Chapter

Inflammatory Diseases and the Role of n-7 Unsaturated Fatty Acids as Functional Lipids

Akio Nakamura, Hikari Nakamura and Ritsuko Kawaharada

Abstract

With the increasing childbearing age, the number of mothers with diabetes and gestational diabetes is escalating. Maternal hyperglycemia creates an intrauterine hyperglycemic environment via the placenta, which causes signaling abnormalities in various fetal organs due to excessive glycation. This is associated with future disease development in the child. We have shown that insulin signaling defects are induced in fetal cardiomyoblasts using a rat gestational diabetes mellitus model and cellular models. Furthermore, we reported that maternal intake of eicosapentaenoic acid (EPA), an n-3 unsaturated fatty acid, during pregnancy can ameliorate this signaling defect. However, EPA has anti-coagulant effects, and the pollution of marine fish oil, the source for EPA supplements, raises concerns about active intake by pregnant women. Recently, palmitoleic acid, an n-7 unsaturated fatty acid, garnered attention as a candidate functional lipid alternative to EPA because it has been reported to have anti-obesity, lipid metabolism improvement, and cardioprotective effects similar to those of EPA. Palmitoleic acid has cis and trans structural isomers, which differ in their food intake route and metabolism in humans. This article introduces recent findings on the biological functions of palmitoleic acid in lifestyle-related diseases and cardiovascular diseases, ranging from basic research to clinical studies.

Keywords: dairy products, eicosapentaenoic acid, gestational diabetes mellitus, heart disease, hyperglycemia, intrauterine hyperglycemic environment, lipid metabolism, palmitic acid, palmitoleic acid, trans fatty acid

1. Introduction

Prenatal nutrition has a significant impact on the long-term health of the unborn child. In particular, the cardiovascular epidemiological studies by Barker et al. have shown that the intrauterine environment during pregnancy is closely related to the development of future lifestyle-related diseases [1–5]. Gluckman and Hanson proposed the Developmental Origins of Health and Disease hypothesis, which states that predisposition to lifestyle-related diseases is shaped by gene-environment interactions during fertilization, embryonic development, fetal life, and infancy, and that mismatches with the fetal environment after birth lead to the development of diabetes and hypertension [6, 7]. Many of these studies have suggested that a low-nutrition

environment in the womb during the fetal period increases the likelihood that the child will later suffer from lifestyle-related diseases, such as obesity, diabetes, and hypertension in the future [8–10].

In the post-World War II period, economically developed countries entered an era of global food satiation. Economic growth also changed people's lifestyles. These social conditions have been accompanied by an increase in late marriages, an increase in maternal obesity, an increase in maternal age, an increase in the incidence of gestational diabetes mellitus (GDM), and an increase in pregnant women with type 2 diabetes. The nutritional environment of pregnant women has increasingly become overnourished rather than undernourished [11–13]. The fetus of a pregnant woman with such an abnormal glucose metabolism is exposed to an intrauterine hyperglycemic environment, through the umbilical cord, due to maternal hyperglycemia. As a result, neonatal complications, such as gigantism, hypoxia, respiratory disorders, congenital malformations, and myocardial hypertrophy, have been reported in children born to diabetic pregnant women [14–18]. However, the molecular mechanisms by which this intrauterine hyperglycemic environment during the fetal period contributes to the future health and disease development of the child after birth are not well understood. We are conducting basic research using animal and cellular models to elucidate the underlying molecular mechanisms and to search for foods that show diabetes-preventive effects in pregnant women. In this chapter, we present recent findings on functional lipids that may prevent cardiac disease in children born to diabetic mothers.

2. Fetal heart in an intrauterine hyperglycemic environment

We created a GDM model rat by administering streptozotocin into the tail vein of Wistar rats on gestation day 2. To determine the effects of a high-fat diet during pregnancy on the infants, we fed the GDM model rats a high-fat lard diet containing saturated fatty acids and a control diet [19]. The stillbirth rate of GDM model rats fed a high-fat lard diet was significantly higher than that of GDM model rats fed a control diet [19]. Palmitic acid loading in lard has been reported to cause inflammation and cardiomyocyte dysfunction in animal- and cellular-level experiments [20–25]. The GDM rat study suggested that not only was the fetus exposed to intrauterine hyperglycemia, but that the mother's intake of palmitic acid from a high-fat lard diet during gestation may have further impaired cardiac function in the offspring [19].

Based on reports that fish oil has a positive effect on cardiovascular disease [26, 27], we fed GDM model rats a high-fat fish oil diet, a high-fat lard diet, and a control diet and analyzed the nutrient signals from the hearts of the infants. We found that the lard-fed GDM model rat offspring had decreased phosphorylation levels of Akt, which is important for sugar uptake [28]. However, when mothers were fed fish oil during pregnancy, the Akt phosphorylation level was increased, and insulin signaling was improved in the hearts of GDM model rat offspring [28]. The biological functional components in fish oil may have ameliorated the signaling impairment caused by hyperglycemia and palmitic acid loading.

We isolated primary cardiomyoblasts from the hearts of rat infants and established a cellular model of a hyperglycemic environment by elevating the glucose concentration in the medium to address two questions: Why was insulin signaling abnormal in the hearts of GDM model rat offspring, and what components of fish oil ameliorated this signaling abnormality? We focused on eicosapentaenoic acid (C20:5n-3: EPA),

which is abundant in fish oil and has known cardiovascular protective effects [29–33]. We orally administered EPA to GDM model rats during gestation and analyzed neonatal primary cardiomyoblasts isolated from the offspring. The results showed that insulin signaling was inhibited in primary cardiomyoblasts of GDM model rat offspring and that insulin resistance had been induced in these rat infants [34].

However, insulin resistance was improved in the hearts of infants born to GDM model rat mothers that were orally administered EPA [34]. Furthermore, in primary cardiomyocytes from neonatal rats exposed to an intrauterine hyperglycemic environment, intracellular reactive oxygen species (ROS) were chronically elevated, and excess advanced glycation end-products (AGEs) were observed, as compared with normal cells. AGE formation has recently attracted attention as a cause of aging and disease [35–40]. Furthermore, AGEs increase the expression of receptors for AGEs (RAGEs) and induce AGE-RAGE signaling. This signaling also increases the expression of genes encoding various inflammatory cytokines (IL-6, TNFα, NF-κB) via phosphorylation of Jun amino-terminal kinase (JNK).

These results indicated that the fetuses of GDM model rats are exposed to a hyperglycemic environment in utero, resulting in chronic inflammation by accumulating AGEs. However, feeding EPA to pregnant GDM model rats suppressed the production of AGEs and intracellular ROS in the offspring, resulting in the amelioration of signaling abnormalities [34]. Therefore, it is highly likely that EPA was responsible for the improvement of cardiac insulin signaling. In that regard, a summary is shown in **Figure 1**.

