UNIVERSIDAD DE SANTIAGO DE COMPOSTELA

LAS PRUEBAS DIAGNOSTICAS DESDE LA PERSPECTIVA POBLACIONAL: EPIDEMIOLOGIA DE LA ENFERMEDAD RENAL CRONICA Y LA RESISTENCIA A LA INSULINA

TESIS DOCTORAL

PILAR GAYOSO DIZ

Santiago de Compostela, Enero 2013

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FACULTAD DE MEDICINA

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LAS PRUEBAS DIAGNOSTICAS DESDE LA PERSPECTIVA POBLACIONAL: EPIDEMIOLOGIA DE LA ENFERMEDAD RENAL CRONICA Y LA RESISTENCIA A LA INSULINA

MEMORIA PARA OPTAR AL GRADO DE DOCTOR
PRESENTADA POR

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El Dr. Arturo González Quintela, catedrático de Medicina de la Facultad de Medicina de la Universidad de Santiago de Compostela, el Dr. Alfonso Otero González, jefe de servicio de Nefrología del Complexo Hospitalario Universitario de Ourense, y el Dr. Francisco Gude Sampedro, jefe de la Unidad de Epidemiologia Clínica del Hospital Clínico Universitario de Santiago de Compostela,

CERTIFICAN:

Que Pilar Gayoso Diz, licenciada en Medicina y Cirugía por la Universidad de Santiago de Compostela, ha realizado la presente Tesis Doctoral **LAS PRUEBAS DIAGNOSTICAS DESDE LA PERSPECTIVA POBLACIONAL**: **EPIDEMIOLOGIA DE LA ENFERMEDAD RENAL CRONICA Y LA RESISTENCIA A LA INSULINA** y que, a su juicio, reúne plenamente todos los requisitos necesarios para optar al **Grado de Doctor**, a cuyos efectos será presentada en la Universidad de Santiago de Compostela. El trabajo ha sido realizado bajo su dirección, autorizando su presentación ante el Tribunal Calificador.

Y para que así conste, se expide el presente certificado en Santiago de Compostela a 30 de enero de 2013.

Vº Bº de los Directores de la Tesis:

Dr. Arturo González Quintela	Dr. Alfonso Otero González	Dr. Francisco Gude Sampedro
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Sorprenderse es comenzar a entender.

José Ortega y Gasset

Las que conducen y arrastran al mundo no son las máquinas, sino las ideas.

Víctor Hugo

La alegría de ver y entender es el más perfecto don de la naturaleza.

Albert Einstein

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CLAVE DE ABREVIATURAS

Abreviaturas utilizadas en esta Tesis Doctoral relacionadas por orden alfabético:

ACR	Cociente albumina creatinina en orina (*Albumin creatinine ratio*)
AUC	Área bajo la curva (*área under curve*)
AP	Atención Primaria
CAP	Centro de Atención Primaria
CVRS	Calidad de vida relacionada con la salud
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ECV	Enfermedad Cardiovascular
ERC	Enfermedad Renal Crónica
ERCT	Enfermedad Renal Crónica Terminal
FG	Filtrado Glomerular
FRCV	Factores de Riesgo Cardiovascular
GAM	Modelos aditivos generalizados (*Generalized Aditive Models*)
GFR	Tasa de filtrado glomerular (*glomerular filtration rate*)
eGFR	Tasa de filtrado glomerular estimada (*estimated glomerular filtration rate*)
mGFR	Tasa de filtrado glomerular medida (*measured glomerular filtration rate*)
GPC	Guía de Práctica Clínica
HOMA-IR	Homeostasis Model Assesment of Insulin Resistance
HR	Cociente de riesgo instantáneo (*Hazard Ratio*)
IC 95%	Intervalo de Confianza al 95%
IMC	Índice de Masa Corporal
IR	Resistencia a la insulina (i*nsulin resistance*)
IRC	Insuficiencia Renal Crónica

KDOQI	Kidney Disease Outcomes Quality Initiative
MDRD	Modification of Diet in Renal Disease
NRI	Índice neto de reclasificación (*Net Reclassification Index*)
OR	Razón de prbabilidades (*Odds Ratio*)
ROC	curva ROC (Recieve Operating Characteristics)
SM	Síndrome Metabólico
TRS	Tratamiento Renal Sustitutivo

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I. ANTECEDENTES DEL TEMA

I.1 Marcadores biológicos como herramientas de clasificación y diagnostico

La utilización de biomarcadores como herramientas de diagnóstico y clasificación de pacientes es una situación habitual en clínica. Su adecuada utilización, e interpretación de resultados, condiciona no solo el diagnóstico sino también la decisión terapéutica y la valoración de efectividad de la intervención terapéutica elegida. Por tanto, una adecuada evaluación de cada prueba diagnóstica es de alta importancia en biomedicina.

I.1.1 Definición de marcador biológico

Biomarcador es un término introducido por primera vez en 1989 por el Medical Subject Heading (MESH). En 2001 el National Institutes of Health (NIH) estandarizó su definición como una característica ó parámetro biológico que puede ser objetivamente medido y evaluado como indicador de procesos biológicos normales, procesos patológicos ó de la respuesta farmacológica ante una intervención terapéutica (Biomarkers Definitions Working Group 2001).

Su estudio permite la realización de un diagnostico en fases tempranas de la enfermedad, una correcta clasificación del estado de la misma, la determinación del pronóstico de su evolución y el seguimiento de la respuesta a las actuaciones terapéuticas. En consecuencia pueden ser empleados con intención diagnóstica, pronostica ó de seguimiento. Una parte relevante de la actividad clínica está representada por la determinación e interpretación de biomarcadores para la toma de decisiones clínicas.

Ningún biomarcador puede por si mismo ofrecer una total y única respuesta al abanico de situaciones que se presentan en práctica clínica. Cuando se utilizan con finalidad tanto diagnóstica como pronóstica, los biomarcadores deben ser adecuadamente validados en el entorno clínico específico dónde serán empleados (Bonomini 2010).

I.1.2 Metodología de análisis de pruebas diagnosticas.

Las pruebas diagnosticas pueden emplearse en diferentes entornos ó con distintas finalidades. De manera general pueden distinguirse los siguientes escenarios (Pepe 2003):

- Clasificación.- identificar la presencia/ausencia de un proceso patológico determinado. El objetivo al analizar una prueba diagnóstica es comprobar un adecuado comportamiento en relación a un patrón de referencia que identifica adecuadamente el estado de presencia/ausencia del proceso patológico de interés.

- Pronóstico.- valorar la capacidad de una prueba diagnostica para clasificar en función de riesgo de eventos futuros a los sujetos en los que se aplica la prueba. Con frecuencia, considerando la multicausalidad presente en la mayoría de los procesos biológicos, esto requiere la consideración de otras variables que influyen en el riesgo de eventos, incorporadas, como covariables, en modelos multivariantes de predicción de riesgo. Kannel y cols. propusieron por primera vez en 1976 un modelo de predicción de riesgo cardiovascular a partir de los resultados del Estudio de Framingham (Kannel et al. 1976). En los últimos 20 años, se ha generalizado la utilización de algoritmos multivariantes de predicción de riesgo derivados de estos modelos.

Por otra parte, en términos generales puede considerarse que el análisis de pruebas diagnósticas engloba dos grandes aspectos complementarios entre si: estudio de la calibración y estudio de la capacidad de discriminación.

Calibración.- Término empleado para describir la precisión de una estimación, el grado en que una prueba diagnóstica produce los mismos resultados al aplicarse a la misma población. (Schmid & Griffith 1998)

En un biomarcador estudiado en fases iniciales frente a un patrón de referencia, su precisión depende de características del método de medida y/o del observador. Para su cuantificación en el caso de biomarcadores continuos habitualmente se emplea el intervalo de confianza al 95% (IC 95%) de la estimación puntual, el coeficiente de variación (CV), el coeficiente de correlación intraclase (CCI) ó métodos gráficos (como los propuestos por Bland y Altman). Por su parte, el índice kappa mide la variabilidad interobservador en el caso de biomarcadores de naturaleza categórica, en los que interviene la interpretación del observador.

En un modelo de predicción, su calibración describe cuanto se aproximan las probabilidades predichas por el modelo a los resultados encontrados. Se dice que un modelo de predicción está bien calibrado cuando los valores predichos se aproximan suficientemente a los realmente observados. Para medir la calibración de un modelo predictivo se utiliza habitualmente la prueba de bondad de ajuste de Hosmer-Lemeshow (versión de D'Agostino-Nam).(R. B. D'Agostino & Nam 2004)

La verificación de la calibración es un prerrequisito para estudiar la capacidad de discriminación (clasificación ó de estratificación de riesgo) de un biomarcador ó modelo diagnóstico. Por tanto su análisis debe acompañar siempre al estudio de utilidad diagnóstica.

Discriminación.- Se define como la capacidad de clasificación adecuada de los sujetos que presenta el biomarcador ó modelo de predicción que se estudia. Es la base de la utilidad diagnóstica de la prueba analizada. Se define también la

discriminación de una prueba diagnóstica como su capacidad para distinguir entre 2 ó más categorías de resultado.

Los principales métodos de análisis de la calibración y capacidad de discriminación de una prueba diagnóstica se resumen a continuación.

- Validez diagnóstica. Precisión y Fiabilidad:

Para definir los principales aspectos que caracterizan a un biomarcador se toma como referencia teórica el escenario de una prueba diagnóstica ó biomarcador dicotómico, con dos posibles resultados (positivo y negativo).

En este escenario, al contrastar los resultados obtenidos con el biomarcador a estudio respecto a los obtenidos con una prueba de referencia, patrón oro, en una misma población de sujetos, se recoge la correcta clasificación del biomarcador (resultados verdaderos positivos ,VP, y verdaderos negativos, VN) frente a la clasificación incorrecta (resultados falsos positivos, FP, y falsos negativos, FN). La siguiente tabla de contingencia refleja esta situación:

		PATRON ORO		
	RESULTADO	POSITIVO	NEGATIVO	
PRUEBA A ESTUDIO	POSITIVO	VP	FP	TPP
	NEGATIVO	FN	VN	TPN
		TVP	TVN	

En la tabla 1 se resumen las propiedades que caracterizan el comportamiento de un biomarcador como instrumento de clasificación entre estados en los diferentes escenarios diagnósticos: presencia/ausencia de un proceso patológico; establecimiento de la fase de severidad/afectación de una patología.

Tabla 1. Propiedades de un biomarcador diagnóstico.

Propiedad	Definición	Fórmula	Características
Sensibilidad	Probabilidad de resultado positivo de la prueba entre los enfermos	$\frac{VP}{TVP}$	Magnitud varia con la prevalencia ó probabilidad preprueba
Especificidad	Probabilidad de resultado negativo de la prueba entre los no enfermos	$\frac{VN}{TVN}$	Magnitud varia con la prevalencia ó probabilidad preprueba
Valor predictivo positivo (VPP)	Probabilidad de tener la enfermedad entre los resultados positivos de la prueba	$\frac{VP}{VP+FP}$	Magnitud varia con la prevalencia ó probabilidad preprueba
Valor predictivo negativo (VPN)	Probabilidad de no tener la enfermedad entre los resultados negativos de la prueba	$\frac{VN}{VN+FN}$	Magnitud varia con la prevalencia ó probabilidad preprueba
Cociente de probabilidad positivo, CP + **(Likelihood ratio, LR +)**	Probabilidad de que el resultado positivo se presente en un sujeto con la enfermedad de interés versus que el resultado positivo se presente en un sujeto sin la enfermedad de interés.	$\frac{sensibilidad}{1-especificidad}$	Magnitud independiente de la prevalencia (probabilidad preprueba). Permite calcular la probabilidad postprueba.
Cociente de probabilidad negativo, CP- **(Likelihood ratio, LR -)**	Probabilidad de que el resultado negativo se presente en un sujeto con la enfermedad de interés versus que el resultado negativo se presente en un sujeto sin la enfermedad de interés.	$\frac{1-sensibilidad}{especificidad}$	Magnitud independiente de la prevalencia (probabilidad preprueba). Permite calcular la probabilidad postprueba.
INDICADORES GLOBALES DE RENDIMIENTO			
Exactitud (Accuracy)	Proporción de sujetos clasificados correctamente.	$\frac{VP+VN}{VP+FP+VN+FN}$	Dependiente de la prevalencia ó probabilidad preprueba.
Índice de Youden		Sensibilidad+Especificidad -1	Transformación lineal de las medias de Sens. y Esp.
Odds Ratio Diagnostica, ORD(Glas et al. 2003)	Grado en que los resultados de una prueba diagnóstica coinciden con un patrón de referencia contrastado y objetivo.	$\frac{CP+}{CP-}$	Indica la capacidad de discriminación de una prueba diagnóstica. Uso en meta análisis. Valores entre 0 e ∞

- Curvas ROC

Cuando se analizan biomarcadores continuos, que toman valores a lo largo de un rango continuo, el estudio de la curva ROC (Reciever Operating Characteristics) es la metodología habitualmente empleada. En la curva ROC de un biomarcador continuo empleada con finalidad diagnostica, se representa la sensibilidad (proporción de verdaderos positivos) en función del complementario de la especificidad (proporción de falsos positivos) para todos los posibles resultados del biomarcador (J. A. Hanley 1982; McNeil 1984). Así definida la curva ROC, el área bajo la curva ó AUC (area under curve), calculada como la integral de la función que describe la curva ROC, representa la probabilidad de que ante dos sujetos uno enfermo y otro sano seleccionados al azar, la prueba los clasifique como enfermo y no enfermo respectivamente.

El AUC toma valores entre 1, correspondiente a una prueba perfecta con buena clasificación en todos los casos y 0.5 correspondiente a la situación de ausencia de capacidad de discriminación de la prueba, cuando la probabilidad de verdaderos positivos es igual a la de falsos positivos. El AUC puede también interpretarse como la sensibilidad media a lo largo de las posibles especificidades.

