escritas

De la sospita a la Taula

V Workshop Anual INSA·UB

Al·lèrgies i intoleràncies alimentàries: de la sospita a la taula

Nelly C. Muñoz Esparza

ha rebut el premi a la

Millor Comunicació Oral

pel treball titulat "**Polyamines in breast milk and infant formula**" dels autors Muñoz-Esparza NC, Comas-Basté O, Sánchez-Pérez S, Hernández-Macias S, Latorre-Moratalla ML, Veciana-Nogués MT, Vidal-Carou MC.

presentat al V Workshop de l'Institut de Recerca en Nutrició i Seguretat Alimentària de la Universitat de Barcelona (INSA·UB) que ha tingut lloc el 13 de novembre de 2019 al Campus de l'Alimentació de Torribera de la Facultat de Farmàcia i Ciències de l'Alimentació (UB)

Rosa Mª

Dra. Rosa Lamuela Raventós
Directora de l'INSA·UB

UNIVERSITAT DE BARCELONA

INSA Institut de Recerca en Nutrició i Seguretat Alimentària

Campus de l'Alimentació

VII Spanish Nutrition Society Young Researchers' Meeting

November 12th-13th, 2020

Oral communication certificate

We hereby certify that

Nelly Carolina Muñoz Esparza

[Dpto. de Nutrición, Ciencias de los Alimentos y Gastronomía, Facultad de Farmacia y Ciencias de los Alimentos, Universidad de Barcelona, Instituto de Investigación en Nutrición y Seguridad Alimentaria de la Universidad de Barcelona]

Has presented the abstract entitled:

Polyamines profile and content in breast milk.

at the VII Spanish Nutrition Society Young Researchers' Meeting
on 12 th -13th November 2020,
Virtual event.

María Puy Portillo Baquedano
President of the SEÑ

Paloma Flores-Barrantes
President Organizing Committee

Pilar De Miguel-Etayo
President Scientific Committee

POLIAMINAS: ¿LOS ANTIOXIDANTES OLVIDADOS?

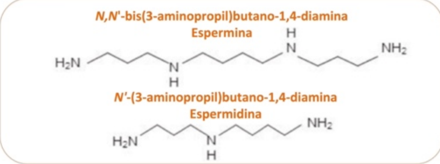
Muñoz-Esparza NC, Sánchez-Pérez S, Latorre-Moratalla ML, Veciana-Nogués MT, Vidal-Carou MC.

Departament de Nutrició, Ciències de l'Alimentació i Gastronomia, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona (UB). Av. Prat de la Riba 171, 08921 Santa Coloma de Gramenet (Spain); Institut de Recerca en Nutrició i Seguretat Alimentària (INSA-UB), Universitat de Barcelona (UB); Xarxa de Referència en Tecnologia dels Aliments de la Generalitat de Catalunya (XaRTA). mcvidal@ub.edu

UNIVERSITAT DE BARCELONA

ANTECEDENTES

Las poliaminas espermina y espermidina son moléculas alifáticas presentes en todos los organismos vivos, principalmente en tejidos con una alta renovación celular. Entre sus funciones está la capacidad de actuar como antioxidantes, principalmente como quelantes de metales. Los resultados de una búsqueda bibliográfica han mostrado que esta actividad está ampliamente estudiada en sustratos biológicos, pero son muy escasos los trabajos que estudian su papel como antioxidantes en alimentos.



OBJETIVOS

1) Estudiar la actividad antioxidante de la espermina y de la espermidina en comparación con otros antioxidantes en aceite de soja.
2) Identificar qué alimentos podrían ser una buena fuente de poliaminas.

METODOLOGÍA

1) Se determinaron los productos de oxidación primarios (índice de peróxidos[2]) y secundarios (compuestos carbonílicos, TBARS *Tiobarbituric Acid reactive especies*[3]) en aceite de soja (control) y aceite de soja adicionado con 100µg/g de espermina, espermidina, α-tocoferol, palmitato de ascorbilo o galato de octilo, mantenidos a 50ºC en la oscuridad. Las determinaciones se realizaron por triplicado.
2) Se utilizaron los contenidos medios de poliaminas (espermina + espermidina) procedentes de la base de datos del grupo de investigación que incluye más de 100 alimentos diferentes. Para su comparación los contenidos se expresan en peso seco (ps).