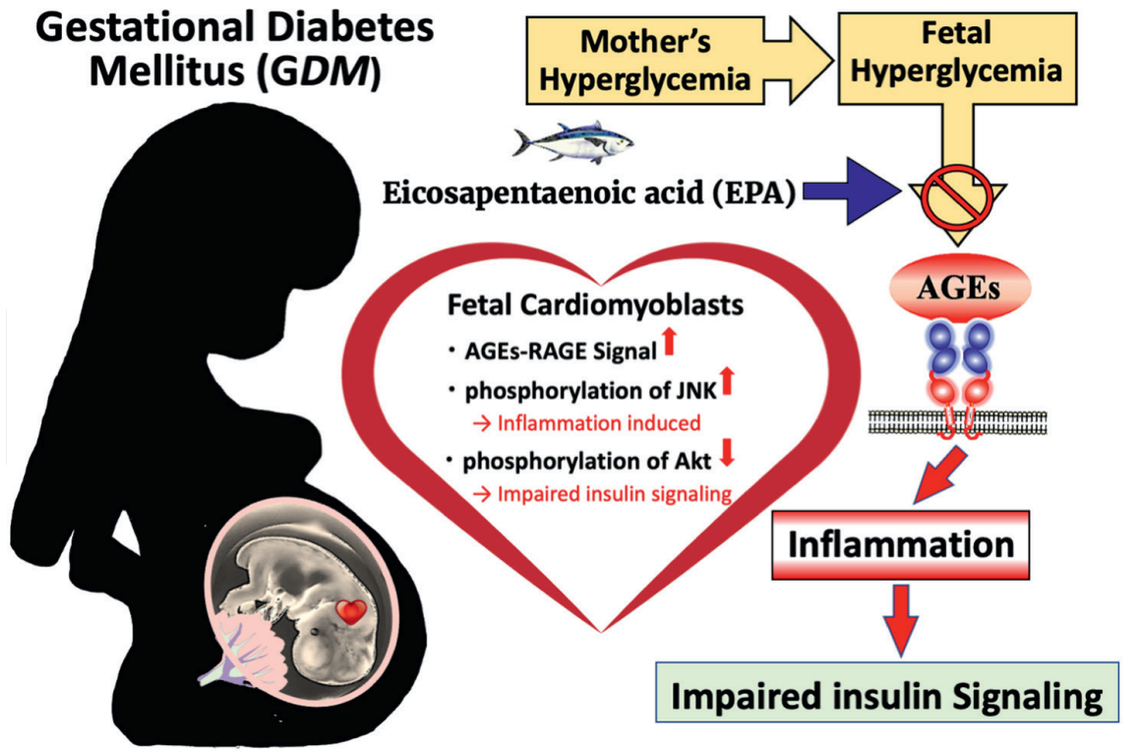

Figure 1.
Intrauterine hyperglycemia environment causes impaired signaling in the fetal heart. In gestational diabetes mellitus, maternal hyperglycemia creates a hyperglycemic intrauterine environment via the placenta. In this environment, advanced glycation end-products (AGEs) of proteins accumulate in fetal cardiomyoblasts, triggering inflammatory signals and impairing nutrient signaling by reactive oxygen species in the cells. Maternal intake of eicosapentaenoic acid (EPA), present in fish oil, during fetal life improves signaling by inhibiting formation of AGEs.

3. n-3 unsaturated fatty acid intake issues for pregnant women

Our experiments with the GDM rat model revealed that EPA improves the intrauterine hyperglycemic environment during pregnancy. EPA is one of the fatty acids transported from the mother to the fetus via the placenta [41, 42] and is a very important essential fatty acid for the fetus [43–45]. However, EPA is known to have anticoagulant and thromboprophylaxis effects [46–49]. Therefore, very high intakes or levels of EPA may cause health problems, such as hemorrhage, prolonged gestation, or premature delivery, and thus intakes in pregnant women are being examined from various perspectives [50, 51]. In addition, given marine pollution in many areas, EPA and DHA extracted from fish oil have been found to be contaminated with environmental contaminants, such as methylmercury and polychlorinated biphenyls, which are known to cause neurological disorders when ingested by pregnant women and which can adversely affect the fetus [45, 50–56]. Therefore, it is recommended that EPA derived from marine products with high methylmercury concentrations, such as tuna and swordfish, be avoided.

4. Palmitoleic acid as n-7 unsaturated fatty acid

Our research using GDM model rats revealed that intrauterine hyperglycemia causes chronic inflammation in cardiomyocytes and various organs during fetal development due to the oxidative stress caused by excessive AGEs and that this causes disease development in the offspring. It was also found that maternal intake of EPA, an n-3 unsaturated fatty acid, during the fetal period ameliorates this chronic inflammation. However, given the concerns about the intake of EPA by pregnant women in terms of a bleeding tendency during delivery, we have been searching for alternative food functional ingredients to replace EPA. Palmitoleic acid, an n-7 unsaturated fatty acid, has recently been suggested to improve type 2 diabetes and to have anti-inflammatory effects. It has been called a lipokine because of its versatile physiological functions [57, 58]. Here, we describe the physiological properties of palmitoleic acid as a functional lipid that has been elucidated to date.

Among the unsaturated fatty acids, palmitoleic acid (C16:1, n-7; also known as 9-hexadecenoic acid) is a fatty acid found in blood and tissues, particularly in the adipose tissue and liver [59], as well as in human milk [60]. Palmitoleic acid is an n-7 monounsaturated fatty acid that is also naturally present in plants and fish oils [61, 62]. The classification of unsaturated fatty acids and the position of n-7 monounsaturated fatty acids are shown in **Figures 2** and **3**. In the human body, palmitoleic acid exists as cis and trans isomers. Cis-palmitoleic acid (cis-C16:1n-7, CPA) is synthesized from palmitic acid (C16:0), a saturated fatty acid produced in the body, in addition to normal dietary intake), which is synthesized mainly in the liver by stearoyl-CoA desaturase 1 (SCD1) (Δ9 desaturase) and is incorporated into triglycerides and other products. A portion is further converted to cis-vaccenic acid (cis-C18:1n-7) by an elongase-mediated elongation reaction [63]. Trans-palmitoleic acid (trans-C16:1n-7, TPA) is not biosynthesized from saturated fatty acids in the body and is mainly derived from trans fatty acids found in dairy and in ruminants [64, 65]. Ruminant trans-vaccenic acid (trans-C18:1n-7) is also biosynthesized endogenously in the human body by a chain-shortening reaction [66]. The metabolism of CPA and TPA as palmitoleic acid in the body is shown in **Figure 2**. Fish oil and macadamia nut oil