La aplicación tradicional de la curva ROC en el contexto de variables de resultado binarias (enfermedad presente/ausente) se ha extendido a los modelos con variables de resultado dependientes del tiempo y con covariables. El desarrollo de metodología para el análisis de curvas ROC con covariables permite el análisis del impacto que otras características del paciente (tales como edad, sexo ó características clínicas) puede tener sobre el comportamiento del biomarcador, tanto en clasificación como en predicción. (Janes & Pepe 2009)

En estos modelos el estadístico c representa el concepto de AUC y cuantifica de forma adecuada la capacidad de discriminación del modelo.

Además la curva ROC permite tanto la comparación entre dos pruebas diagnósticas mediante la comparación de los AUC respectivos; como la selección del mejor punto de corte, definido como el valor que optimiza el rendimiento de la prueba para separar a afectados de no afectados (J. A. Hanley 1983). La determinación de puntos de corte óptimos debe incorporar consideraciones sobre la razón daño-beneficio de la prueba diagnostica y del entorno en que se aplicara. La razón daño-beneficio define el peso relativo de las decisiones falso-positivas frente a las verdadero-positivas. Si se asume que el daño por un tratamiento innecesario (decisión falso positivo) es limitado, el punto de corte podría ser un valor que permita identificar todos los afectos, alta sensibilidad, junto a una elevada tasa de falsos positivos; por el contrario, si el tratamiento innecesario causa elevado daño por iatrogenia ó costes innecesarios, el punto de corte debería ser un valor que minimice los falsos positivos, alta especificidad, para orientar la toma de decisiones .

- Modelos multivariantes de predicción de riesgo. Modelos flexibles GAM

En los modelos multivariantes de análisis de pruebas diagnósticas, el empleo de los Modelos Aditivos Generalizados (Generalized Aditive Models, GAM), que no establecen a priori ninguna asunción paramétrica en la distribución del efecto de las variables explicativas permite aproximarse mejor a la realidad biológica que los modelos paramétricos. En estos análisis , la medida de adecuación general del modelo se establece a partir del AIC (Akaike Information Criteria) y BIC (Bayesian Information Criteria) respectivamente. (Pepe et al. 2004)

I.1.3 Impacto en las decisiones clínicas: capacidad de discriminación. Análisis reclasificación; análisis utilidad diagnóstica.

Tanto si se estudia un biomarcador para utilizarlo en diagnóstico, como indicador pronóstico ó en cribado precoz, la información más relevante es conocer su utilidad clínica. El impacto que el resultado de la prueba diagnóstica tiene en la toma de decisiones clínicas viene condicionado por la información que aporta adicional a la ya existente, ya que la justificación para la incorporación de un nuevo biomarcador requiere demostrar que mejora la capacidad de clasificación de las pruebas ya existentes. Para cuantificar esta mejora se dispone de varios métodos:

Cambio en el AUC de la curva ROC.

El análisis del cambio producido en el AUC al incorporar el nuevo biomarcador al modelo previo es el utilizado más habitualmente. Sin embargo, se precisan cambios importantes en el efecto (OR) para que se produzca un incremento significativo en el AUC lo que puede llevar a desestimar por bajo impacto la incorporación de nuevos biomarcadores por otra parte relevantes para una adecuada clasificación de riesgo(Pepe et al. 2004; Ware 2006). Además el cambio producido en el AUC depende de la fortaleza del modelo basal, por lo que es menor cuando el modelo incluye ya los principales factores de riesgo.

Tablas de reclasificación.

Las tablas de reclasificación, introducidas por Cook en 2007 analizan los cambios que se producen en la clasificación diagnostica al utilizar el nuevo biomarcador respecto al previo, cuantificándolos como la proporción de sujetos reasignados a cada categoría ó estado clínicamente relevante (Cook 2007).
En el caso de modelos de predicción, se propuso cuantificar la tasa de reclasificación y compararla en términos de los eventos producidos / no producidos entre los sujetos reclasificados.

Sin embargo, este análisis presenta limitaciones para evaluar la mejora en la capacidad de discriminación, ya que realiza un análisis conjunto de la reclasificación producida en afectos y no afectos. Pencina en 2008 propone dos nuevas medidas de la ganancia en la utilidad diagnostica, aplicables para comparar modelos anidados: Net Reclassification Index, NRI, e Integrated Discrimination Improvement, IDI (Pencina et al. 2008).

Net Reclassification Index (NRI)

Para superar la limitación de la propuesta de Cook, Pencina et al, proponen el análisis separado en sanos y enfermos, construyendo las respectivas tablas de reclasificación y estimando el NRI en cada una. El NRI global es la suma de NRI en población con evento y NRI en población sin evento.

En situaciones con dos categorías de riesgo, el NRI en población con evento representa la proporción de sujetos afectados que han sido reclasificados a la categoría de alto riesgo; de forma similar el NRI en población sin evento representa la proporción de sujetos libres de evento reclasificados a bajo riesgo. Su interpretación es por tanto intuitiva y clínicamente útil.

Presenta no obstante algunas limitaciones. Cuando existen más de dos categorías de riesgo, esta medida considera por igual la reclasificación entre categorías, cuando la relevancia clínica de pasar de muy bajo riesgo a alto riesgo puede ser (y habitualmente es) muy diferente a la de pasar de riesgo medio a alto riesgo. Una alternativa que proponen algunos investigadores es comunicar el NRI para cada categoría de riesgo además del NRI global. Por otra parte, las técnicas estadísticas usadas para el contraste de hipótesis y la construcción de intervalos de confianza del NRI no han sido aun validadas (Pepe & Janes 2011).

Integrated Discrimination Improvement (IDI)

Por su parte el IDI refleja la diferencia entre la mejora media producida en la integral de la sensibilidad (IS) y el potencial incremento en la integral del complementario de la especificidad (IP).
Se considera que un nuevo biomarcador es útil cuando aporta una mejora en la sensibilidad (mayor tasa de verdaderos positivos) sin incrementar el complementario de la especificidad (igual/menor tasa de falsos positivos).

$$IDI = (IS_{nuevo\ mod.} - IS_{mod.\ basal}) - (IP_{nuevo\ mod.} - IP_{mod.\ basal})$$

I.1.4 Análisis de las utilidades en la toma de decisiones

Este análisis incorpora al comportamiento (calibración y capacidad de discriminación) de la prueba diagnóstica o nuevo biomarcador las consecuencias de tratar/no tratar a sujetos sin/con el proceso patológico de interés a través de los conceptos de utilidades, relacionados con los valores y preferencias del enfermo.

Se trata de un indicador diagnóstico más complejo, que aporta mayor valor en la toma de decisiones tanto en clínica como en planificación (Greenland 2008). Debe ser incluido en la evaluación de un modelo predictivo sobre todo cuando vaya a ser utilizado para tomar decisiones en clínica (Steyerberg et al. 2010).

Vickers y Elkin han propuesto el análisis de curva de decisiones como aproximación a la cuantificación de la utilidad clínica de un modelo de predicción (Vickers 2006); tanto daños como beneficios deben ser cuantificados para llegar a identificar el punto de corte optimo que minimice los primeros maximizando los segundos. Con frecuencia la información necesaria para cuantificar daños y beneficios resulta incompleta; por otra parte, su peso relativo varía según las preferencias de cada individuo. Por estas razones,

establecer un único punto de corte resulta complejo proponiéndose considerar un rango de puntos de corte a semejanza de lo que ocurre en la curva ROC.

Para abordar el análisis de utilidades en la toma de decisiones deben considerarse ante una decisión de tratamiento/intervención dos aspectos contrapuestos: las consecuencias de actuar ante un sujeto considerando que tiene el proceso patológico cuando no lo tiene (consecuencias de actuación en un falso positivo, FP); frente a las consecuencias de no actuar ante un sujeto por considerarlo libre del proceso patológico cuando realmente lo tiene (consecuencias de no actuación en un falso negativo, FN). La utilidad es un valor normalizado (entre 0 y 1) que dependerá de las consecuencias que la decisión tenga para el paciente y de sus preferencias.

Se define el coste neto (consecuencias de tratar pacientes no enfermos) a la diferencia en beneficio entre no tratar a un no enfermo y tratar a un falso positivo.

Coste neto = Utilidad de los VN – Utilidad de los FP.

Se define el beneficio neto (consecuencias de tratar a un sujeto enfermo) como la diferencia en beneficio entre tratar a un sujeto enfermo y no tratar a un paciente falso negativo.

Beneficio neto = Utilidad de los VP- Utilidad de los FN

Tabla 2 Principales medidas de adecuación de un biomarcador para su uso con finalidad diagnóstica ó pronostica. Tabla adaptada de Steyerberg (Steyerberg et al. 2010).

Característica	Medida	Representación
Rendimiento global	R^2, Brier	Grafico de validación
Calibración	Pendiente de calibración	
	Prueba de Hosmer-Lemeshow	
Discriminación	AUC, estadístico c	Curva ROC
Reclasificación	Pendiente de discriminación	Diagrama de cajas
	Tabla de reclasificación	Tabla de contingencia
	Estadísticos de reclasificación	
	NRI	
	IDI	Diagramas de cajas (modelo basal y nuevo modelos)
Utilidad clínica	Beneficio neto / Coste neto	Tabla de contingencia
	Análisis de curvas de decisión	Curva de decisión

I.2 Enfermedad renal crónica (ERC).

I.2.1 Definición de ERC

Se define como enfermedad renal crónica (ERC) la disminución de la función renal, expresada como una tasa de filtrado glomerular (GFR, glomerular filtration ratio) inferior a 60 mL/min/1.73 m^2 ó evidencia de daño renal (expresada como presencia de proteinuria, hematuria o lesión estructural), documentada al menos en dos ocasiones en un espacio no inferior a tres meses.

La definición y clasificación de ERC en estadios se estandarizó a nivel internacional en febrero 2002 como resultado del trabajo de revisión sistemática y consenso desarrollado por la Kidney Disease Outcomes Quality Initiative (KDOQI) de la National Kidney Foundation (Levey et al. 2003).

Los objetivos de esta iniciativa fueron: definir la ERC y su clasificación en estadios de creciente severidad, con independencia de la causa de la afectación renal; evaluar los métodos de laboratorio disponibles para el diagnostico de ERC; asociar los estadios de ERC con la presencia de complicaciones; evaluar según estadio ERC el riesgo de eventos clínicos relevantes: la progresión a enfermedad renal crónica terminal (ERCT) y diálisis; la enfermedad cardiovascular (ECV).

Como resultado de esta iniciativa, en 2002 se estableció una clasificación en cinco estadios, 1 a 5, de creciente severidad en términos de afectación de la función renal y riesgo de complicaciones. Esto supuso un hito que permitió unificar criterios en práctica clínica y hacer comparables los resultados de investigación epidemiológica sobre esta patología.

La Conferencia celebrada en Londres en 2009, revisó la evidencia científica disponible relativa a la ERC.(Levey et al. 2011)(Kidney Disease Outcomes

Quality Initiative 2009). En sus conclusiones se revisa la clasificación establecida en 2002, con el objetivo de mejorar su capacidad de clasificación de la severidad de la ERC y por tanto su capacidad pronostica.

Las modificaciones introducida supusieron:
Incorporar, con independencia del nivel de GFR, la cuantificación de la albuminuria, en tres estadios de ACR: < 30 mg/g; 30-300 mg/gr; > 300 mg/gr.
Diferenciar el estadio 3 de ERC en dos niveles:

- 3a, GFR 45-59 mL/min/1.73m^2;
- 3b, GFR 30-44 mL/min/1.73m^2.

Tabla 3 Clasificación en estadios de ERC según niveles de filtrado glomerular y albuminuria. Comparación criterios KDOQI y NICE.

<table>
<tr><td rowspan="2">Albuminuria
(ACR, mg/g)</td><td colspan="6">GFR estimado (mL/min/1.73 m^2)</td></tr>
<tr><td>≥90</td><td>60-89</td><td>45-59</td><td>30-44</td><td>15-29</td><td>< 15</td></tr>
<tr><td colspan="7">Guías KDOQI 2009</td></tr>
<tr><td>Normal (<30)</td><td>Normal</td><td>Normal</td><td rowspan="3">Est. 3a</td><td rowspan="3">Est. 3b</td><td rowspan="3">Est. 4</td><td rowspan="3">Est. 5</td></tr>
<tr><td>Microalbuminuria
(30-300)</td><td rowspan="2">Est. 1</td><td rowspan="2">Est. 2</td></tr>
<tr><td>Macroalbuminuria
(>300)</td></tr>
<tr><td colspan="7">Guías NICE 2008</td></tr>
<tr><td>Normal (<30)
Microalbuminuria
(30-300)</td><td>Normal</td><td>Normal</td><td>Est. 3a</td><td>Est. 3b</td><td>Est. 4</td><td>Est. 5</td></tr>
<tr><td>Macroalbuminuria
(>300)</td><td>Est. 1P</td><td>Est. 2P</td><td>Est. 3aP</td><td>Est. 3bP</td><td>Est. 4P</td><td>Est. 5P</td></tr>
</table>

ACR: cociente albumina creatinina en muestra de orina. GFR- Tasa de filtrado glomerular estimado.

En la tabla 3 se recoge la clasificación en estadios de ERC según niveles de filtrado glomerular estimado y presencia de albuminuria, observándose alguna variabilidad en la propuesta KDOQI y la utilizada por el National Institute for Health and Clinical Excellence (NICE) de Reino Unido.

Se define como Insuficiencia Renal Crónica (IRC) los estadios 3 a 5 de la clasificación K/DOQI, es decir los individuos con una tasa de filtrado glomerular inferior a 60 mL/min/1.73 m^2.

Finalmente, el término Enfermedad Renal Crónica Terminal (ERCT) se emplea para los casos en estadio 4 ó 5 de la clasificación KDOQI que presentan un deterioro de la función renal por el que precisan tratamiento renal sustitutivo (TRS), tanto diálisis, en cualquiera de sus formas, como trasplante renal.

I.2.2 Impacto de la Enfermedad Renal Crónica.

I.2.2.1 Prevalencia de la Enfermedad Renal Crónica.