RESULTADOS

Las poliaminas redujeron la formación de los diferentes productos de oxidación analizados, con una efectividad igual o superior a la del resto de los antioxidantes estudiados. En la Figura 1, se observa que la espermina fue el compuesto que más retrasó la formación de peróxidos y en fases posteriores de la oxidación mostró la misma eficacia que la espermidina y el galato de octilo sobre la formación de compuestos carbonílicos, expresados como valor TBARS (Figura 2).

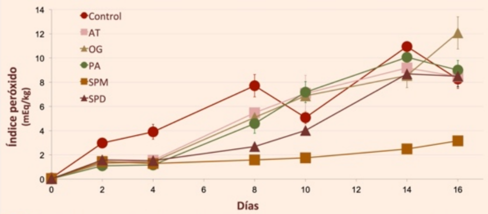


Figura 1. Evolución del índice peróxido en muestras de aceite de soja, control y adicionadas con espermidina (SPD), espermina(SPM), palmitato de ascorbilo(PA), galato de octilo(OG) o alfa-tocoferol(AT).

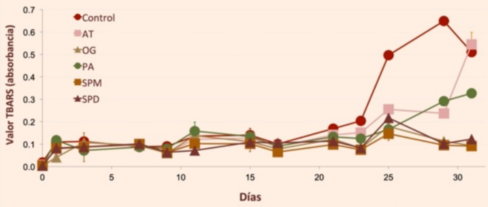


Figura 2. Evolución de la formación de compuestos carbonílicos expresados en valor TBARS en muestras de aceite de soja, control y adicionadas con espermidina (SPD), espermina(SPM), palmitato de ascorbilo(PA), galato de octilo(OG) o alfa-tocoferol(AT).

El contenido total de poliaminas en alimentos mostró una amplia variabilidad. Los alimentos de origen animal (carne, pescado, alimentos fermentados, queso, entre otros) tienen un alto contenido de poliaminas. Sin embargo, cuando se expresan en peso seco los alimentos de origen vegetal son más ricos en estos compuestos, principalmente verduras de hoja verde y algunos productos derivados de la soja Figura 3.

Figura 3. Contenido medio de espermina + espermidina en alimentos de origen animal (mg/kg) y vegetal (mg/kg peso seco).

CONCLUSIONES

Por su actividad antioxidante las poliaminas podrían adicionarse como antioxidantes naturales en alimentos. Para este fin pueden utilizarse extractos de vegetales (champiñón, germen de trigo y espárrago). También es posible que estos productos sean utilizados para enriquecer alimentos o como complementos alimentarios para aumentar la ingesta de estas sustancias, de especial interés en personas de la tercera edad, debido a que la síntesis endógena de poliaminas disminuye con el paso de los años. No obstante, hay que realizar más estudios para verificar la viabilidad de estas aplicaciones.

Agradecimientos: Nelly C. Muñoz Esparza becaria de la Universidad de Guadalajara, México.

Referencias: [1]Toro-Funes N et al. In vitro antioxidant activity of dietary polyamines. Food Research Internat. 2013. [2]Hornero-Méndez D et al. A rapid spectrophotometric method for the determination of peroxide value in food lipids with high carotenoid content. JAOCS. 2001. [3]AOCS Official method Cd 19-90: 2-thiobarbituric acid value direct method. In Official methods and recommended practices of the American Oil Chemists' Society. American Oil Chemists' Society. Ed. Firestone: Champaign, Illinois. (1992, revised in 2001).

Campus de l'Alimentació INSA Institut de Recerca en Nutrició i Seguretat Alimentària XaRTA Catalonian Reference Network on Food Technology

¿Es comparable el contenido y perfil de poliaminas entre leche materna y fórmulas infantiles?

Nelly C. Muñoz-Esparza, Oriol Comas-Basté, Sonia Sánchez-Pérez, Salvador Hernández-Macías, M. Luz Latorre-Moratalla, M. Teresa Veciana-Nogués, M. Carmen Vidal-Carou

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Introducción

Las poliaminas espermina, espermidina y putrescina son sustancias policatiónicas de bajo peso molecular, a las que se les atribuye un papel indispensable en la estimulación del crecimiento y diferenciación celular, así como en la proliferación y maduración intestinal del recién nacido. También intervienen en la diferenciación de células inmunes y en la regulación de la respuesta inflamatoria, que confiere protección al lactante contra infecciones y alergias. La leche materna es la primera fuente exógena de poliaminas en el ser humano.

Objetivo

Estudiar y comparar el contenido y perfil de poliaminas en la leche materna y en fórmulas infantiles.