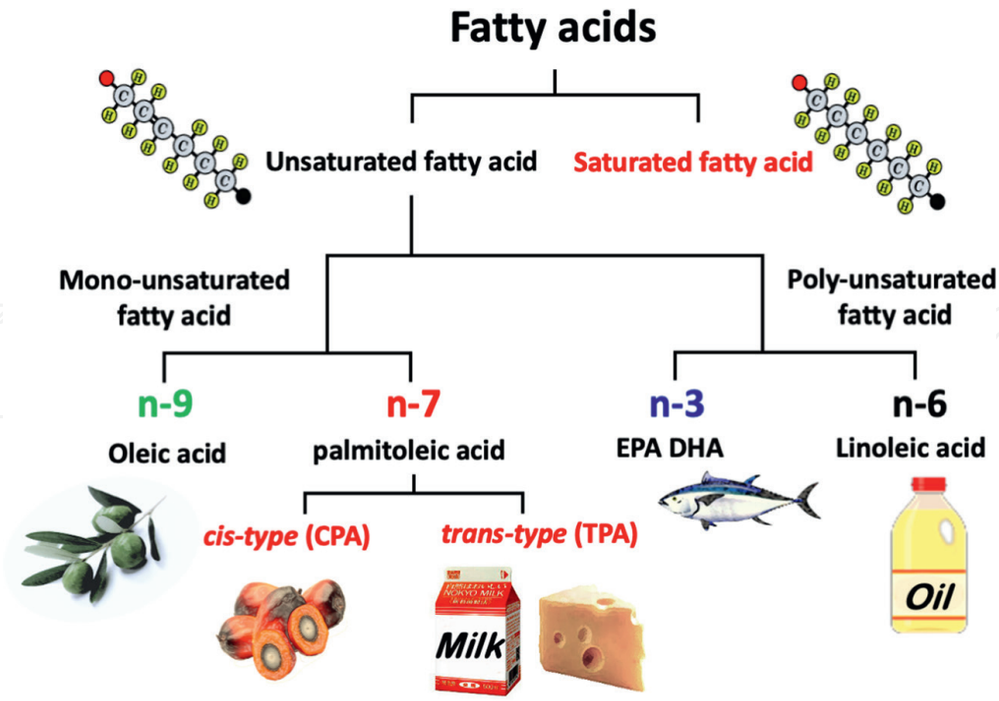

Figure 2.
Classification of fatty acids. Fatty acids are broadly classified into unsaturated and saturated fatty acids, depending on whether the molecule contains or does not contain double bonds between the carbons. Saturated fatty acids are abundant in meat and milk and include palmitic acid (16:0) and stearic acid (18:0). Unsaturated fatty acids are further classified into monounsaturated fatty acids, which have one double bond, and polyunsaturated fatty acids, which contain two or more double bonds. Among monounsaturated fats, oleic acid (18:1), found in olive oil, which has one double bond on the ninth carbon in the chain, is termed an n-9 unsaturated fatty acid. Palmitoleic acid (16:1), a fatty acid with one double bond on the seventh carbon, is referred to as an n-7 unsaturated fatty acid. Palmitoleic acid is further classified into two structural isomers: cis-type palmitoleic acid (CPA), which is abundant in meat fats and oils and in sea buckthorn fruit oil; and trans-type palmitoleic acid (TPA), which is found in milk and dairy products. Polyunsaturated fatty acids include eicosapentaenoic acid (20:5, EPA) and docosahexaenoic acid (20:6, DHA), which are found in fish oil, with the first double bond found on the third carbon from the methyl terminal of the carbon chain. Linoleic acid (18:2), a polyunsaturated fatty acid abundant in plant oil, has its first double bond on the sixth carbon from the methyl end of the carbon chain.

are dietary sources with higher amounts of CPA than other vegetable oils [67–69]. In addition, the oil of the fruit of sea buckthorn (*Hippophae rhamnoides L.*), which is widely grown in Asia, Europe, and Canada, contains about 40% palmitoleic acid [70, 71]. TPA is found in full-fat dairy products, and plasma concentrations of TPA correlate with the intake of full-fat dairy products and butter [72, 73]. Presumably, TPA is typically obtained by ingesting full-fat dairy products. Palmitoleic acid derived from food and its metabolism in the body are shown in **Figure 4**.

5. Palmitoleic acid as a functional lipid

In humans, palmitoleic acid is abundant in the muscle, liver, and adipose tissue, although the content of palmitoleic acid in the adipose tissue decreases with age [74, 75]. Cis-palmitoleic acid, an adipose-derived lipid hormone (lipokine), is intrinsically synthesized by SCD-1 in adipocytes through palmitic acid and acts in the liver and skeletal muscle to improve insulin sensitivity and metabolism in animal models [58, 76]. In addition, circulating levels of palmitoleic acid in humans are strongly correlated with insulin action [77]. Interestingly, the peroxisome proliferator-activated

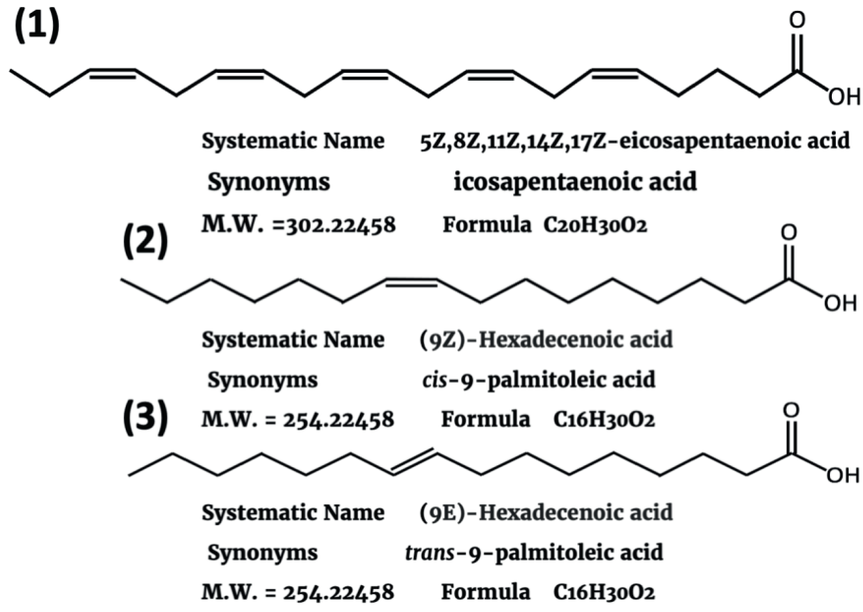

Figure 3.
Structural formulas for three functional lipids. (1) Eicosapentaenoic acid (EPA), an n-3 unsaturated fatty acid. (2) Cis-palmitoleic acid (CPA), an n-7 unsaturated fatty acid. (3) trans palmitoleic acid (TPA), an n-7 unsaturated fatty acid.