La ERC es reconocida como un problema de salud pública por la creciente prevalencia observada y el elevado riesgo asociado de complicaciones cardiovasculares (Levey et al. 2007). Según muestran diferentes estudios internacionales, la prevalencia poblacional de ERC se estima entre el 10% y 16% (Q.-L. Zhang & Rothenbacher 2008; Coresh, Selvin, L. A. Stevens, Manzi, et al. 2007). Por su parte la incidencia de ERCT se ha doblado en la última década; en Reino Unido ha pasado de 523 casos pmp en el año 2000 a 832 casos pmp en 2010 (The Renal Association 2011). Aunque los factores responsables de este incremento no están completamente identificados, entre ellos se ha señalado la prevalencia de patologías crónicas, como obesidad, diabetes e hipertensión (Meguid El Nahas & Bello 2005; Coresh, Selvin, L. A. Stevens, Manzi, et al. 2007).

Una revisión sistemática de estudios observacionales en población general halló una prevalencia de ERC en estadios 3-5 del 7.2% (Q. L. Zhang & Rothenbacher 2008).

En Estados Unidos de América, según datos del estudio National Health and Nutrition Examination Survey (NHANES) III, en el periodo 1999 a 2006 la prevalencia de ERC en estadios 3-5 fue de 6.7% (7).

En España, existen múltiples estudios sobre presencia de ERC en grupos de riesgo como pacientes con diabetes mellitus (DM) ó hipertensión arterial (HTA). Sin embargo se carecía, hasta el desarrollo del proyecto de investigación objeto de la presente Tesis Doctoral, de estudios en población general que permitieran establecer la prevalencia poblacional de ERC.

Villa et al establecieron en el año 2010 una prevalencia de 25.002 pacientes con ERCT (pacientes en estadios 4 ó 5 de la clasificación KDOQI que reciben tratamiento renal sustitutivo) incluidos en programas de diálisis (90.3%,22582, en hemodiálisis y 9.7%,2420, en diálisis peritoneal), con 6231 casos incidentes (86.8%,4509, en hemodiálisis y 13.2%,822, en diálisis peritoneal). Analizando el periodo 1996-2010, la prevalencia de pacientes con ECRT muestra un incremento sostenido, tanto en casos prevalentes (Fig. 1) como incidentes (Fig. 2) en España (Villa et al. 2011).

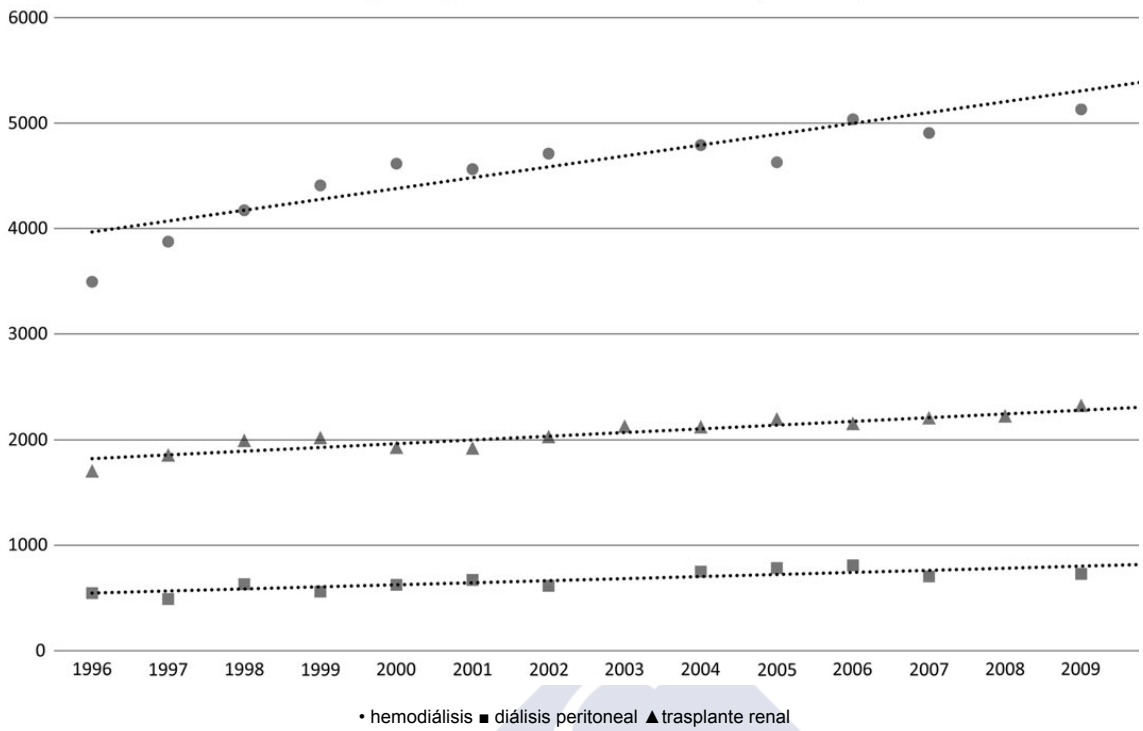


Figura 1. Incidencia de Enfermedad Renal Crónica Terminal en España. Datos ponderados y tendencia estimada para el periodo 1996-2010 (Villa et al. 2011).

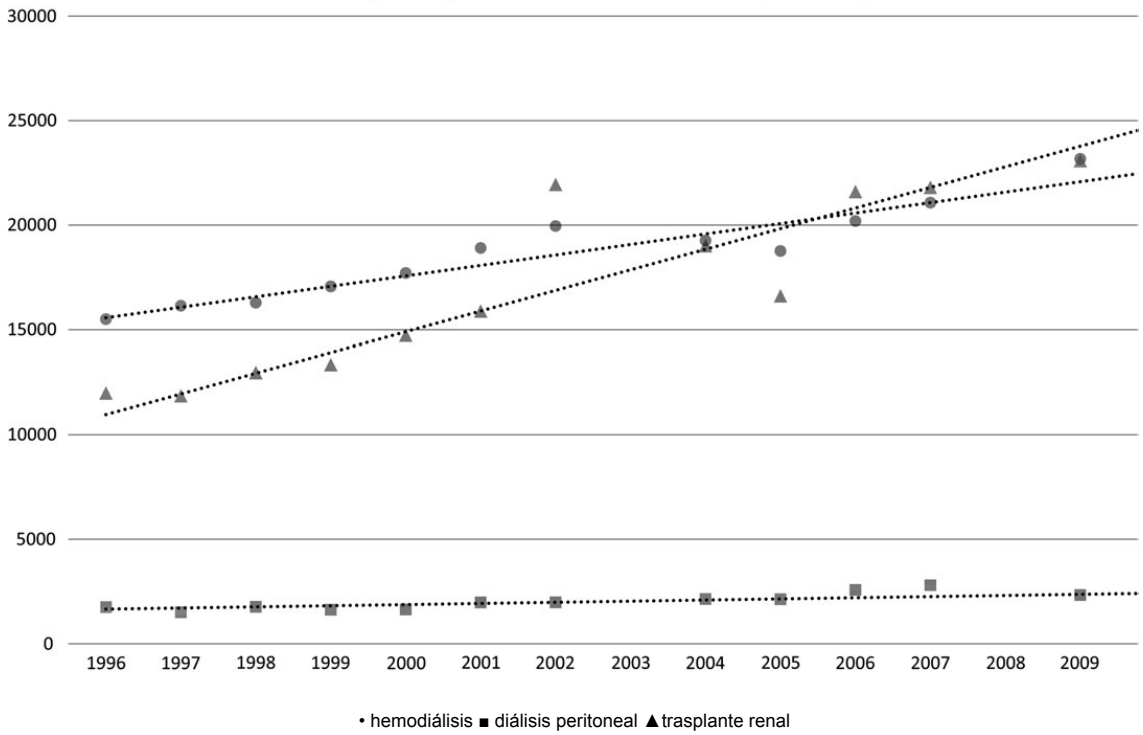


Figura 2. Prevalencia de Enfermedad Renal Crónica Terminal en España. Datos ponderados y tendencia estimada para el periodo 1996-2010(Villa et al. 2011).

El estudio EROCAP por su parte, analizó la prevalencia de IRC, TFG<60 mL/min/1.73m^2, en población demandante de atención sanitaria estudiando pacientes atendidos en centros de atención primaria en España. Con una muestra de 7202 pacientes, la prevalencia de ERC fue del 21.3%, distribuyéndose según estadio como sigue: 19.7% en estadio 3, 1.2% en estadio 4 y 0.2% en estadio 5 respectivamente (De Francisco et al. 2007). Cabe destacar que el 37.3% de los pacientes con IRC presentaban niveles de creatinina sérica en rango de normalidad (<1.1 mg/dl en mujeres y 1.2 mg/dl en varones), siendo esta proporción significativamente mayor en mujeres respecto a varones y en grupo de edad mayor a 70 años respecto a los más jóvenes.

Esto supone que en más de un tercio de pacientes atendidos en los centros de atención primaria, con ERC grado 3 a 5 no se identifican considerando únicamente los valores de creatinina plasmática (De Francisco et al. 2007).

Considerando que la carga total de enfermedad atribuible a la ERC es 50 a 70 veces mayor que la correspondiente a los pacientes en ERCT, esta tendencia supone una creciente carga en términos de cuidados de salud (S. I. Hallan et al. 2006; van Dijk et al. 2001).

I.2.2.2 Morbi-mortalidad cardiovascular asociada a ERC

La ERC se asocia a un riesgo elevado de enfermedad cardiovascular (ECV), tanto eventos isquémicos como mortalidad cardiovascular con una correlación inversa entre tasa de filtrado glomerular y riesgo de eventos, independiente de otros factores de riesgo y presente ya desde fases iniciales de deterioro de función renal. Los individuos en estadio 3a, con una tasa de filtrado glomerular entre 45 y 59 mL/min/1.73m^2, presentan una razón de riesgos instantáneos (hazard ratio, HR) de 1.2 para muerte por cualquier causa y 1.4 para evento isquémico, respecto a sujetos con función renal superior a 60.
Este riesgo se incrementa en estadio 3b (HR 1.8 y 2.0 respectivamente), estadio 4 (HR 3.2 y 2.8) y en estadio 5 (HR 5.9 y 3.4) (Go et al. 2004).

Aproximadamente un 50% de pacientes en ERCT fallecen por causa cardiovascular, lo que supone una mortalidad cardiovascular ajustada por edad superior en 15 a 30 veces que la descrita para población general (Parfrey & Foley 1999). La evidencia disponible muestra que la ERC incrementa el riesgo de desarrollo de ateroesclerosis, coronaria y carotidea, y ocurrencia de síndromes coronarios agudos (Cachofeiro et al. 2008; Foley et al. 1998).

En la tabla 4 se recogen los factores de riesgo cardiovascular (FRCV) en ERC; se diferencia entre FRCV tradicionales, entendiendo por tales aquellos identificados en el Framingham Heart Study, y los no tradicionales, que comprende aquellos no utilizados en las ecuaciones de estimación de riesgo de Framingham.

Aunque muy prevalentes, los FR clásicos no explican completamente el papel de la ERC como factor de riesgo cardiovascular. Entre los múltiples nuevos factores de riesgo propuestos, la inflamación crónica (expresada por niveles de biomarcadores de inflamación: PCR, IL-6 entre otras citokinas pro-inflamatorias; moléculas de adhesión como ICAM-1 y VCAM1; homocisteina) y el estrés oxidativo aparecen como los más relevantes.

Tabla 4.- Factores de riesgo cardiovascular en Enfermedad Renal Crónica.

Factores de riesgo tradicionales	Factores de riesgo no tradicionales
Edad	Albuminuria
Sexo masculino	Anemia
Hipertensión Arterial	Homocisteina plasmática elevada
LDL-colesterol elevado	Inflamación
HDL-colesterol disminuido	Estrés Oxidativo
Diabetes Mellitus	Alteración metabolismo Ca/P
Tabaquismo	Calcificación vascular
Sedentarismo	Patología ósea urémica
Menopausia	Malnutrición
Historia familiar de ECV	Actividad Simpática
Hipertrofia VI	Exceso de vol. Extracelular
Insuficiencia Cardiaca	Lipoproteína a
	Alteraciones de coagulación
	Alteración balance NO/endotelina
	Resistencia a la insulina
	Hipotiroidismo subclínico
	Toxina urémica
	Tej. Adiposo: imbalance adipokinas

Estrés oxidativo, disfunción endotelial e inflamación representan una tríada esencial en el desarrollo y progresión de la aterosclerosis en población con ERC (Filiopoulos 2009). Se han demostrado que están asociados a la evolución de la placa ateromatosa, con un papel tanto en su formación como en su ruptura; por su parte, biomarcadores de inflamación se asocian a peor pronóstico en ECV en estos pacientes (Weiner et al. 2008b; Menon et al. 2005; Bhatt 2008).

Además de ser un factor de riesgo independiente para ECV, la ERC empeora el pronóstico en pacientes con cardiopatía ya establecida. El riesgo de IAM, tanto incidente como recurrente, está inversamente relacionada con la función renal, elevándose significativamente cuando la GFR se hace menor de 15 mL/min/1.73m^2. Por otra parte, el riesgo de muerte cardiovascular se incrementa hasta cuatro veces cuando el GFR disminuye de 75 a 45 mL/min/1.73m^2 (Anavekar & McMurray 2004).

En pacientes con ERC el riesgo de fallecer por causa cardiovascular es mayor que el de recibir tratamiento renal sustitutivo (Foley 2005; Keith 1994).