Metodología

Se determinaron los contenidos de poliaminas en muestras de leche materna (n=12) y de fórmulas infantiles (n=11) mediante cromatografía liquida de ultra eficacia y detección-fluorimétrica (UHPLC-FL) por el método descrito en Latorre-Moratalla y col.(2009).

Resultados

El contenido total de poliaminas en las diferentes muestras de leche materna fue muy variable, con valores que oscilaron desde los 200 nmol/dL a los 1000 nmol/dL (Figura 1). En todas ellas se encontró espermina y espermidina, con un valor medio de 331 ±116 nmol/dL y 242.9 ±159 nmol/dL, respectivamente. La putrescina se detectó únicamente en dos muestras y en contenidos mucho más bajos (8.2±19 nmol/dL).

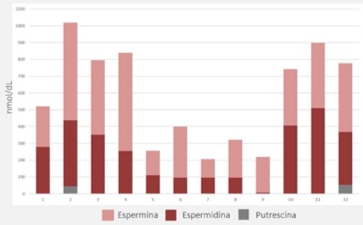

Figura 1. Contenido de poliaminas en la leche materna

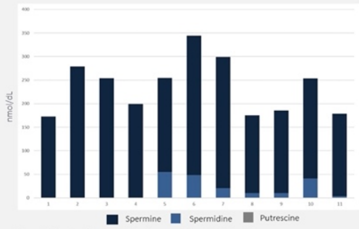

Figura 2. Contenido de poliaminas en fórmulas infantiles

En las fórmulas infantiles la espermina fue la poliamina mayoritaria (200 ±79 nmol/dL), seguida de espermidina (16 ±21 nmol/dL) mientras que la putrescina no se detectó (Figura 2).

El contenido de poliaminas fue significativamente mayor ($p < 0.05$) en la leche materna que en la fórmula infantil (Figura 3).

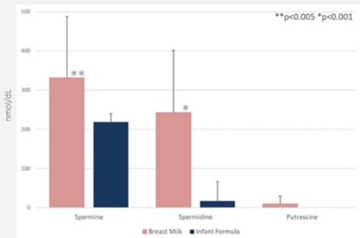

Figura 3. Contenidos medios de poliaminas en fórmulas infantiles

Conclusión

A pesar de la variabilidad encontrada, el contenido de poliaminas fue significativamente mayor en la leche materna. Es necesario estudiar con más detalle la posible influencia de diferentes factores, como la fase de lactancia, en el contenido de poliaminas de la leche materna. Además, teniendo en cuenta la importancia de las poliaminas en las primeras etapas de la vida, los resultados ponen de manifiesto la necesidad de mejorar la formulación de las leches infantiles aumentando su contenido en poliaminas.

Agradecimientos: Nelly C. Muñoz-Esparza es becaria de la Universidad de Guadalajara, México.
Referencias: Latorre-Moratalla. M. y col. 2009. J. Chrom A, 1216 7715–7720

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CONTENIDOS Y EVOLUCIÓN DE POLIAMINAS EN LECHE MATERNA DURANTE EL PRIMER SEMESTRE DE LACTANCIA

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Antecedentes y Objetivo

Las poliaminas son compuestos nitrogenados de bajo peso molecular que participan en diversos procesos biológicos, como por ejemplo, en la proliferación y diferenciación celular y en la síntesis de proteínas. Además, en el recién nacido tienen un papel esencial en la maduración intestinal y desarrollo del sistema inmunológico. La leche materna es la primera fuente exógena de poliaminas y su contenido puede variar en función de factores relacionados tanto con la lactancia como con la díada madre-hijo. El objetivo de este estudio fue evaluar el contenido y evolución de las poliaminas en la leche de madres lactantes durante el primer semestre de lactancia.

Metodología

- Se siguió una cohorte de 83 madres hasta los cuatro meses de lactancia que dieron a luz a un bebe sano y a término en el Nuevo Hospital Civil de Guadalajara (México). Además, también se siguió a un subgrupo de 33 madres hasta el sexto mes de lactancia materna.
- Se recolectaron muestras de leche materna al inicio y final de la toma a los dos, cuatro y seis meses de lactancia.
- La determinación de putrescina, espermidina y espermina se realizó mediante cromatografía líquida de ultra eficacia y detección-fluorimétrica (UHPLC-FL) de acuerdo al método descrito por Latorre-Moratalla et al. (2009).