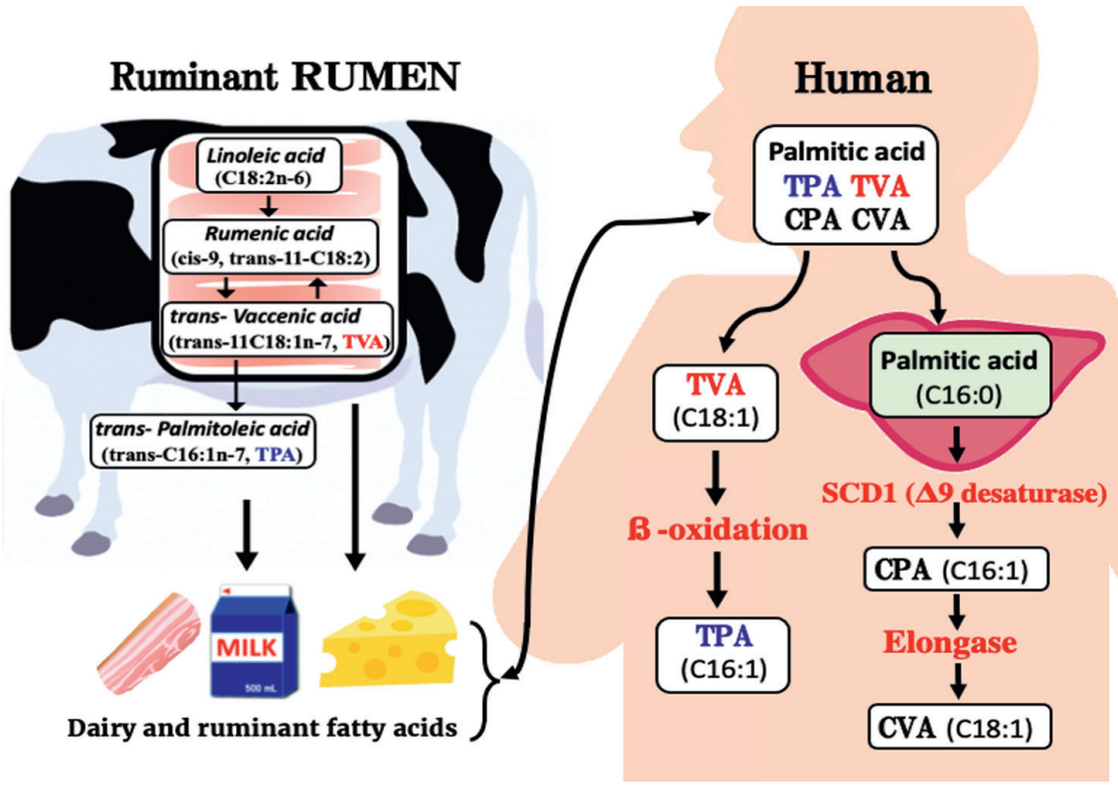

Figure 4.
Palmitoleic acid as a food and its metabolism in the human body. Palmitoleic acid (CPA) and trans-palmitoleic acid (TPA) have different routes of intake and metabolism in the body. In the human body, a double bond is introduced into palmitic acid, which is biosynthesized via de novo fatty acid synthesis in the liver and other organs, by SCD1 to form CPA. TPA cannot be biosynthesized in the human body and can only be obtained from milk and dairy products of ruminant origin. In ruminants, the gut bacteria biosynthesize conjugated linoleic acid, rumenic acid, from linoleic acid and store it as trans-vaccenic acid (TVA) in the body's adipose tissue, etc. TVA is further converted to TPA in the mammary gland and secreted into ruminant milk. Another route for obtaining TPA is through ingestion of TVA in the fat of pork and beef, which is partially converted to TPA by β-oxidation in the human body.

receptors (PPARs) are nuclear receptors that regulate DNA transcription, and three types are known: PPARα, PPARγ, and PPARδ. The oral administration of palmitoleic acid has been shown to suppress feeding by increasing cholecystokinin levels without involving this PPARα pathway [78]; moreover, it decreases phosphorylation of NF-κB p65 in mouse liver macrophages and inhibits the expression of inflammatory cytokines [79]. Palmitoleic acid also suppresses gene expression of palmitin-induced inflammatory cytokines via AMP-activated protein kinase, indicating a mechanism by which it exerts an anti-inflammatory effect [80]. Topical administration of palmitoleic acid has been reported to heal wounds due to its anti-inflammatory effects [81]. In humans, an association between dietary-derived and blood palmitoleic acid levels and a decreased incidence of diabetes, risk of cardiovascular disease, and inflammatory status have been suggested [77, 82, 83]. Thus, palmitoleic acid is thought to have an inhibitory effect on the development of diabetes by improving insulin resistance and increasing pancreatic beta cell proliferation and insulin secretion in animal and cellular models [84–89].

Thus, in summary, many studies have shown that palmitoleic acid, as a functional lipid, is effective in preventing the onset of lifestyle-related diseases and has anti-inflammatory, anti-diabetic, and anti-obesity effects. Palmitoleic acid has two structural isomers: the cis-type CPA and the trans-type TPA. The former is biosynthesized from palmitic acid, a saturated fatty acid that causes inflammation and organ stress in skeletal and cardiac muscle, by introducing double bonds and chain-elongation reactions, while the latter cannot be synthesized in the human body and is derived from dietary fatty acids found in meat and milk of ruminant origin (**Figure 4**).

Little research has been done on the differential effects of the CPA and TPA isomers on biological functions. Recently, we found that high-glucose-exposed myoblasts show increased phosphorylation levels of MAPK/ERK1/2, ROS production, and inflammatory signals; however, their treatment with TPA and EPA suppressed both ROS production and inflammation. In contrast, the opposite was found with a CPA treatment, which increased ROS production and demonstrated higher cytotoxicity than TPA [90]. Thus, CPA and TPA are functional lipids that may affect the organism differently.

Recently, an increasing number of clinical studies have focused on TPA derived from dairy products. In the Cardiovascular Health Study, a large prospective cohort study in the United States, it was found that older adults with a higher percentage of TPA in their blood total fat content had lower insulin resistance and a significantly lower incidence of type 2 diabetes [91]. The Multi-Ethnic Study of Atherosclerosis (MESA) found that TPA in blood was associated with elevated LDL cholesterol, but reduced triglycerides, fasting insulin, blood pressure, and diabetes incidence [92]. Two cohort studies, the Nurses' Health Study and the Health Professionals Follow-Up Study, of 3333 adults without diabetes aged 30–75 years, found that higher plasma milk-derived TPA levels were associated with a lower risk of developing diabetes mellitus [93]. In a meta-analysis examining the association of saturated and trans-unsaturated fat intake with all-cause mortality, cardiovascular disease, coronary heart disease, ischemic stroke, and type 2 diabetes, TPA intake from a ruminant-derived diet was inversely associated with type 2 diabetes [94]. Another study showed that, as a potential biomarker of milk fat intake, high levels of TPA in circulating blood or adipose tissue were associated with a lower risk of developing type 2 diabetes [95].

In a nonclinical basic research study using db/db mice, TPA was shown to ameliorate hypercholesterolemia by reducing serum cholesterol, low-density lipoprotein,

high-density lipoprotein, and hepatic free cholesterol levels, while CPA had none of these effects [96]. TPA also inhibited cholesterol absorption from the intestinal tract by markedly reducing the expression of intestinal Niemann-Pick C1-like 1 protein. However, histological examination of the liver showed that CPA more effectively ameliorated hepatic lipidosis than did TPA. These results suggest that TPA and CPA may prevent hypercholesterolemia by different mechanisms [96]. In a mouse model of diet-induced obesity, TPA prevented weight gain caused by a high-fat diet, reduced visceral adipose tissue weight and adipocyte size, and increased expression of lipolysis-related genes [97]. In vascular endothelial cells and hepatocytes, TPA reduced TNF-α-induced inflammation [98], and in experiments with β-cell lines, TPA and the branched-chain fatty acid 15-methylhexadecanoic acid (iso 17:0) increased PPARγ activity by about two fold and enhanced β-cell function, thereby improving insulin resistance. TPA has been reported to improve insulin resistance by increasing β-cell function [99]. Palmitic acid and CPA decreased hepatocyte viability at concentrations above 1 mM, whereas TPA treatment had a cell proliferative effect: TPA had a beneficial effect on hepatocyte survival signals by activating sirtuin 1 and inducing PPARα activity [100].