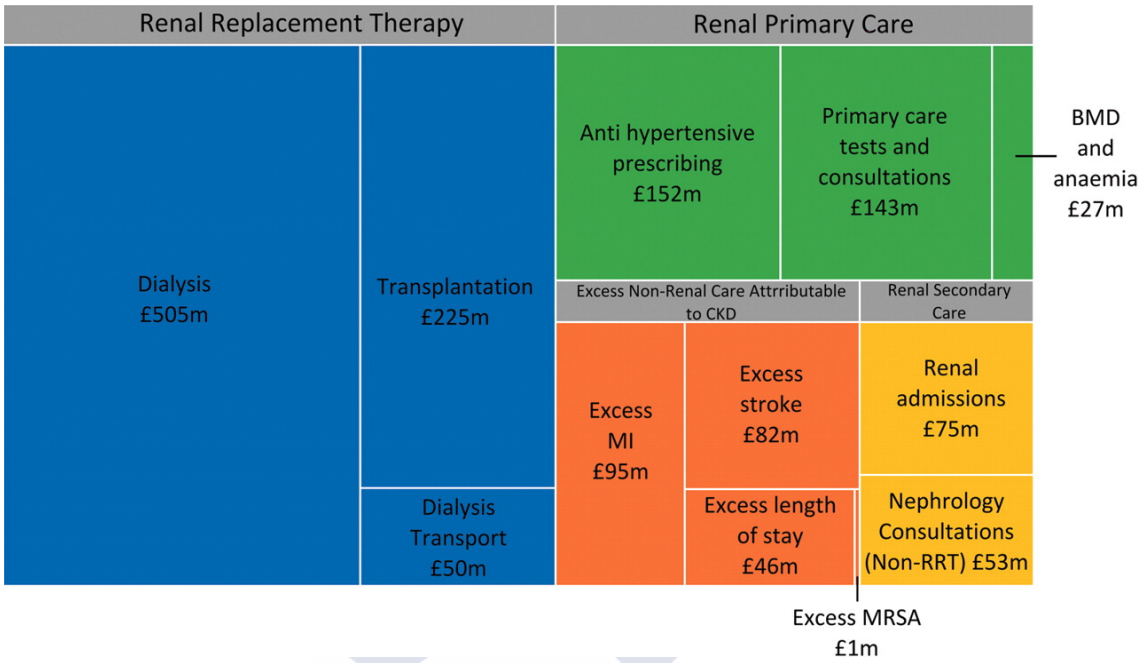
La insuficiencia renal crónica (IRC) es una patología severa precedida de una fase preclínica asintomática, habitualmente de prolongada duración. Durante dicha fase, que corresponde a los estadios 1, 2 y 3a de ERC, está presente el daño renal y una situación de inflamación subyacente. Se ha demostrado que durante esta fase, las intervenciones dirigidas a un adecuado control de los factores de riesgo vascular y patologías vasculares (HTA) y metabólicas (DM) disminuyen la incidencia de enfermedad cardiovascular y mortalidad.

I.2.2.3 Utilización servicios sanitarios

Por su parte, los costes sanitarios asociados a la atención a la ERC son elevados. Un reciente estudio en Reino Unido ha estimado que los costes atribuibles a la atención de la ERC representan para en sistema sanitario público un total de 1.523 millones de euros para el periodo 2009-2010. De ellos, un 53.6% corresponde al tratamiento renal sustitutivo (diálisis y trasplante) a pesar de que la población en tratamiento renal sustitutivo representa el 2% del total de pacientes con ERC; el 22.2% a cuidado en atención primaria a ERC; el 8.8% a cuidado en atención secundaria a ERC; finalmente los costes derivados de la morbilidad evitable se estiman en un 15.3% (Kerr et al. 2012).

En la siguiente figura los autores desglosan los principales conceptos de gasto de la atención a la ERC en el sistema sanitario público de Reino Unido, National Health Service, con un modelo de atención sanitaria universal.

Figura 3. Principales conceptos de gasto que comporta la atención a ERC en el National Health Service, Reino Unido. Figura tomada de Kerr y col, 2012 (Kerr et al. 2012).



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En España, la atención a la ERCT, fase final de la progresión de la ERC en la que se requiere tratamiento sustitutivo, supuso en 2010 unos costes directos al Sistema Nacional de Salud de 1.407 millones de euros, que se incrementan hasta 1829 millones de euros si se consideran también los costes indirectos (estimados como pérdida de capacidad productiva). Analizándolo según modalidad de tratamiento, Villa et al hallan que el 73% de este coste se debe a la atención a pacientes en programas de hemodiálisis, 21% a los incluidos en trasplante renal y 6% a los incluidos en programa de diálisis peritoneal (Villa et al. 2011).

Aunque no se dispone en España de estudios directos sobre el coste atribuible de la atención a la ERC, se estima que el coste asistencial de la atención a la ERC en estadios 1 a 4 podría ser 1.6 a 2.4 veces mayor que el correspondiente a la ERCT (Gorriz Teruel & Otero Gonzalez 2008).

I.2.2.4 Disminución calidad de vida relacionada con la salud atribuible a ERC

La ERC conlleva un deterioro de la calidad de vida relacionada con la salud (CVRS), ya desde los estadios iniciales. Estudios en diversas poblaciones muestran desde el estadio 2 de ERC una progresiva disminución de la CVRS percibida (medida usando instrumentos generales, como Cuestionario de Salud SF-36, y específicos, como Kidney Disease Quality Of Life, KDQOL, cuestionario), sobre todo en el ámbito físico, en comparación con población general de similar edad, sexo y estilos de vida (Mujais 2009; Pagels 2012; Perlman et al. 2005). Esta asociación inversa entre progresión ERC y CVRS se encuentra relacionada con factores como HTA y anemia (Soni 2010). La presencia de comorbilidades, concretamente inflamación ó ECV ha demostrado que son predictores fuertes de un mayor deterioro en la CVRS (Pagels 2012).

Dado el impacto en calidad de vida que supone la ERCT y los costes que conlleva el tratamiento renal sustitutivo, las estrategias orientadas a evitar la progresión de la ERC en estadios precoces presentan un elevado interés. Una revisión sistemática realizada por Kutner recoge evidencias de estudios que demuestran mejora en la CVRS como resultado de estrategias de tratamiento que incluyen control de anemia, programas de ejercicio físico y abordaje de la depresión en población mayor de 65 años con ERC (Kutner 2008).

Esta ganancia en la puntuación de las escalas habitualmente utilizadas para medir CVRS refleja una mejor situación del individuo y por tanto mayor capacidad para el desarrollo de sus actividades diarias, objetivos relevantes en toda práctica clínica centrada en el paciente, más allá de la significación estadística de las diferencias observadas en los estudios de investigación (Fukuhara 2012).

Los indicadores de CVRS deben formar parte por tanto de los criterios de evaluación de toda estrategia de manejo de ERC (Finkelstein 2009) para una completa cuantificación del impacto de las intervenciones.

I.3 Inflamación, Enfermedad Renal Crónica y Resistencia a la insulina

El estado crónico de inflamación es común a un número creciente de patologías, según la evidencia actualmente disponible. La comprensión de los mecanismos fisiopatológicos subyacentes es un elemento esencial para orientar tanto las pruebas diagnosticas como las intervenciones terapéuticas con criterios de efectividad y coste-utilidad.

I.3.1 Inflamación, disfunción endotelial y aterosclerosis.

La respuesta inflamatoria es tanto un proceso local como sistémico, con múltiples mediadores entre los que se encuentran proteínas de fase aguda, citokinas, complemento, moléculas de adhesión y células de serie blanca (Cachofeiro et al. 2008). Aunque no existe un consenso general sobre cómo evaluar el estado inflamatorio, tanto en población general ó en pacientes con ERC se ha estudiado el valor pronóstico de varios marcadores de inflamación: interleukina 6 (IL6), proteína C reactiva (PCR), factor de necrosis tumoral α (TNF-α), moléculas de adhesión, resistencia a la insulina ó CD40. En varios estudios se ha demostrado una asociación independiente de estos factores con eventos cardiovasculares, tanto en población general como en pacientes con ERC (Blake & Ridker 2002).

El estado inflamatorio constituye, junto con el estrés oxidativo y la disfunción endotelial, una relevante contribución al desarrollo y rápida progresión de aterosclerosis (Cachofeiro et al. 2008). Un incremento de los niveles de estrés oxidativo favorece la disfunción endotelial al disminuir la disponibilidad de oxido nítrico. En esta situación, además de un incremento de citokinas pro inflamatorias, se producen cambios en la permeabilidad vascular que permiten la entrada de LDL-colesterol en la íntima, dónde se transforma, al oxidarse, en moléculas altamente aterogénicas que inician el proceso inflamatorio endovascular.

La progresión de estas lesiones conlleva la transformación de monocitos en células espumosas y la migración de miocitos desde la media a la intima vascular donde proliferan produciendo matriz extracelular que constituye la capa fibrosa que engloba y define la lesión aterosclerosa. Finalmente la ruptura de la placa, desencadenada habitualmente por un proceso inflamatorio agudo que favorece la liberación de moduladores de la matriz extracelular, lleva a la formación del trombo y a eventos clínicamente relevantes (tales como IAM o ACV) por oclusión de la luz vascular.

I.3.2 Inflamación en la enfermedad renal crónica.

La presencia de un estado inflamatorio crónico favorece el deterioro en la función renal y está ampliamente documentada en la progresión de la ERC (Locatelli et al. 2003). Ya en estadios precoces de ERC, los principales marcadores de inflamación, estrés oxidativo y disfunción endotelial se encuentran alterados respecto a población general. Estas alteraciones han demostrado valor pronóstico, de forma independiente a otros factores, para eventos clínicamente relevantes (muerte por cualquier causa ó causa cardiovascular, y eventos cardiovasculares). En la tabla 5 (adaptada de Roberts et al. 2006) se resume el valor pronóstico de los principales biomarcadores cardiovasculares en la ERC en función de la evidencia disponible.

Tabla 5.- Biomarcadores cardiovasculares: situación en ERC y valor pronóstico para mortalidad y eventos cardiovasculares según estadio ERC. Tabla adaptada de Roberts y col, 2006.

Biomarcador	Dirección cambio niveles biomarcador en ERC	Evidencia valor pronostico para el evento señalado **			
		IRC sin TRS	IRC en TRS		
			Diálisis peritoneal	Hemodiálisis	Trasplante renal
Disfunción endotelial					
• ADMA	↑			M, ECV	
• Homocisteina	↑	ECV	ECV	M, MCV, ECV	ECV
Calcificación vascular					
• AHSG (Fetuina A)	↓	M, MCV			
Moléculas de adhesión					
• ICAM-1	↑				
• VCAM-1	↑	M			
• MCP-1	↑				
Inflamación					
• PCR	↑	M, MCV	M, ECV	M, MCV	M,MCV,ECV
• IL-6	↑	MCV		M, MCV	
• TNF-α	↑			M	
• Fibrinógeno	↑	ECV	ECV	M, MCV, ECV	
• Amiloide A sérico	↑				
Estrés oxidativo					
• F_2-isoprostanos	↑				
• Plasmalógenos	↓	MCV			
• PAOP*	↑	ECV			
Hiperactividad SNsimpático					
• Neuropéptido Y	↑		ECV		
• Norepinefrina	↑		M, ECV		
Glicosilacion de proteínas					
• AGEs	↑		M		

Función medula ósea • Hemoglobina • EPCs	↓ ↓		M, ECV	M	M, MCV
Activación plaquetaria • CD40L	↑				
Estructura y función VI • BNP-32 • NT-proBNP	↑ ↑	ECV M		M, MCV	
Necrosis miocárdica • Troponina T • Troponina I	↑ ↑	M	M, MCV	M,MCV,ECV M	
Otros • Adiponectina • Relaxina • Il-8	↑			ECV M M, MCV	

* ERC- estadios 1 a 5 de enfermedad renal crónica. IRC- estadios 3 a 5 de enfermedad renal crónica. ADMA-dimetilarginina asimétrica. ICAM-1- molécula 1 de adhesión interceluar. VCAM-1- molecula 1 de adhesión celular vascular. MCP-1- proteína 1 quimiotactica de monocitos. PAOP- productos avanzados de oxidacion de proteinas. EPCs- células progenitoras endoteliales. AGEs-productos finales de glicacion avanzada. ** Solo se incluyen resultados de estudios en los que el valor pronostico del biomarcador fue evaluado en modelos multivariantes, contorlando por otras factores de demostrado valor pronostico. Eventos considerados: M-muerte por cualquier causa. MCV-mortalidad de causa cardiovascular. ECV-evento cardiovascular.

Del análisis de los hallazgos para cada biomarcador se puede afirmar:

La proteína C reactiva (PCR) se encuentra elevada en un 35% de pacientes con ERC estadios 3 y 4 (Stenvinkel 2002). En el estudio MDRD (Modification of Diet in Renal Disease) un elevado nivel de PCR se asoció a mayor riesgo de mortalidad por todas las causas y por causa cardiovascular (Menon et al. 2005); por su parte Weiner et al en un estudio con 1678 pacientes en estadios 3 y 4 de ERC demostraron que tanto PCR como fibrinógeno eran factores independientes de riesgo para el evento combinado de IAM, ictus y mortalidad por cualquier causa (Weiner et al. 2008a). Un reciente estudio realizado con los datos conjuntos del Atherosclerosis Risk in Communities Study (ARIC) y el Cardiovascular Heart Study (CHS), 20.423 individuos, demostró que tanto en pacientes con CKD como en población sana, la PCR presentaban similar valor

pronóstico para eventos cardiovasculares que la combinación de albumina sérica y recuento leucocitario (Weiner et al. 2008a).

Por su parte la interleukina 6 (IL-6), reconocida por muchos autores como el principal mediador en la respuesta inflamatoria de fase aguda, contribuye al desarrollo de aterosclerosis por mecanismos metabólicos, procoagulantes y endoteliales (Zoccali et al. 2004). Parece ser la mejor opción para estratificación de riesgo en pacientes en diálisis por su superioridad a otros biomarcadores, aunque los autores concluyen que en la práctica clínica la PCR puede considerarse una adecuada alternativa por aportar una estimación de riesgo muy próxima, no presentar problemas metodológicos en su determinación y ser de menor coste (Filiopoulos 2009).

La homocisteina es otro de los factores de riesgo no tradicionales objeto de estudio, tanto en población general como en ERC. En ambos casos, niveles elevados (ya desde magnitudes moderadas) de homocisteina suponen un factor de riesgo independiente para ECV (Kendrick & Chonchol 2008).