Resultados

El contenido de poliaminas encontrado en la leche procedente de las diferentes madres fue muy variable, con contenidos totales que oscilaron entre los 45–1575 nmol/dL. Además, las concentraciones totales de poliaminas fueron siempre más altas en la leche obtenida al final de la toma con respecto a la inicial ($p<0.001$). En cuanto a la evolución a lo largo de la lactancia, los niveles totales de poliaminas tendieron a disminuir, con contenidos un 25% más bajos a los seis meses ($p<0.05$).

La espermidina y la espermina estuvieron presentes en todas las muestras de leche y en contenidos muy similares, con un ratio de 1.1. La putrescina se encontró siempre en niveles mucho más bajos que las otras dos poliaminas.

Tal como se puede observar en las Figuras 1A y 1B, la concentración de putrescina, espermidina y espermina fue siempre mayor en la leche obtenida al final de la toma que en la del inicio, con un incremento medio del 50%, 73% y 97%, respectivamente ($p<0.001$).

Durante el primer semestre de lactancia, los contenidos de putrescina se mantuvieron constantes, mientras que los niveles de espermidina y espermina tendieron a disminuir (Figura 1B). Concretamente, en la leche obtenida al inicio de la toma, los niveles de espermidina y espermina fueron significativamente menores a los cuatro y seis meses en comparación con los dos meses. En la leche final, solo se observaron diferencias significativas entre los dos y seis meses de lactancia.

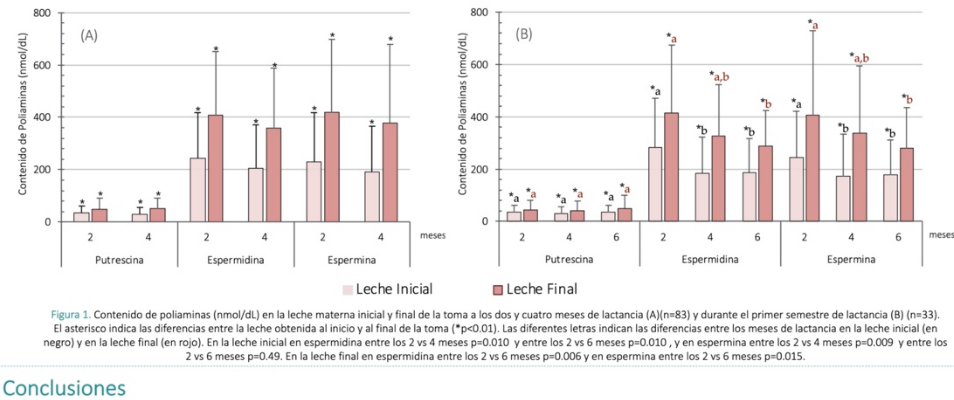

Figura 1. Contenido de poliaminas (nmol/dL) en la leche materna inicial y final de la toma a los dos y cuatro meses de lactancia (A)(n=83) y durante el primer semestre de lactancia (B) (n=33). El asterisco indica las diferencias entre la leche obtenida al inicio y al final de la toma (*p<0.01). Las diferentes letras indican las diferencias entre los meses de lactancia en la leche inicial (en negro) y en la leche final (en rojo). En la leche inicial en espermidina entre los 2 vs 4 meses p=0.010 y entre los 2 vs 6 meses p=0.010 , y en espermina entre los 2 vs 4 meses p=0.009 y entre los 2 vs 6 meses p=0.49. En la leche final en espermidina entre los 2 vs 6 meses p=0.006 y en espermina entre los 2 vs 6 meses p=0.015.

Conclusiones

Los contenidos de poliaminas en leche materna disminuyeron conforme avanzó la lactancia, concretamente los de espermidina y espermina. Esto podría explicarse por el mayor requerimiento de poliaminas del lactante durante los primeros meses a consecuencia de la elevada proliferación/diferenciación celular y síntesis de proteínas durante esta etapa. También se observó que los contenidos de poliaminas varían dentro de una misma toma, observándose contenidos significativamente más altos en la leche obtenida al final de la toma.

Agradecimientos: Nelly C. Muñoz-Esparza es becaria de la Universidad de Guadalajara, México.

Referencias: Latorre-Moratalla. M. y col. 2009. J. Chrom A, 1216 7715–7720.

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Cita bibliográfica sugerida

Muñoz-Esparza N.C. (2021). Poliaminas en alimentos, leche materna y fórmulas infantiles. Tesis doctoral. Universidad de Barcelona, Barcelona.

Créditos

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