In the Ludwigshafen Risk and Cardiovascular Health (LURIC) clinical study of the association between trans fatty acids and mortality, TPA was associated with a reduced risk of death due to cardiovascular causes, but this effect was not observed with industrially produced hydrogenated fats and oils [101]. The effects of palmitoleic acid were examined using isoproterenol-induced myocardial damage model mice and primary mouse cardiomyocytes, and the results showed that palmitoleic acid may have a protective effect against cardiac fibrosis and inflammation by regulating PPAR-specific signaling pathways in the heart [102].

6. Conclusions

When a woman has diabetes during pregnancy, her hyperglycemia creates a hyperglycemic intrauterine environment for the fetus via the placenta. Exposure to this environment during the fetal period is closely related to the future development of cardiac and neurological diseases in the offspring. We have been conducting research to find food ingredients that reduce insulin resistance in pregnant women. While EPA has anti-diabetic effects, there are concerns about the active use of EPA in pregnant women due to its anticoagulant effect and due to the marine pollution of fish oil, which is a primary source of EPA supplementation. In this paper, we propose the use of palmitoleic acid, an n-7 unsaturated fatty acid, which has anti-obesity, lipid metabolism improving, and cardioprotective effects similar to those of EPA. Palmitoleic acid is classified into cis-type CPA and trans-type TPA. Further basic molecular studies are needed to clarify the differences in the mechanisms of action of these structural isomers. In particular, TPA has beneficial effects on the cardiovascular system. However, the intake of TPA, which is only marginally present in dairy products, must be carefully considered from a mother-child nutritional perspective, as excessive intake of dairy products by the mother may lead to over-nutrition and allergic reactions in the child. Recently, a synthesis that converts CPA, which is abundant in macadamia nut oil and sea buckthorn fruit oil, to TPA has been developed, and research on palmitoleic acid-producing bacteria is underway. Thus, it is expected that TPA will be available as an inexpensive, safe, and accessible supplement in the future.

Acknowledgements

We gratefully acknowledge the work of past and present members of our laboratory. This work was supported in part by the JSPS KAKENHI Grants (nos. 22 K 11882, 20 K11611, and 18 K11136 to AN and RK), the Dairy Products Health Science Council and Japan Dairy Association (to AN), and the Research Program of Jissen Women's University (to AN).

Conflict of interest

The authors declare no conflict of interest.

Author details

Akio Nakamura[1*], Hikari Nakamura[2] and Ritsuko Kawaharada[3]

1 Faculty of Human Life Sciences, Department of Molecular Nutrition, Jissen Women's University, Hino, Tokyo, Japan

2 Laboratory of Membrane Trafficking Mechanisms, Department of Integrative Life Sciences, Graduate School of Life Sciences, Tohoku University, Sendai, Japan

3 Department of Health and Nutrition, Takasaki University of Health and Welfare, Takasaki, Gunma, Japan

*Address all correspondence to: nakamura-akio@jissen.ac.jp

References

[1] Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986;**1**:1077-1081. DOI: 10.1016/s0140-6736(86)91340-1

[2] Barker DJ, Winter PD, Osmond C. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;**2**:577-580

[3] Barker DJ. The fetal and infant origins of adult disease. British Medical Journal. 1990;**30**:1111. DOI: 10.1136/bmj.301.6761.1111

[4] Barker DJ, Gluckman PD, Godfrey KM. Fetal nutrition and cardiovascular disease in adult life. Lancet. 1993;**341**:938-941. DOI: 10.1016/0140-6736(93)91224-a

[5] Barker DJ. The fetal and infant origins of disease. European Journal of Clinical Investigation. 1995;**25**(7):457-463. DOI: 10.1111/j.1365-2362.1995.tb01730.x

[6] Gluckman PD, Hanson MA. Living with the past:Evolution, development, and patterns of disease. Science. 2004;**305**:1733-1736. DOI: 10.1126/science.1095292

[7] Gluckman PD, Hanson MA. Developmental origins of disease paradigm:A mechanistic and evolutionary perspective. Pediatric Research. 2004;**56**:311-317. DOI: 10.1203/01.PDR.0000135998.08025.FB

[8] Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. International Journal of Epidemiology. 2012;**42**:1215-1222

[9] Arima Y, Fukuoka H. Developmental origins of health and disease theory in cardiology. Journal of Cardiology. 2020;**76**:14-17. DOI: 10.1016/j.jjcc.2020.02.003. Epub 2020 Feb 27

[10] Hoffman DJ, Powell TL, Barrett ES. Developmental origins of metabolic diseases. Physiological Reviews. 2021;**101**(3):739-795. DOI: 10.1152/physrev.00002.2020

[11] McAllister EJ, Dhurandhar NV, Keith SW. Ten putative contributors to the obesity epidemic. Critical Reviews in Food Science and Nutrition. 2009;**49**(10):868-913. DOI: 10.1080/10408390903372599

[12] Popkin BM. Global nutrition dynamics: The world is shifting rapidly toward a diet linked with noncommunicable diseases. The American Journal of Clinical Nutrition. 2006;**84**(2):289-298. DOI: 10.1093/ajcn/84.1.289

[13] Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. Obstetrics and Gynecology Clinics of North America. 2007;**34**(2):173-199, vii. DOI: 10.1016/j.ogc.2007.03.002

[14] Barnes-Powell LL. Infants of diabetic mothers: The effects of hyperglycemia on the fetus and neonate. Neonatal Network. 2007;**26**:283-290. DOI: 10.1891/0730-0832.26.5.283

[15] Kong L, Nilsson IAK, Gissler M. Associations of maternal diabetes and body mass index with offspring birth weight and prematurity. JAMA Pediatrics. 2019;**173**:371-378. DOI: 10.1001/jamapediatrics.2018.5541

[16] Clausen TD, Mathiesen ER, Hansen T. High prevalence of type 2 diabetes and pre-diabetes in adult

offspring of women with gestational diabetes mellitus or type 1 diabetes: The role of intrauterine hyperglycemia. Diabetes Care. 2008;**31**:340-346

[17] Ornoy A, Becker M, Weinstein-Fudim L. Diabetes during pregnancy: A maternal disease complicating the course of pregnancy with long-term deleterious effects on the offspring. A clinical review. International Journal of Molecular Sciences. 2021;**22**(6):2965. DOI: 10.3390/ijms22062965

[18] Choudhury AA, Devi RV. Gestational diabetes mellitus—A metabolic and reproductive disorder. Biomedicine and Pharmacotherapy. 2021;**143**:112183. DOI: 10.1016/j.biopha.2021.112183. Epub 2021 Sep 21