Entre los más recientes marcadores de inflamación objeto de estudio destacan por su interés las modificaciones epigenéticas del DNA que pueden tener un importante papel en el desarrollo de un fenotipo específico en ERC (Filiopoulos 2009). Modificaciones epigenéticas de DNA pueden atribuirse, al menos en parte, a la uremia; en esta situación se han observado interacciones entre homocisteinemia, inflamación y metilación de DNA, demostrándose asociación entre hipermetilacion global de DNA, inflamación y aumento de mortalidad en ERC (Stenvinkel et al. 2007).

Por su parte CYBA, gen que regula el citocromo b, es relevante en la actividad microbicida observándose que sus mutaciones determinan enfermedad granulomatosa crónica, una patología caracterizada por frecuentes infecciones severas (Dinauer et al. 1990). En pacientes en estadio 5 de ERC se ha observado una reducida expresión de CYBA en tejido adiposo. Se ha propuesto que la desregulación de este gen puede ser un factor importante en

la alta tasa de infecciones, y mortalidad asociada, que presentan los pacientes en ERC (Zoccali 2011).

I.3.3 Inflamación, tejido adiposo y resistencia a la insulina.

La obesidad, esencialmente la debida a adiposidad visceral, se relaciona con presencia de inflamación y mayor riesgo cardiovascular (Wisse 2004). La grasa visceral es productora de citokinas pro inflamatorias que contribuyen al proceso de daño vascular; además puede secretar proteínas como la adiponectina, cuyos niveles plasmáticos están inversamente relacionados con riesgo cardiovascular, tanto en población general como en ERC (Wellen & Hotamisligil 2003).

Por otra parte, las citokinas pro inflamatorias del tejido adiposo junto con los ácidos grasos saturados alteran la señalización de la insulina en tejidos no grasos contribuyendo de esta forma a la resistencia a la insulina, factor de riesgo mayor para eventos cardiovasculares en individuos obesos (Funaki 2009; Montecucco et al. 2008; J.-P. Bastard et al. 2006).

En pacientes con ERC en diálisis se ha descrito un perfil pro inflamatorio asociado a obesidad (Cordeiro et al. 2010). Al igual que en otras enfermedades crónicas como insuficiencia cardíaca, el índice de masa corporal (IMC) está inversamente relacionado con la supervivencia en pacientes con ERCT.

Algunos estudios indican posibles causas genéticas que contribuyen a explicar la asociación existente entre tejido adiposo e inflamación crónica en ERC (Zoccali 2011). En un reciente trabajo, Witasp et al demuestran en tejido adiposo subcutáneo abdominal un descenso, significativo tras ajuste por otras variables, en la expresión de los genes UCP-2 y CYBA entre sujetos con ERC estadio 5 pre-diálisis y controles sanos, apareados por edad y sexo (Witasp et

al. 2011). La vía de UCP-2 parece la vía determinante de las alteraciones en la resistencia a la insulina ligadas a la obesidad en pacientes con ERC. La inhibición in vitro de la UCP-2 en adipocitos no solo incrementa la producción de ROS sino también afecta la incorporación de la glucosa mediada por insulina, proceso indispensable para mantener la homeostasis glucosa-insulina, y suprime la transducción de señal de la insulina. Estos hallazgos sugieren que UCP-2 puede tener un importante papel en la resistencia a la insulina (Zhou et al. 2009).

En la población del NAHNES III se demostró que los marcadores de inflamación están directamente asociados a una mayor resistencia a la insulina (medida por HOMA-IR), siendo esta asociación independiente de otras características epidemiológicas ó clínicas (J. Chen, R. Wildman, et al. 2004). Además en sujetos no diabéticos, estar en el cuartil más alto de HOMA-IR suponía respecto al cuartil mas bajo, un OR de 2.65 (IC 95% 1.25, 5.62) para presentar IRC (GFR < 60 mL/min/1.73 m^2) ajustado por variables potencialmente confusoras (J. Chen 2003).

Clínicamente la resistencia a la insulina (IR, insulin resistance) se define como la incompetencia de unas determinadas concentraciones de insulina para mantener los niveles de glucemia en límites de normalidad. Se trata de una anormalidad celular compleja que fundamentalmente implica a tejido hepático, tejido adiposo y músculo esquelético. En su génesis se han implicado, además de una susceptibilidad genética, factores ambientales entre los que destacan por su demostrada asociación en estudios prospectivos de cohortes: sedentarismo, obesidad central, dieta hipercalórica y tabaquismo. También se ha encontrado mayor incidencia de IR en patologías como: hiperuricemia, síndrome de ovario poliquístico, hiperandrogenismo ó acantosis nigricans.

I.4 Criterios diagnósticos en enfermedad renal crónica y resistencia a la insulina.

I.4.1 Diagnóstico de enfermedad renal crónica

Los criterios actualmente aceptados para el diagnostico de ERC, están basados en la tasa de filtrado glomerular (GFR) y la presencia de albuminuria como expresión de daño renal.

I.4.1.1 Tasa de filtrado glomerular (GFR)

I.4.1.1.1 Medición directa de filtrado glomerular

El parámetro que mejor refleja la función renal es la medición directa de filtrado glomerular (mGFR) como aclaramiento de inulina; sin embargo esta técnica, considerada el patrón oro, es inviable en práctica clínica por su complejidad quedando reservada para entornos de investigación. El aclaramiento de radioisótopos (I^{125}-iothalamato,^{51}Cr-EDTA, ^{99}Tc-DPTA y ^{169}I-DPTA.) ó contrastes radiológicos (Iothalamate, Iohexol) previamente infundidos en el sujeto también se utiliza. En general la medición directa de FG, con cualquiera de las técnicas señaladas, tiene una aplicación limitada ya que se trata de un método invasivo y complejo poco adecuado para su uso en práctica clínica. Por estas razones el filtrado glomerular se estima a partir de biomarcadores séricos.

La estimación de la tasa de filtrado glomerular (eGFR) se utiliza tanto para valorar la situación de filtrado glomerular, como para predecir el riesgo de ocurrencia de eventos clínicos adversos. La estimación de GFR depende de dos factores: la ecuación de estimación empleada; y el biomarcador usado.

La concentración de creatinina sérica se ha utilizado como biomarcador de FG. En condiciones estables, un aumento de creatinina sérica indica un deterioro de FG, aunque valores estables de creatinina no garantizan ausencia de alteración del FG; solo el 60% de los pacientes con descenso del FG tienen el evada la creatinina sérica.

El FG puede estimarse mediante el cálculo del aclaramiento de creatinina, a partir de la creatinina sérica, creatinina urinaria y volumen de diuresis. Sin embargo este método no se recomienda para su uso habitual. Presenta limitaciones por: alta variabilidad interindividual, dependiente de la masa muscular; frecuentes problemas por recogida incorrecta de orina (lo que supone un coeficiente de variación en la excreción de creatinina de hasta el 70%); y marcadas variaciones intra e interindividuales en la excreción tubular proximal de creatinina que hacen imposible predecir los cambios en el FG a partir de cambios en el aclaramiento de creatinina.

Existen algunas situaciones clínicas en las que debe medirse directamente el filtrado glomerular, mediante aclaramiento de creatinina con recogida de orina de 24 horas. En la tabla 6 se recogen las indicaciones establecidas por Stevens y Levey en 2009. (L. A. Stevens & Levey 2009)

Tabla 6. Indicaciones para una medición directa de filtrado glomerular

Indicaciones para medir directamente el filtrado glomerular
Sujetos con dieta vegetariana estricta
Importantes alteraciones masa muscular: perdida severa masa muscular, paraplejia, tetraplejia, amputación.
Desviaciones extremas IMC
Etnias en las que no se ha validado la ecuación de estimación
Estudio potenciales donantes de riñón
Monitorización impacto/toxicidad de tratamientos de eliminación renal

I.4.1.1.2 Ecuaciones de estimación del filtrado glomerular.

Se han establecido como medidas subrogadas de GFR los métodos de estimación de FG utilizando ecuaciones basadas en la concentración de una sustancia de producción endógena, la creatinina como la más habitual, con ajustes en función de variables como edad, sexo ó grupo étnico. Entre las

ecuaciones propuestas a lo largo del tiempo para estimación de la función renal, destacan por su utilización en práctica clínica y en investigación las siguientes:

I.4.1.1.2.1 Ecuaciones basadas en el nivel de creatinina sérica.

En todas ellas, se considera el inverso de la creatinina sérica como la variable independiente para calcular el FG. La creatinina sérica refleja el balance entre su producción (dependiente del sexo, edad y situación metabólica/catabólica del individuo) y su excreción renal, siendo esta principalmente definida por el filtrado glomerular (con una escasa secreción tubular activa).

Tabla 7. Métodos propuestos para la estimación de filtrado glomerular a partir de los niveles séricos de creatinina.

Autor	Año	Variables
Jelliffe & Jelliffe	1971	Cr
Mawer	1972	Cr, edad, peso
Kapmann	1974	Cr, edad, peso
Cockroft-Gault	1976	Cr, edad, peso
Hull	1981	Cr, edad
Bjornsonn	1983	Cr, edad
Walser	1993	Cr, edad, peso
Levey (MDRD)(Levey et al. 1999)	1999	Cr, edad, sexo, raza*, BUN, Albumina sérica
Levey (MDRD-4)(A S Levey 2006)	2000	Cr, edad, sexo, raza*
Levey (CKD-EPI)(A S Levey et al. 2009)	2009	Cr, edad, sexo, raza*

Las ecuaciones de estimación de filtrado glomerular basadas en el nivel de creatinina sérica más significativas se recogen en la tabla 7. A continuación se describen las características de las mas utilizadas, tanto en el ámbito de práctica clínica como de investigación:

I.4.1.1.2.1.1 Ecuación de Cockroft Gault (C-G).

Propuesta en 1976 a partir de un estudio de 249 sujetos sin ERC y desarrollada con el objetivo de predecir el aclaramiento de creatinina. Sus principales limitaciones son que sobreestima el FG hasta en un 23%, sobre todo en los valores bajos, presenta alta dispersión de los datos y elevada variabilidad.(Cockcroft & Gault 1976) (Botev et al. 2009)

$$GFR\ (ml/mn) = \frac{(140 - edad \times peso)}{72 \times Cr\ serica} \times (0.85\ si\ mujer)$$

Ecuación de Cockroft &Gault de estimación de GFR.

I.4.1.1.2.1.2 Ecuación MDRD

A partir de los datos del estudio **Modification of Diet in Renal Disease, MDRD**, se han propuesto varias ecuaciones que predicen el FG a partir de diversas combinaciones de variables bioquímicas (creatinina, albúmina, nitrógeno ureico en sangre y orina) y epidemiológicas (edad, sexo, raza). en 1999,. Fue desarrollada y validada en una cohorte de 1628 pacientes con ERC (FG inferior a 60), mayoritariamente no diabéticos, con una media de mGFR de 40 ml/min/1.73 m^2 y una edad media de 51±13 años.(Levey et al. 1999) siendo conocida como MDRD-7.

Una versión simplificada a 4 variables (MDRD 4) fue posteriormente desarrollada y validada (Levey et al. 2006). En 2007 los autores evaluaron su comportamiento en una cohorte mayor (5504 individuos) y más diversa en cuanto a características epidemiológicas. (L. A. Stevens et al. 2007)

$$GFR\ (ml/mn\ por\ 1.73m^2) = 1.86 \times Cr\ s^{-1.154} \times Edad^{-0-203} \times (0.742\ si\ mujer) \times (1.210\ si\ afroamericano)$$

Ecuación MDRD 4 de estimación de GFR.

La ecuación MDRD-4 ha sido ampliamente utilizada, sin embargo se ha demostrado que infra estima el FG, sobre todo en los valores altos por lo que su utilización conlleva un sobre diagnóstico de ERC con lo que supone para el paciente y el sistema sanitario.

I.4.1.1.2.1.3 Ecuación CKD-EPI

A partir del trabajo de la Chronic Kidney Disease Epidemiology Collaboration se desarrolló la ecuación CKD-EPI que estima el FG a partir de la creatinina sérica, ajustada por sexo, edad y considerando un factor de corrección si el sujeto es de raza negra. (Levey et al. 2009). Se trata de una iteración de la MDRD desarrollada en 2009 en una cohorte de 8254 individuos adultos incluidos, con independencia de la presencia de ERC, en estudios epidemiológicos (GFR medio medido de 68mL/min/1.73m^2). Posteriormente fue sometida a validación externa en una cohorte formada por 3896 personas.

$$GFR = 141 \times \min\left(Cr/_k \text{ ó } 1\right)^{\alpha} \times max\left(Cr/_k \text{ ó } 1\right)^{-1.209} \times 0.993^{edad} \times (1.118, si\ mujer) \times (1.159, si\ raza\ negra)$$

Ecuación CKD-EPI creatinina de estimación de GFR.

k= 0.7 (mujer) ó 0.9 (varón); α = -0.329 (mujer) ó -0.411 (varón)

I.4.1.1.2.1.4 Comparación del comportamiento de las diferentes ecuaciones de estimación de filtrado glomerular basadas en la creatinina sérica.

La ecuación MDRD presenta un error sistemático infra estimando el filtrado glomerular en los niveles superiores a 60 ml/min/1.73 m^2. Es además impreciso a lo largo de todo el rango de valores de GFR.

Estudios comparando las ecuaciones de estimación de GFR CKD-EPI, MDRD y C-G han demostrado que la primera es más fiable ya que presenta mayor precisión (rango intercuartilico de la diferencia GFR estimado (eGFR) vs. medido (mGFR) 16.6 % para CKD-EPI y 18.3% para MDRD) e infra estima menos el filtrado glomerular (84% casos con $eGFR_{CKD-EPI}$ vs. 80% con $eGFR_{MDRD}$, en el 30% del mGFR), sobre todo en los valores de mGRF >60 ml/min 1.73m^2. (Levey et al. 2009)

Estudios prospectivos en poblaciones de Australia, Estados Unidos y Canadá muestran que la clasificación de GRF estimado con la ecuación CKD-EPI predice mejor el riesgo de eventos clínicos respecto a MDRD.(Matsushita, Van der Velde, et al. 2010; White et al. 2010; Levey et al. 2011).

Dos recientes meta análisis han comparado la capacidad predictiva de GFR estimado usando las ecuaciones CKD-EPI y MDRD para mortalidad, tanto cardiovascular como por cualquier causa, y progresión a ERCT.
En el estudio de Matsushita y col, incluyendo un total de 1.1 millón de sujetos procedentes de 45 estudios prospectivos de cohortes (25 con población general, 7 con población de alto riesgo y 13 con población diagnosticada de ERC), un 36% de sujetos clasificados por MDRD en ERC grado 3 (eGFR 45-59 mL/min/1.73m^2) pasaron a no ERC (eGFR 60-89 mL/min/1.73m^2) por CKD-EPI, presentando menor riesgo de eventos clínicos respecto a los no reclasificados, HR 0.8, 0.73 y 0.49 para mortalidad por todas las causas, mortalidad cardiovascular y ERCT respectivamente. El NRI (rango 0.06-0.13) fue significativamente positivo para todos los eventos estudiados.(Matsushita et al. 2012)
Por su parte, en el meta análisis realizado por Hallan y col. sobre datos individuales de 2.051.244 individuos, procedentes de 46 estudios prospectivos de cohortes, tanto un GFR inferior a 60 ml/min/1.73 m^2 como albuminuria (ACR>30 mg/g) se asociaron, con independencia de la edad, a mayor riesgo de mortalidad y progresión a ERCT. (S. I. Hallan et al. 2012)

Aunque ni la ecuación CKD-EPI ni la MDRD muestran un comportamiento optimo en todas las poblaciones y rangos de FG, desde una perspectiva de

salud pública y práctica clínica habitual, CKD-EPI parece la que presenta mejor rendimiento (Earley et al. 2012)

I.4.1.1.2.2. Ecuaciones basadas en niveles de cistatina C

La cistatina C es una proteína de la familia de los inhibidores de la cisteína proteinasa producida de forma estable por todas las células nucleadas. De bajo peso molecular, presenta filtración glomerular libre, pero no secreción tubular. A diferencia de la creatinina, sus niveles no están sometidos a la influencia de la masa muscular; sin embargo hoy se conocen factores extra renales de variabilidad como la hipo o hiperfunción tiroidea, tabaquismo, inflamación y tratamiento con corticoides. Estas características hacen de la cistatina C un interesante marcador para estimar FG, aunque pendiente de estudios más amplios que caractericen completamente su comportamiento.

Estudios realizados en poblaciones diversas, incluyendo personas ancianas ó diabéticos, han mostrado que las formulas de estimación de FG a partir de cistatina-C. (L. A. Stevens et al. 2009) aportan una estimación de similar precisión que las basadas en creatinina con un rango intercuartilico de la diferencia entre eGFR y mGFR , de 11.2% para cistatina C y 10.8% para creatinina (en ambos casos con edad, sexo y raza como covariables). Su validez es también similar (83% casos con $eGFR_{Cist}$ vs. 85% con $eGFR_{MDRD}$, en el 30% del mGFR).

$$GFR = 133 \times \min\left({Cist}/{0.8}\ \text{ó}\ 1\right)^{-0.499} \times max\left({Cist}/{0.8}\ \text{ó}\ 1\right)^{-1.328} \times 0.996^{edad} \times (0.932, si\ mujer)$$

Ecuación CKD-EPI con cistatina C de estimación de GFR.

I.4.1.1.2.3 Estimación de filtrado glomerular utilizando conjuntamente creatinina y cistatina C

Recientemente, se ha propuesto una ecuación de estimación de FG que utiliza conjuntamente creatinina y cistatina (Inker et al. 2012). Desarrollada en una cohorte de 5352 sujetos participantes en 13 estudios epidemiológicos, fue posteriormente sometida a validación externa en una cohorte de 1119 participantes en 5 estudios epidemiológicos diferentes.

$$GFR = 135 \times \min\left({Cr}/{k} \text{ ó } 1\right)^{\alpha} \times max\left({Cr}/{k} \text{ ó } 1\right)^{-0.601} \times \min\left({Cist}/{0.8} \text{ ó } 1\right)^{-0.375} \times max\left({Cist}/{0.8} \text{ ó } 1\right)^{-0.711} \times 0.995^{edad} \times (0.969, si\ mujer) \times (1.08, si\ raza\ negra)$$

Ecuación CKD-EPI creatinina-cistatina C de estimación de GFR.

k= 0.7 (mujer) ó 0.9 (varón); α = -0.248 (mujer) ó -0.207 (varón)

Los autores compararon la estimación de FG obtenida tanto a partir de ecuaciones con ambos marcadores juntos como con cada marcador por separado, frente a medición directa de FG. La ecuación conjunta presenta mayor validez y precisión que las respectivas ecuaciones individuales, con un sesgo similar como se observa en la Tabla 8 (Inker et al. 2012).

Tabla 8. Precisión en la estimación de creatinina mediante una ecuación con creatinina y cistatina C conjuntamente. Comparación frente a ecuaciones basadas en creatinina o cistatina C aisladamente.

	Mediana dif.	**RIC**	**P_{30}**
$eGFR_{cistatina}$	3.4	16.4	85.9
$eGFR_{creatinina}$	3.7	15.4	87.2
$eGFR_{cist\text{-}creat}$	3.9	13.4	91.5

Mediana dif: mediana de la diferencia mGFR-eGFR RIC- rango intercuartilico de la diferencia mGFR-eGFR.
P_{30}: porcentaje de eGFR que difieren <30% de la respectiva mGF

I.4.1.2 Estimación de proteinuria

La presencia de proteínas por encima de un umbral en orina es indicativo de afectación renal, con independencia de la tasa de filtrado glomerular. No todos los pacientes con ERC desarrollarán proteinuria, sin embargo su presencia identifica una subpoblación con mayor riesgo de progresión a ERCT, de enfermedad cardiovascular y de mortalidad (Cirillo et al. 2008; Ishani et al. 2006). En la cohorte del estudio PREVEND, Brantsma y col estudiando el evento combinado de morbilidad y mortalidad cardiovascular hallaron que la presencia de ERC grado 3 con ACR > 30 mg/gr representa, respecto a no ERC, un HR de 1.6 (IC 95% 1.1, 2.4), mientras que el riesgo para ERC grado 3 sin ACR>30 mg/gr es similar al de pacientes sin ERC, HR 1.0 (IC 95% 0.7, 1.4) (Brantsma et al. 2008).

Estudiar la presencia de proteínas en orina constituye una parte esencial del diagnóstico de ERC ya que permite una mejor estratificación del riesgo y como consecuencia dirigir las intervenciones de forma priorizada a los pacientes de alto riesgo (Obermayr et al. 2008).

Los métodos de medición de proteínas totales son más complejos en orina que en sangre. La concentración de proteínas en orina es habitualmente baja (100-200 mg/L); presenta frecuente variabilidad inter muestra en la cuantificación y composición de proteínas; y existe una relativamente elevada y variable interferencia por sustancias no proteicas. Por estas razones, los métodos de determinación de proteinuria presentan baja precisión a concentraciones bajas, menor sensibilidad y especificidad y elevado porcentaje de falsos positivos y falsos negativos.

Por su parte, la determinación de albúmina en orina proporciona una medición estandarizada de la pérdida de la proteína más significativa, común a la mayor parte de las nefropatías (Lamb et al. 2009; Miller et al. 2009).

En el estudio AusDiab, en población general adulta, la utilización de albuminuria para identificar proteinuria tuvo una especificidad el 95% con un valor predictivo negativo de 99.8%. En este estudio, un 92% de los sujetos con proteinuria (2.4% de la población general) tenían albuminuria, mientras un 8% (0.2% de la población general) presentaba niveles de albuminuria en rango de normalidad (Atkins et al. 2003). Atkins y col. postulan que estos pacientes podrían presentar proteinuria de cadenas ligeras ó nefropatía intersticial.

Por tanto, la utilización de determinación de albuminuria como biomarcador de proteinuria podría no identificar los casos de proteinuria tubular, sin embargo, debe tenerse en cuenta que el reconocimiento de proteínas tubulares es muy pobre con varios métodos empleados para cuantificar proteinuria. Por otra parte, en las enfermedades tubulares la perdida urinaria de albumina suele elevarse como resultado de la disminución de reabsorción tubular de albumina filtrada por glomérulo; Gosling y col estiman que cuando falla la reabsorción tubular por completo, la perdida de β2-microglobulina se incrementa aproximadamente a 1800 veces los niveles normales, pero también la perdida de albumina se incrementa aproximadamente 20 veces lo normal (Gosling 2008).

Así pues, la medición de albuminuria resulta el método de elección para determinación poblacional de proteinuria, mientras que cuando se sospecha una patología tubular debe cuantificarse la presencia de proteínas tubulares especificas (como la α1-microglobulina) mediante técnicas de inmunoanálisis (Lamb et al. 2009).

La cuantificación de albuminuria en orina de 24 horas constituye la prueba patrón oro de referencia, sin embargo la evidencia disponible apoya el uso del cociente albumina-creatinina (ACR) en una muestra de orina recogida a primera hora de la mañana como una adecuada alternativa por su capacidad predictiva, seguridad y mayor facilidad de una correcta obtención de muestra

(Ruggenenti et al. 1998; J. M. Ginsberg et al. 1983; Price et al. 2005; Côté et al. 2008).

Lambers y col. en una muestra representativa de población general (n=3432) estudiaron la capacidad predictiva de ECV entre diferentes métodos de estimación de albuminuria (Lambers Heerspink 2008).

En la tabla 9 se recoge el área bajo la curva (AUC) correspondiente a ocurrencia de eventos cardiovasculares para diferentes métodos de obtención de muestra.

Tabla 9. Capacidad predictiva de ECV de la estimación de albuminuria. Análisis del área bajo la curva (AUC) de las respectivas curvas ROC según grupos de edad y sexo para los diferentes métodos de recogida de orina.

		Orina 24 h.	**Muestra primera hora de la mañana**	
		EAO (mg / 24 h)	**CUA (mmol/L)**	**ACR (mg/mmol)**
Total		0.65	0.62	0.66
Subgrupo según sexo	Varones	0.64	0.62	0.68
	Mujeres	0.66	0.59 +	0.66**
Subgrupo según edad	< 47 años	0.58	0.52	0.52
	≥ 47 años	0.65	0.64	0.64

+ p<0.05 CUA vs EAO; ** p < 0.05 ACR vs CUA. EAO- excreción albumina en orina de 24 horas, ACR- albumina-creatinina ratio en muestra de primera hora de la mañana, CUA- concentración urinaria de albumina en muestra de primera hora de la mañana.

Como puede observarse la determinación de la ratio albumina creatinina (ACR) en muestra de primera hora de la mañana presenta similar AUC que el patrón oro (EAO), sin cambios significativos según grupo de edad ó sexo. Por el

contrario, la concentración urinaria de albumina (CUA) tiene menor AUC que la prueba patrón oro, con diferencias significativas según sexo.

Como reflejo de la variabilidad entre los diferentes métodos de estimación de proteinuria disponibles, las recomendaciones recogidas en las guías de práctica clínica presentan sensibles diferencias respecto al tipo de muestra de orina y método de estimación usado para el diagnóstico de proteinuria.

En la tabla 10 se recogen las más recientes recomendaciones.

Tabla 10. Recomendaciones de las principales guías de práctica clínica (GPC) en relación a la identificación de proteinuria.

GPC	Determinación recomendada: Albumina vs proteínas totales	Definición
KDOQI (2002)	Albumina mejor que proteínas totales. Excepción en niños.	Prot. Totales > 23 mg/mmol
KDIGO (2005)	Albumina (ACR)	ACR > 3.4 mg/mmol
SIGN (2008)	Proteínas totales. Excepción sujetos diabéticos en los que recomienda albumina	Prot. Totales ≥100 mg/mmol
NICE (2008)	Albumina (ACR)	ACR ≥ 30 mg/mmol
KDIGO (2010)	Albumina (ACR)	ACR > 3.4 mg/mmol Considerar albuminuria leve vs moderada vs severa

GPC- Guía de práctica clínica. ACR- albumina-creatinina ratio en muestra de primera hora de la mañana,

El criterio progresivamente uniforme es emplear la determinación de albuminuria mediante el ratio albúmina creatinina (ACR), así lo recogen tanto las guías KDIGO como las del National Institute for Health and Clinical Excellence (NICE) de Reino Unido ó del Scottish Intercollegiate Guidelines Network (SIGN). Persisten sin embargo diferencias en el punto de corte establecido en cada una.

Los niveles que determinan la presencia de albuminuria según las guías KDIGO se recogen en la tabla 11. Aunque los términos micro y macroalbuminuria han sido ampliamente utilizados tanto en investigación epidemiológica como en práctica clínica, las recomendaciones de las guías KDIGO 2010 son recoger la presencia de albuminuria siempre que esté presente cuantificándola en tres niveles crecientes: leve; moderada y severa. Una de las razones para este cambio es reflejar el incremento de riesgo de ECV encontrado ya a partir de valores de albuminuria de 10 mg/gr (ACR), evitando la infraestimación de riesgo que puede conllevar en clínica la anterior clasificación.

Tabla 11. Clasificación de albuminuria: valor de corte según método de determinación y sexo (KDIGO 2010).

		Muestra de orina (primera de la mañana ó aleatoria)		**Orina de 24 h.**
	Concentración albumina (mg/l)	**ACR (mg/gr)**		**Excreción albumina (mg/24 h)**
Normal/ Alb. leve	< 20	M	< 17	< 30
		F	< 25	
Microalb./Alb. moderada	20-200	M	17-170	30-300
		F	25-250	
Macroalb./Alb. severa	> 200	M	> 170	> 300
		F	> 250	

ACR: cociente albumina-creatinina en orina; Alb.: albuminuria; M: sexo masculino; F: sexo femenino.