[19] Nasu R, Seki K, Nara M. Effect of a high-fat diet on diabetic mother rats and their offspring through three generations. Endocrine Journal. 2007;**54**:563-569. DOI: 10.1507/endocrj.k06-175

[20] Perdomo L, Beneit N, Otero YF. Protective role of oleic acid against cardiovascular insulin resistance and in the early and late cellular atherosclerotic process. Cardiovascular Diabetology. 2015;**14**:75. DOI: 10.1186/s12933-015-0237-9

[21] Kwon B, Lee HK, Querfurth HW. Oleate prevents palmitate-induced mitochondrial dysfunction, insulin resistance and inflammatory signaling inneuronal cells. Biochimica et Biophysica Acta. 2014;**1843**:1402-1413. DOI: 10.1016/j.bbamcr.2014.04.004

[22] Salvado L, Coll T, Gomez-Foix AM. Oleate prevents saturated-fatty-acid-induced ER stress, inflammation and insulin resistance in skeletal muscle cells through an AMPK-dependent mechanism. Diabetologia. 2013;**56**:1372-1382. DOI: 10.1007/s00125-013-2867-3

[23] Gao D, Griffiths HR, Bailey CJ. Oleate protects against palmitate-induced insulin resistance in L6 myotubes. British Journal of Nutrition. 2009;**102**:1557-1563. DOI: 10.1017/S0007114509990948

[24] Yang L, Guan G, Lei L. Oxidative and endoplasmic reticulum stresses are involved in palmitic acid-induced H9c2 cell apoptosis. Bioscience Reports. 2019;**39**(5):BSR20190225. DOI: 10.1042/BSR20190225

[25] Gui T, Li Y, Zhang S. Docosahexaenoic acid protects against palmitate-induced mitochondrial dysfunction in diabetic cardiomyopathy. Biomedicine and Pharmacotherapy;**128**:110306. DOI: 10.1016/j.biopha.2020.110306

[26] Park S, Park Y. Effects of dietary fish-oil and trans fat on rat aorta histopathology and cardiovascular risk markers. Nutrition Research and Practice. 2009;**3**:102-107. DOI: 10.4162/nrp.2009.3.2.102

[27] Kromhout D, Geleijnse JM, Goede J. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. Diabetes Care. 2011;**34**:2515-2520. DOI: 10.2337/dc11-0896

[28] Nasu-Kawaharada R, Nakamura A, Kakarla S. A maternal diet rich in fish oil may improve cardiac Akt-related signaling in the offspring of diabetic mother rats. Nutrition. 2013;**29**:688-692. DOI: 10.1016/j.nut.2012.11.017

[29] Watanabe T, Ando K, Daidoji H. CHERRY study investigators. A randomized controlled trial of eicosapentaenoic acid in patientswith

coronary heart disease on statins. Journal of Cardiology. 2017;**70**:537-544. DOI: 10.1016/j.jjcc.2017.07.007

[30] Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. Atherosclerosis. 2015;**242**:357-366. DOI: 10.1016/j.atherosclerosis.2015.07.035

[31] Cawood AL, Ding R, Napper FL. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis. 2010;**212**:252-259. DOI: 10.1016/j.atherosclerosis.2010.05.022

[32] Nishio R, Shinke T, Otake H. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. Atherosclerosis. 2014;**234**:114-119. DOI: 10.1016/j.atherosclerosis.2014.02.025

[33] Nosaka K, Miyoshi T, Iwamoto M. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. International Journal of Cardiology. 2017;**228**:173-179. DOI: 10.1016/j.ijcard.2016.11.105

[34] Kawaharada R, Masuda H, Chen Z. Intrauterine hyperglycemia-induced inflammatory signalling via the receptor for advanced glycation end products in the cardiac muscle of the infants of diabetic mother rats. European Journal of Nutrition. 2018;**57**:2701-2712. DOI: 10.1007/s00394-017-1536-6

[35] Qiu HY, Hou NN, Shi JF. Comprehensive overview of human serum albumin glycation in diabetes mellitus. World Journal of Diabetes. 2021;**12**:1057-1069. DOI: 10.4239/wjd.v12.i7.1057

[36] Hegab Z, Gibbons S, Neyses L. Role of advanced glycation end products in cardiovascular disease. World Journal of Cardiology. 2012;**4**:90-102. DOI: 10.4330/wjc.v4.i4.90

[37] Akhter F, Chen D, Akhter A. High dietary advanced glycation end products impair mitochondrial and cognitive function. Journal of Alzheimer's Disease. 2020;**76**:165-178. DOI: 10.3233/JAD-191236

[38] Nishad R, Tahaseen V, Kavvuri R. Advanced-glycation end-products induce podocyte injury and contribute to proteinuria. Frontiers in Medicine. 2021;**8**:685447. DOI: 10.3389/fmed.2021.685447

[39] Rungratanawanich W, Qu Y, Wang X. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. Experimental & Molecular Medicine. 2021;**53**:168-188. DOI: 10.1080/2162402X.2021.1874159

[40] Petriv N, Neubert L, Vatashchuk M. Increase of -Dicarbonyls in liver and receptor for advanced glycation end products on immune cells are linked to nonalcoholic fatty liver disease and liver Cancer. Oncoimmunology. 2021;**10**:1874159. DOI: 10.1080/2162402X.2021.1874159

[41] Lewis RM, Childs CE, Calder PC. New perspectives on placental fatty acid transfer. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2018;**138**:24-29. DOI: 10.1016/j.plefa.2018.10.001

[42] Devarshi PP, Grant RW, Ikonte CJ. Maternal Omega-3 nutrition, placental transfer and fetal brain development in gestational diabetes and preeclampsia. Nutrients. 2019;**11**(5):1107. DOI: 10.3390/nu11051107

[43] Shrestha N, Sleep SL, Cuffe JSM. Role of omega-6 and omega-3 fatty acids in fetal programming. Clinical and Experimental Pharmacology and Physiology. 2020;**47**(5):907-915. DOI: 10.1111/1440-1681.13244

[44] Greenberg JA, Bell SJ, Ausdal WV. Omega-3 fatty acid supplementation during pregnancy. Reviews in Obstetrics and Gynecology. 2008;**1**(4):162-169

[45] Coletta JM, Bell SJ, Roman AS. Omega-3 fatty acids and pregnancy. Reviews in Obstetrics and Gynecology. 2010;**3**(4):163-171

[46] Golanski J, Szymanska P, Rozalski M. Effects of Omega-3 polyunsaturated fatty acids and their metabolites on Haemostasis-current perspectives in cardiovascular disease. International Journal of Molecular Sciences. 2021;**22**(5):2394. DOI: 10.3390/ijms22052394

[47] Larson MK, Tormoen GW, Weaver LJ. Exogenous modification of platelet membranes with the omega-3 fatty acids EPA and DHA reduces platelet procoagulant activity and thrombus formation. American Journal of Physiology. 2013;**304**(3):C273-C279. DOI: 10.1152/ajpcell.00174.2012

[48] McEwen B, Morel-Kopp MC, Tofler G. The effect of Omega-3 polyunsaturated fatty acids on fibrin and thrombin generation in healthy subjects and subjects with cardiovascular disease. Seminars in Thrombosis and Hemostasis. 2015;**41**:315-322. DOI: 10.1055/s-0034-1395352