I.4.2 Diagnóstico de resistencia a la insulina

I.4.2.1 Estimación de HOMA-IR

La estimación de resistencia a la insulina (RI) se realiza de forma habitual a través del empleo del Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), tanto en ámbito clínico como en estudios epidemiológicos.

Para su cálculo se emplea la siguiente ecuación, a partir de los niveles séricos de insulina y glucemia basales, propuesta por Matthews (D. R. Matthews et al. 1985)

$$HOMA - IR = insulinemia\ basasl(\mu U/ml) \times glucemia\ basal\ (mmol/L)/22.5$$

Establecer la distribución poblacional de niveles de HOMA-IR es importante para una adecuada interpretación de sus valores por parte de los profesionales clínicos. Las guías para la definición y establecimiento de intervalos de referencia en el laboratorio, señalan que debe además considerarse la existencia de diferencias significativas entre subgrupos definidos por edad, sexo ó exposiciones comunes, para comunicar resultados diferenciados para cada subgrupo.

Las principales fuentes de variabilidad en la definición de resistencia a la insulina son:

a) Las características de la población estudiada. Así en unos estudios se analiza una muestra poblacional aleatoria, mientras en otros se trata de una población seleccionada. Algunos trabajos incluyen individuos con y sin diagnostico de diabetes mientras que otros estudios únicamente incluyen a sujetos no diabéticos. El rango de edad es también muy variable, mientras la mayoría seleccionan únicamente población adulta, otros incluyen a niños.

b) El criterio de selección del punto de corte considerado óptimo. En la mayoría de los estudios publicados, se toma como criterio un percentil de la distribución hallada en la muestra a estudio, siendo éste el P75, P80 ó P90 según los casos. Una minoría de estudios analiza el comportamiento del HOMA-IR a través de curvas ROC.

Por otra parte, los estudios epidemiológicos publicados presentan una amplia variabilidad en los valores percentil de HOMA-IR como se recoge en la Tabla 12. La heterogeneidad en las características de cada población de estudio, sobre todo la relacionada con factores como la presencia de obesidad o diabetes, impide la comparabilidad en los resultados comunicados y dificulta la interpretación de los valores obtenidos en entorno clínico. Destaca la inclusión de individuos diabéticos en algunos estudios poblacionales, ya que la resistencia a la insulina es una alteración presente en la fisiopatología de la enfermedad por lo que está por definición presente en mayor o menor grado en todo paciente diabético.

Tabla 12. Distribución valores percentil de HOMA-IR en estudios poblacionales, ordenados por año de publicación.

Estudio	*Año*	*País*	*n*	*edad (años)*	*Características sujetos*	*HOMA-IR niveles*				
						P 50	P 66	P 75	P 80	P 90
Matsumoto	1997	Japón	530	15-70	No DM, IMC< 25kg/m^2					1.9
Bonora	1998	Italia	225	40-79	Sin alt met.[b]				2.7	
			888	40-79	DM + No DM	2.5		3.7		
Hedblad	2000	Suiza	4092	45-64	No DM			2.0		
Ascaso	2001	España	96	20-65	Sin alt met					3.8
Marques-Vidal	2002	Francia	1156	35-64	DM + No DM			3.8		
Nakai	2002	Japón	346	36.5± 0.8	Sin alt met[c]					1.8
Rojo-Martinez	2004	España	626	18-65	No DM	1.7		2.4		
Geloneze	2006	Brasil	312	37.2± 9	Sin alt met[c]					2.7
Bertoni	2007	USA	5810	45-84	No DM,	1.2				
Sumner	2008	USA	2804	≥ 20	No DM, NHANES 1999-2002		2.7			
De Luis	2009	España	213	45.1± 16	No DM IMC> 30kg/m^2)	4.4±4.1[a]				
Esteghamati	2009	Iran		20-77	Sin alt met [b]	1.4±0.9[a]		1.6	1.8	2.3
			1276	20-77	No DM ni HTA	1.8±1.2[a]		2.3	2.6	3.3
Do	2010	Tailandia	1217	> 35	No DM, IMC< 25kg/m^2	0.9		1.4		1.6
Tomé	2010	Spain	2860	18 - 104	DM + No DM	1.7				

[a] Media ± desviación estándar.

[b] Sujetos con: IMC <25 kg/m^2, triglicéridos <2.8 mmol/L, HDL-colesterol >1.0 mmol/L, colesterol sérico total>6.2 mmol/L, glucemia basal <7.7 mmol/L, TA sistólica <160 mm Hg y TA diastólica <95 mm Hg.

[c] Sujetos con IMC <25 kg/m^2, triglicéridos <1.7 mmol/L, HDL-colesterol >1.0 mmol/L, colesterol sérico total >5.7 mmol/L, glucemia basal <6.1 mmol/L, TA sistólica <130 mm Hg y TA diastólica <95 mm Hg

II. JUSTIFICACION GENERAL

La definición de estados patológicos a partir de puntos de corte en la distribución de marcadores biológicos continuos está sujeta a importantes fuentes de variabilidad (y por tanto de sesgo). Un adecuado estudio de la fiabilidad y precisión del método utilizado en la estimación del biomarcador es imprescindible para la correcta clasificación diagnóstica de los individuos. Al analizar el comportamiento de los biomarcadores, es necesario identificar el impacto de variables como edad y genero junto con otras características potencialmente modificadoras del mismo.

En la presente Tesis Doctoral se analiza el comportamiento poblacional de biomarcadores utilizados en el diagnostico de dos trastornos prevalentes de base inflamatoria como son la Enfermedad Renal Crónica y la Resistencia a la Insulina. De acuerdo a lo expuesto en la sección anterior, existe una importante variabilidad en los criterios utilizados para clasificación diagnóstica tanto de deterioro de la función renal como de resistencia a la insulina. Variabilidad relacionada con los métodos de estimación y con los criterios de selección del punto de corte optimo empleados.

Previamente a la realización del proyecto objeto de esta Tesis Doctoral, no se conocía la prevalencia de ERC ni la distribución de valores de HOMA-IR en población general en España, por lo que los resultados pueden contribuir a un precoz diagnóstico y correcta clasificación del riesgo de eventos clínicamente relevantes en la población general.

Por otra parte, son elementos a considerar en la planificación de los recursos disponibles orientándolos a una utilización más segura y eficiente de los dispositivos sanitarios.

III. OBJETIVOS

OBJETIVO GENERAL

Estudiar el comportamiento poblacional de biomarcadores en el diagnostico de enfermedades prevalentes, aplicado a dos trastornos de base inflamatoria como son la Enfermedad Renal Crónica, ERC, y la Resistencia a la Insulina, RI.

OBJETIVOS ESPECIFICOS

I. Estudiar las variaciones producidas en la estimación de prevalencia poblacional de ERC, por la utilización de diferentes métodos de estimación de la tasa de filtrado glomerular. Describir la prevalencia poblacional de ERC en España y su asociación con patologías crónicas y estilos de vida.

II. Estimar la distribución de HOMA-IR en población general española, identificando las principales fuentes de variabilidad.

III. Analizar los valores de HOMA-IR con mejor capacidad de discriminación de sujetos con factores de riesgo cardio-metabólico.

IV. Analizar en población general española la clasificación de ERC utilizando estimadores de riesgo de eventos finales clínicamente relevantes. Proponer una nueva clasificación de la ERC para el manejo clínico.

IV. MATERIALES Y METODOS

DISEÑO

Estudio epidemiológico transversal, de base poblacional.

POBLACIÓN DE ESTUDIO

Población diana: población española de ambos sexos mayor de 20 años.

Población de estudio: conformada por los sujetos que cumplen todos los criterios de inclusión y no tienen ningún criterio de exclusión.

- Criterios de inclusión

Sujetos de ambos sexos, de edad igual o superior a 20 años,

Residentes (inscritos en el censo correspondiente y que habitualmente vivan más de 6 meses al año) en la zona de estudio.

Seleccionados en el muestreo realizado según protocolo.

Aceptar su participación y firmar el consentimiento informado.

- Criterios de exclusión

Edad menor de 20 años en el momento de realizar el estudio.

Residencia actual fuera del municipio de estudio en situación que impida acudir a las citas programadas. No se considerará criterio de exclusión si la persona, aunque inscrita en un determinado domicilio, habita en otro de la misma ciudad o municipio.

Estar institucionalizados (ingresados en residencias, establecimientos sanitarios de larga estancia, instituciones penitenciarias, etc.) en el momento del estudio.

No poder contactar con el sujeto después de seguir el protocolo establecido.

Rechazar su participación en el estudio.

Ningún sujeto podrá ser excluido del estudio sin haberse solicitado 3 veces su participación y obtener respuesta negativa.

ESTIMACION DEL TAMAÑO MUESTRAL

Para estimar una prevalencia de ERC del 11% en la población, el número de sujetos de edad igual o superior a 20 años que se deben estudiar serían 5880 individuos, con un error máximo probable del 0,8%, un nivel de confianza del 95%. Considerando unas posibles pérdidas del 30% se incrementó el tamaño muestral a 8.400 individuos.

La selección de esta muestra contempla un muestreo estratificado, por conglomerados y polietápico:.

Para realizar la estratificación se han considerado las variables: comunidad autónoma (CA), hábitat de residencia (urbano >10.000 hab. / rural < 10.000 hab.), sexo y grupos de edad (20-39 / 40-64 / ≥ 65 años).

TECNICA DE MUESTREO

La técnica de muestreo se diseñó en forma de un proceso estratificado, por conglomerados y polietápico. Se tomó como base de muestreo el Censo 2001.
En primer lugar se ha estimado el número de sujetos que se deben estudiar en cada CA. Esta estimación se ha realizado en función del % de población que representa cada CA (17 más Ceuta y Melilla) respecto al total de población española con edad igual o superior a 20 años.

A continuación, se fijó para la muestra de cada CA la cuota de población rural y urbana que le corresponde, y se han seleccionado de manera aleatoria los municipios rurales y urbanos de los que se extraerá la población de estudio, de tal forma que la carga muestral por punto de muestreo no sea excesiva.

Para este propósito se ha seguido el siguiente criterio:

- En las CC.AA. que contribuyen a la muestra con más de 1.000 sujetos, 4 puntos de muestreo, uno de ellos rural (Andalucía, Cataluña, Madrid).
- En las CC.AA. que contribuyen con 800 a 1.000 sujetos, 3 puntos de muestreo, uno de ellos rural (Comunidad Valenciana).
- En el resto de CC.AA. 2 puntos de muestreo, uno rural y uno urbano, excepto en Ceuta y Melilla, donde se selecciona un solo punto.

Una vez definidos los 42 puntos de muestreo resultantes (tabla 13), se fijaron los tamaños de los estratos de edad (20-39, 40-64, ≥ 65 años) y sexo (hombre, mujer) que le corresponden a cada uno. Por último, en caso de puntos de muestreo en municipios con más de un área básica de salud, se aleatorizó la selección de un CAP en cada municipio seleccionado.

La lista de municipios seleccionados para cada CA en cada estrato fue remitida al INE con el fin de que procedan a la extracción aleatoria de los sujetos con las características indicadas en cuanto edad y sexo que corresponden a cada uno de los municipios o áreas básicas seleccionadas.

Tabla 13. Distribución de los puntos de muestreo según comunidad autónoma (C.A.) y municipio.

C. A.	Muestra			CAP urbano		CAP rural	
	Total	Urbana	Rural	n	Carga muestral	n	Carga muestral
Andalucía	1440	1107	333	3	369	1	333
Aragón	256	173	83	1	173	1	83
Asturias	232	199	33	1	199	1	83
Baleares	171	135	36	1	135	1	36
Canarias	337	288	49	1	288	1	49
Cantabria	113	75	38	1	75	1	38
Castilla-León	525	188	237	1	288	1	237
Castilla-LaMancha	355	176	179	1	176	1	179
Cataluña	1326	1057	269	3	352	1	269
C. Valenciana	854	682	172	2	341	1	172
Extremadura	211	93	118	1	93	1	118
Galicia	574	379	195	1	379	1	195
Madrid	1121	1057	64	3	352	1	64
Murcia	235	217	18	1	217	1	18
Navarra	116	60	56	1	60	1	56
País Vasco	447	361	86	1	361	1	86
La Rioja	60	36	24	1	36	1	24
Ceuta-Melilla	27	27	0	1	27	0	0
TOTAL	8400	6410	1990	25		7	

Durante el estudio piloto se observó un gran número de perdidas en la captación, identificándose como causa errores en los datos censales tales como cambio de domicilio, teléfonos no operativos, fallecimiento, etc. Por este motivo se solicitó al INE un incremento en el muestreo, manteniendo los mismos criterios muestrales, hasta un total de 13.013 sujetos.

COMPOSICION FINAL DE LA MUESTRA A ESTUDIO

Finalizado el trabajo de campo, se completo el estudio en 2790 individuos, un 21.44% de los 13013 muestreados como potenciales participantes. La situación y causas de pérdidas se detallan en la tabla 14. No fue posible contactar por error en los datos censales disponibles, a 4560 sujetos, siendo no localizables 1136; 853 sujetos no cumplían los criterios de inclusión y exclusión por lo que fueron considerados no válidos. Un total de 6464 sujetos fueron contactados, siendo realizadas 2790 encuestas lo que supone una tasa de respuesta del 43.16%.

Entre los 2437 que rehusaron participar en el estudio, 389 cumplimentaron el cuestionario (CC) diseñado para recoger información sobre factores de riesgo y estilos de vida.

Tabla 14 Resultado de la identificación de sujetos seleccionados: Situación final.

Situación	N	%
No contactado	4560	35,04
No localizado	1136	8,73
No valido	853	6,55
Rechazo con CC	389	2,98
Rechazo sin CC	2048	15,74
No contesta llamadas	1237	9,50
Encuesta realizada	2790	21,44
TOTAL	13013	100,00

Por errores en la recogida de datos que no permitían la determinación de creatinina sérica y por tanto de la tasa de filtrado glomerular, se excluyeron 44 sujetos (1.57%) siendo la muestra final a estudio de 2746 sujetos con una edad media de 49.47 años (IC 95% 47.35, 51.60).