[49] Yokoyama M, Origasa H, Matsuzaki M. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis.; Japan EPA lipid intervention study (JELIS) investigators. Lancet. 2007;**369**(9567):1090-1098. DOI: 10.1016/S0140-6736(07)60527-3

[50] Schacky CV. Omega-3 fatty acids in pregnancy-the case for a target Omega-3 index. Nutrients. 2020;**12**(4):898. DOI: 10.3390/nu12040898

[51] Simmonds LA, Sullivan TR, Skubisz M. Omega-3 fatty acid supplementation in pregnancy-baseline omega-3 status and early preterm birth: Exploratory analysis of a randomised controlled trial. BJOG : An International Journal of Obstetrics and Gynaecology. 2020;**127**(8):975-981. DOI: 10.1111/1471-0528.16168

[52] Keating MH, Mahaffey KR, Schoemy R. Mercury study report to congress. In: Executive Summary. EPA-452/R-97-003. Vol. I. Washington DC: Environmental Protection Agency; 1997

[53] Yamaguchi N, Gazzard D, Scholey G. Concentrations and hazard assessment of PCBs, organochlorine pesticides and mercury in fish species from the upper Thames: River pollution and its potential effects on top predators. Chemosphere. 2003;**50**:265-273

[54] Guallar E, Sanz-Gallardo MI, Veer P. Mercury, fish oils, and the risk of myocardial infarction. The New England Journal of Medicine. 2002;**347**:1747-1754

[55] Virtanen JK, Voutilainen S, Rissanen TH. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. Arteriosclerosis,

Thrombosis, and Vascular Biology. 2005;**25**:228-233. DOI: 10.1161/01.ATV.0000150040.20950.61

[56] Sacks D, Baxter B, Campbell BCV. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. International Journal of Stroke. 2018;**13**(6):612-632. DOI: 10.1177/1747493018778713

[57] Yang ZH, Miyahara H, Hatanaka A. Chronic administration of palmitoleic acid reduces insulin resistance and hepatic lipid accumulation in KK-Ay Mice with genetic type 2 diabetes. Lipids in Health and Disease. 2011;**10**:120. DOI: 10.1186/1476-511X-10-120

[58] Cao H, Gerhold K, Mayers JR. Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. Cell. 2008;**134**:933-944. DOI: 10.1016/j.cell.2008.07.048

[59] Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Progress in Lipid Research. 2008;**47**(5):348-380. DOI: 10.1016/j.plipres.2008.03.003

[60] Ogunleye A, Fakoya AT, Niizeki S. Fatty acid composition of breast milk from Nigerian and Japanese women. Journal of Nutritional Science and Vitaminology. 1991;**37**(4):435-442. DOI: 10.3177/jnsv.37.435

[61] Yang B, Kallio HP. Fatty acid composition of lipids in sea buckthorn (Hippophaë rhamnoides L.) berries of different origins. Journal of Agricultural and Food Chemistry. 2001;**49**(4):1939-1947. DOI: 10.1021/jf001059s

[62] Fard AM, Turner AG, Willett GD. High-resolution electrospray-ionization fourier-transform ion cyclotron resonance and gas chromatography-mass spectrometry of macadamia nut oil. Australian Journal of Chemistry. 2003;**56**(5):499-508. DOI: 10.1071/CH03038

[63] Gong J, Campos H, McGarvey S. Adipose tissue palmitoleic acid and obesity in humans: Does it behaveas a lipokine? The American Journal of Clinical Nutrition. 2011;**93**:186-191

[64] Guillocheau E, Garcia C, Drouin G. Retroconversion of dietary trans-vaccenic (trans-C18:1 n-7) acid to trans-palmitoleic acid (trans-C16:1 n-7): Proof of concept and quantification in both cultured rat hepatocytes and pregnant rats. The Journal of Nutritional Biochemistry. 2019;**63**:19-26. DOI: 10.1016/j.jnutbio.2018.09.010

[65] Destaillats F, Wolff RL, Precht D. Study of individual trans- and cis-16:1 isomers in cow, goat, and ewe cheese fats by gas-liquid chromatography with emphasis on the trans-delta3 isomer. Journal of Lipids. 2000;**35**:1027-1032. DOI: 10.1007/s11745-000-0614-y

[66] Jaudszus A, Kramer R, Pfeuffer M. Trans-Palmitoleic acid arises endogenously from dietary vaccenic acid. The American Journal of Clinical Nutrition. 2014;**99**:431-435. DOI: 10.3945/ajcn.113.076117

[67] Garg ML, Blake RJ, Wills RB. Macadamia nut consumption lowers plasma total and LDL cholesterol levels in hypercholesterolemic men. Journal of Nutrition. 2003;**133**(4):1060-1063. DOI: 10.1093/jn/133.4.1060

[68] Maguire LS, O'Sullivan SM, Galvin K. Fatty acid profile, tocopherol, squalene and phytosterol content of walnuts, almonds, peanuts, hazelnuts and the macadamia nut. International Journal of Food Sciences

and Nutrition. 2004;**55**(3):171-178. DOI: 10.1080/09637480410001725175

[69] Borompichaichartkul C, Luengsode K, Chinprahast N. Improving quality of Macadamia nut (Macadamia integrifolia) through the use of hybrid drying. Journal of Food Process Engineering. 2009;**93**:348-353. DOI: 10.1016/j.jfoodeng.2009.01.035

[70] Fatima T, Snyder CL, Schroeder WR. Fatty acid composition of developing sea buckthorn (Hippophae rhamnoides L.) berry and the transcriptome of the mature seed. PLoS One. 2012;**7**(4):e34099. DOI: 10.1371/journal.pone.0034099

[71] Ciesarová Z, Murkovic M, Cejpek K. Why is sea buckthorn (Hippophae rhamnoides L.) so exceptional? A review. Food Research International. 2020;**133**:109170. DOI: 10.1016/j.foodres.2020.109170

[72] Micha R, King IB, Lemaitre RN. Food sources of individual plasma phospholipid trans fatty acid isomers: The cardiovascular health study. The American Journal of Clinical Nutrition. 2010;**91**:883-893. DOI: 10.3945/ajcn.2009.28877

[73] Pranger IG, Corpeleijn E, Muskiet FAJ. Circulating fatty acids as biomarkers of dairy fat intake: Data from the lifelines biobank and cohort study. Biomarkers. 2019;**24**:1-39. DOI: 10.1080/1354750X.2019.1583770

[74] McLaren DS, Ajans ZA, Awdeh Z. Composition of human adipose tissue, with special reference to site and age differences. American Journal of Clinical Nutrition. 1965;**17**:171-176. DOI: 10.1093/ajcn/17.3.171

[75] Pinnick KE, Neville MJ, Fielding BA. Gluteofemoral adipose tissue plays a major role in production of the lipokine palmitoleate in humans. Diabetes. 2012;**61**:1399-1403. DOI: 10.2337/db11-1810

[76] Souza CO, Teixeira AA, Lima EA. Palmitoleic acid (n-7) attenuates the immunometabolic disturbances caused by a high-fat diet independently of PPARα. Mediators of Inflammation. 2014;**2014**:582197. DOI: 10.1155/2014/582197

[77] Stefan N, Kantartzis K, Celebi N. Circulating palmitoleate strongly and independently predicts insulin sensitivity in humans. Diabetes Care. 2010;**33**:405-407. DOI: 10.2337/dc09-0544

[78] Yang ZH, Takeo J, Katayama M. Oral administration of omega-7 palmitoleic acid induces satiety and the release of appetite-related hormones in male rats. Appetite. 2013;**65**:1-7. DOI: 10.1016/j.appet.2013.01.009

[79] Guo X, Li H, Xu H. Palmitoleate induces hepatic steatosis but suppresses liver inflammatory response in mice. PLoS One. 2012;**7**:e39286. DOI: 10.1371/journal.pone.0039286

[80] Chan KL, Pillon NJ, Sivaloganathan DM. Journal of Biological Chemistry. 2015;**290**(27):16979-16988. DOI: 10.1074/jbc.M115.646992. Epub 2015 May 18

[81] Weimann E, Silva MBB, Murata GM, Bortolon JR, Dermargos A, Curi R, et al. Topical anti-inflammatory activity of Palmitoleic acid ImprovesWound healing. PLoS One. 2018;**13**:e0205338

[82] Bernstein AM, Roizen MF, Martinez L. Purified palmitoleic acid for the reduction of high-sensitivity C-reactive protein and serum lipids: A double-blinded, randomized, placebo

controlled study. Journal of Clinical Lipidology. 2014;**8**:612-617

[83] Morse N. Lipid-lowering and anti-inflammatory effects of Palmitoleic acid: Evidence from preclinical and epidemiological studies. Lipid Technology. 2015;**27**:107-111. DOI: 10.1002/lite.201500019

[84] Maedler K, Oberholzer J, Bucher P. Monounsaturated fatty acids prevent the deleterious effects of palmitate and high glucose on human pancreatic beta-cell turnover and function. Diabetes. 2003;**52**:726-733. DOI: 10.2337/diabetes.52.3.726

[85] Dimopoulos N, Watson M, Sakamoto K. Differential effects of palmitate and palmitoleate on insulin action and glucose utilization in rat L6 skeletal muscle cells. Biochemical Journal. 2006;**399**:473-481

[86] Welters HJ, Diakogiannaki E, Mordue JM. Differential protective effects of palmitoleic acid and cAMP on caspase activation and cell viability in pancreatic beta-cells exposed to palmitate. Apoptosis. 2006;**11**:1231-1238. DOI: 10.1007/s10495-006-7450-7

[87] Tsuchiya Y, Hatakeyama H, Emoto N. Palmitate-induced down-regulation of sortilin and impaired GLUT4 trafficking in C2C12 myotubes. Journal of Biological Chemistry. 2010;**285**:34371-34381

[88] Matthan NR, Dillard A, Lecker JL. Effects of dietary palmitoleic acid on plasma lipoprotein profile and aortic cholesterol accumulation are similar to those of other unsaturated fatty acids in the F1B golden Syrian hamster. Journal of Nutrition. 2009;**139**:215-221

[89] Morgan NG, Dhayal S. Unsaturated fatty acids as cytoprotective agents in the pancreatic β-cell. Prostaglandins Leukot. Essential Fatty Acid. 2010;**82**:231-236. DOI: 10.1016/j.plefa.2010.02.018

[90] Tokunaga Y, Yoshizaki H, Toriumi A. Effects of omega-7 palmitoleic acids on skeletal muscle differentiation in a hyperglycemic condition. The Journal of Veterinary Medical Science. 2021;**83**:1369-1377. DOI: 10.1292/jvms.21-0309. Epub 2021 Jul 12

[91] Mozaffarian D, Cao H, King IB. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults: A cohort study. Annals of Internal Medicine. 2010;**153**:790-799. DOI: 10.7326/0003-4819-153-12-201012210-00005

[92] Mozaffarian D, Oliveira OMC, Lemaitre RN. Trans-Palmitoleic acid, other dairy fat biomarkers, and incident diabetes: The multi-ethnic study of atherosclerosis (MESA). The American Journal of Clinical Nutrition. 2013;**97**:854-861

[93] Yakoob MY, Shi P, Willett WC. Circulating biomarkers of dairy fat and risk of incident diabetes mellitus among US men and women in two large prospective cohorts. Circulation. 2016;**133**:1645-1654. DOI: 10.1161/CIRCULATIONAHA.115.018410

[94] Souza RJ, Mente A, Maroleanu A. Anand intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: Systematic review and meta-analysis of observational studies. British Medical Journal. 2015;**351**:1-16. DOI: 10.1136/bmj.h3978

[95] Imamura F, Fretts AM, Marklund M. Fatty acid biomarkers of dairy fat consumption and incidence of type 2 diabetes: A pooled analysis of prospective cohort studies. PLoS Medicine. 2018;**15**:1-18. DOI: 10.1371/journal.pmed.1002670

[96] Huang WW, Hong BH, Bai KK. Cis- and trans-Palmitoleic acid isomers regulate cholesterol metabolism in different ways. Frontiers in Pharmacology. 2020;**11**:602115. DOI: 10.3389/fphar.2020.602115

[97] Chávaro-Ortiz LI, Tapia BD, Rico-Hidalgo M. Trans-palmitoleic acid reduces adiposity via increased lipolysis in a rodent model of diet-induced obesity. British Journal of Nutrition. 2022;**127**:801-809. DOI: 10.1017/S0007114521001501

[98] Da Silva MS, Julien P, Bilodeau J-F. Trans fatty acids suppress TNFα-induced inflammatory gene expression in endothelial (HUVEC) and hepatocellular carcinoma (HepG2) cells. Lipids. 2017;**52**:315-325. DOI: 10.1007/s11745-017-4243-4

[99] Kraft J, Jetton T, Satish B. Dairy-derived bioactive fatty acids improve pancreatic ß-cell function. FASEB Journal. 2015;**29**:608-625

[100] Farokh Nezhad R, Nourbakhsh M, Razzaghy-Azar M. The effect of trans-palmitoleic acid on cell viability and sirtuin 1 gene expression in hepatocytes and the activity of peroxisome-proliferator-activated receptor-alpha. Journal of Research in Medical Sciences. 2020;**25**:105. DOI: 10.4103/jrms.JRMS_16_20

[101] Kleber ME, Delgado GE, Lorkowski S. Trans-fatty acids and mortality in patients referred for coronary angiography: The Ludwigshafen risk and cardiovascular health study. European Heart Journal. 2016;**37**:1072-1078

[102] Betz IR, Qaiyumi SJ, Goeritzer M. Cardioprotective effects of Palmitoleic acid (C16:1n7) in a mouse model of catecholamine-induced cardiac damage are mediated by PPAR activation. International Journal of Molecular Sciences. 2021;**22**:12695. DOI: 10.3390/ijms222312695.doi: 10.1093/eurheartj/ehv446