El tamaño muestral final de 2746 sujetos representa una precisión en las estimaciones del 1.17% (en vez del 0.8% inicialmente establecido) para un nivel de confianza del 95%.

Durante el estudio piloto se observó un gran número de perdidas en la captación, identificándose como causa errores en los datos censales tales como cambio de domicilio, teléfonos no operativos, fallecimiento, etc. Por este motivo se solicitó al INE un incremento en el muestreo, manteniendo los mismos criterios muestrales, hasta un total de 13.013 sujetos.

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Al analizar la variación respecto a las características de edad, sexo y hábitat (rural / urbano) entre la muestra prevista y la finalmente obtenida, se observó una diferencia estadísticamente significativa en relación a edad y sexo, ($p<0.0001$). La distribución según hábitat no presentaba diferencias estadísticamente significativas. En la Tabla 16 se describen los resultados de este análisis.

La muestra final de estudio presentaba un mayor porcentaje de sujetos con edad mayor o igual a 65 años, mientras que los sujetos entre 20 y 39 años presentaban menor proporción. Por su parte, la proporción de mujeres fue mayor en la muestra final (58.19% vs 52.6%)

Tabla 16 Distribución según grupo de edad, sexo y hábitat en la nuestra a estudio: comparación con la población de referencia (Censo de 2001).

Muestra	**N**	**% muestra**	**% población**
		Edad p = 0.0001	
20-39	885	32,33	36,50
40-64	1283	46,72	37,70
>64	578	21,05	25,80
		Sexo p< 0.0001	
Hombre	1148	41,81	47,40
Mujer	1598	58,19	52,60
		Hábitat p=0,6821	
Rural	941	34,27	33,90
Urbano	1805	65,73	66,10
Total	2746	100,00	

Por estas razones, antes de iniciar el análisis de datos se realizó una ponderación de cada sujeto en función de la población española de sus mismas características, con la colaboración del INE. Se trabajó con una muestra ponderada, ponderando la no respuesta, de manera que una vez aplicados los pesos correspondientes a nuestra muestra, la distribución en cuanto a cuotas de edad, sexo y hábitat sea exactamente igual que en la población española definida según el censo del año 2001, como se observa en la tabla 17.

Tabla 17 Distribución según grupo de edad, sexo y hábitat en la muestra final ponderada.

Edad /sexo/Hábitat	Porcentaje	IC 95%
20-39 años	36,50	34,60-38,40
40-64 años	37,70	35,50-39,90
> 64 años	25,80	23,82-27,78
Hombre	47,40	45,46-49,30
Mujer	52,60	50,66-54,54
Rural	33,90	31,34-36,46
Urbano	66,10	63,54-68,66

IC 95%: intervalo de confianza del 95%

Además, para verificar la representatividad de la muestra, se realizó un análisis comparativo de las características epidemiológicas, estilos de vida y factores de riesgo cardiovascular entre la muestra de estudio y la población española mayor de 20 años correspondiente al Censo 2001. No se encontraron diferencias estadísticamente significativas en ninguno de los parámetros estudiados.

Todas las decisiones tomadas lo han sido con el objetivo de conseguir una muestra representativa de la población española con una edad de 20 años o más y, a la vez, facilitar la participación de los sujetos seleccionados y la realización del trabajo de campo.

VARIABLES DE ESTUDIO

Características demográficas y epidemiológicas

Edad (años), **sexo** (hombre/mujer), **hábitat** (rural/urbano).

Nivel de estudios. Se registro el nivel máximo de estudios que ha completado el sujeto. También se registro el nivel máximo de estudios del padre.

Situación laboral. Se registro la ocupación del individuo según la clasificación de clase social del British Registrar General (J. Alonso et al. 1997).

Antecedentes familiares. Hipertensión arterial, diabetes, dislipemia, gota, litiasis renal o insuficiencia renal en familiares directos de primer orden (abuelos, padres, hermanos o hijos).

Antecedentes personales. Se pregunto al sujeto si presentaba diagnóstico previo de hipertensión arterial, diabetes mellitus, dislipemia, gota, litiasis renal, insuficiencia renal, trasplante renal, menopausia, cardiopatía isquémica, ACVA o enfermedad vascular periférica, registrando, en caso afirmativo, la antigüedad de dicho diagnóstico o del último episodio (en meses) y el tratamiento que estaba recibiendo en el momento de la recogida de datos para cada trastorno. En caso de duda, ambas informaciones (patologías y/o tratamientos farmacológicos que sigue) se verificaron interrogando al médico de atención primaria correspondiente.

Hábitos higiénico-dietéticos.

Consumo de tabaco, categorizando dicho consumo en no fumador, fumador diario, fumador no diario (en las personas fumadoras se registró el número de cigarrillos, pipas o puros diarios y la edad a la que comenzó a fumar) o ex - fumador (especificando el número de meses y/o años que hace que abandonó el hábito tabáquico y su consumo).

Consumo de alcohol. Se cuantificó en unidades, vasos o copas (1 vaso = 200 ml), el consumo de vino o cava, cerveza, vermut, sidra, licores o combinados, y whisky.

Actividad física, según información del sujeto se clasificó en 4 grupos: Intensa (entrenamiento físico varias veces a la semana); regular (tenis, gimnasia, etc., varias veces al mes); ocasional (caminar o pasear en bicicleta, jardinería, etc.); nula (no hace ejercicio: leer, ver la televisión, etc.).

Consumo de fármacos. Se especificó el consumo de fármacos para las patologías analizadas en antecedentes personales, especificando el equipo terapéutico. Se investigó específicamente por el consumo de fármacos nefrotóxicos y la duración del mismo.

En caso de detectar el consumo de drogas de abuso se registró la sustancia o sustancias consumidas de forma habitual u ocasional.

Datos antropométricos

Exploración física.

Peso - en kilos y fracciones de 10 g.

Talla, en centímetros, usando el tallímetro según técnica estandarizada.

Los individuos se pesaron y tallaron descalzos y en ropa interior (o con el paciente desprovisto de prendas de abrigo u objetos de peso).

Circunferencia de la cintura (en centímetros) medida en el punto medio entre el reborde costal y la cresta iliaca.

IMC, se consideraron los pacientes como obesos si IMC > 30 kg/m^2; sobrepeso a valores entre 25 y 30 kg/m^2; normo peso a valores entre 20 y 25 kg/m^2; y bajo peso a sujetos con IMC inferiores a 20 kg/m^2.

Presión arterial y **frecuencia cardíaca** utilizando el esfigmomanómetro digital Omron. Se realizaron 2 mediciones consecutivas separadas por 3 minutos de intervalo en el brazo izquierdo con el paciente sentado. En caso de diferencias de más de 5 mm Hg entre las tomas, se realizó una tercera determinación pasados unos minutos. Como valor de presión arterial se tomó el promedio

entre las tomas. Se verificó que el sujeto no hubiera fumado, tomado café ni realizado ejercicio brusco en los 30 minutos previos a la realización de la exploración.

Datos bioquímicos

Se recogieron los siguientes parámetros en sangre venosa:

- Hemograma (hematíes expresado en millones/mm3 o x1012/l, hematocrito expresado en %, hemoglobina expresada en g/dl o mmol/l, VCM expresado en micras o fl, HCM expresado en pg y CCMH expresado en g/l).
- Glucemia (glucosa expresada en mg/dl o mmol/l)
- Insulinemia (insulina expresada en uU/ml, resistencia a insulina (test HOMA)).

  HOMA = insulina x glucosa / 22,5
- Perfil lipídico (colesterol total, colesterol-HDL, colesterol-LDL y triglicéridos expresados en mg/dl o mmol/l)
- Uremia (urea y ácido úrico expresados en mg/dl o mmol/l)
- Sideremia (Fe expresada en ug/dl o mmol/l)
- Ferritina (expresada en ng/dl o ug/l)
- Creatinina (expresada en mg/dl o mmol/l)
- Tasa de filtrado glomerular estimado según las ecuaciones MDRD – 4 y CKD-EPI

Se recogieron los siguientes parámetros en orina:

- Proteinuria (expresada en mg/24h)
- Albúmina (expresada en g/dl o mmol/l)
- Cociente Albúmina/creatinina (expresado en g/mg o g/mol)

Definiciones operativas

Insuficiencia renal Crónica (IRC)

Se han considerado como casos todos los sujetos con diagnóstico clínico previo de insuficiencia renal o aquellos cuyo filtrado glomerular, calculado mediante la ecuación MDRD, presentó un valor inferior a 60 mL/min/1,73 m^2 con o sin presencia de lesión renal (proteinuria).

Enfermedad renal Crónica (ERC)

Se ha considerado estadio 5 al fracaso renal (eGFR < 15 mL/min/1,73 m^2); estadio 4 de ERC a valores de eGFR entre 15 y 29 mL/min/1,73 m^2, estadio 3 a valores entre 30 y 59 mL/min/1,73m^2; estadio 2 entre 60-89 mL/min/1,73 m^2; con presencia de proteinuria; y estadio 1 valores superiores a 90 mL/min/1,73 m^2 con proteinuria..

Hipercolesterolemia: sujetos con diagnóstico médico previo y que reciban tratamiento o aquellos sujetos que en la exploración analítica presenten valores anómalos.

Hipercolesterolemia límite: colesterol total entre 200-249 mg/dl (5,17-6,45 mmol) y triglicéridos inferiores a 200 mg/dl (2,26 mmol/l).

Hipercolesterolemia definida: colesterol total > 250 mg/dl (6,45 mmol/l) y triglicéridos > 200 mg/dl (2,26 mmol/l). En prevención secundaria y en pacientes diabéticos se considero hipercolesterolemia definida en valores de colesterol > 200 mg/dl (5,17 mmol/l).

Hipertrigliceridemia: colesterol total < 200 mg/dl (5,17 mmol/l) y triglicéridos > 200 mg/dl (2,26 mmol/l). En prevención secundaria y en pacientes diabéticos la presencia de hipertrigliceridemia se estableció en valores > 150 mg/dl (1,69 mmol/l).

Hipertrigliceridemia mixta: colesterol total > 200 mg/dl (5,17 mmol/l) y triglicéridos > 200 mg/dl (2,26 mmol/l).

Hipertensión arterial (HTA): diagnóstico médico previo de HTA y en tratamiento o cifras de tensión arterial en valores diagnósticos. Se consideraron hipertensos a aquellos pacientes con cifras de presión arterial superiores a 140 mm Hg (PAS) y/o 90 mm Hg (PAD). Para la clasificación de los diferentes estadios se siguieron las directrices propuestas por el Seventh Report of the Joint National Commitee on prevention, detection, evaluation and treatment of high blood preasure (Chobanian, Bakris, H. R. Black, et al. 2003).

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Diabetes mellitus (DM): se consideraron diabéticos aquellos pacientes con diagnóstico médico de DM o que presentaron valores superiores de glucemia en ayunas iguales o superiores a 126 mg/dl.

Presión del pulso: variable categórica definida como diferencia entre PAS y PAD superior a 60 mm Hg (si / no).

Anemia: Presencia de valores de hemoglobina inferiores a 11 mg/dl. Variable categórica (presencia/no presencia)

PLAN DE TRABAJO

Citación

Los individuos seleccionados aleatoriamente para el estudio recibieron una carta tipo de presentación del estudio, en la que se les informó de la realización del estudio y se les invita a participar en él.

Posteriormente, cada sujeto recibió una llamada telefónica para comprobar los criterios de selección del sujeto y corregir cualquier error censal que pudiera existir. Confirmados estos datos, se le invitó a acudir a una entrevista, definiendo el día y la hora más conveniente.

En caso que el sujeto rehúse participar, se procuró recoger en una breve encuesta información sobre patologías y factores de riesgo de ERC que éste presente.

Tras esta entrevista telefónica, el sujeto recibió una segunda carta con información detallada del estudio y la confirmación por escrito de la cita y especificando día, hora y lugar en que tendrá lugar. Los sujetos que lo solicitaron recibieron un justificante para la empresa por su asistencia para participar en el proyecto.

Entrevista de recogida de datos

A cada sujeto seleccionado para el estudio se le realizó una única entrevista personal en el CAP de referencia que corresponda a su domicilio. En dicha entrevista se recogieron en el cuaderno de recogida de datos (CRD) las variables establecidas, se registraron sus características antropométricas y se tomó una muestra de sangre y de orina.

La determinación de creatinina fue realizada de forma centralizada en un mismo laboratorio para todas las muestras. Se evitó así la variabilidad inter laboratorios.

El resto de parámetros analíticos de determinaron en el laboratorio de referencia de cada CAP, una vez recabada la autorización de la estructura directiva correspondiente y con la colaboración de los servicios de análisis clínicos respectivos.

Los datos obtenidos se incorporaron posteriormente en la base central de datos de EPIRCE.

En caso de identificar alguna variable que requiriera especial atención (sobrepeso, HTA, dislipemia, diabetes u otras alteraciones posibles) se trasladó la información al sujeto con el consejo de que consulte con su médico de familia lo antes posible.

Se contó en cada punto de muestreo con la colaboración de :

• Servicio de nefrología: los facultativos especialistas del servicio que mostraron su deseo de participar en el mismo; residentes y, eventualmente, el personal de enfermería designado por el jefe de servicio.

• Servicio de bioquímica: los jefes de servicio y personal de laboratorio que éstos designaron.

• CAP: El jefe de servicio facilitó un local para la realización de las entrevistas y el contacto con los médicos de AP para obtener el conjunto de datos mínimos de los sujetos que no participaron finalmente en el estudio.

ASPECTOS ETICOS

Disposiciones legales vigentes seguidas

- Declaración de Helsinki (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”).
- Guías de la Conferencia Internacional de Armonización para la Buena Práctica Clínica desarrolladas por la UE (CPMP/ICH/135/95), Japón, EE.UU., Canadá, Australia, los países Nórdicos y la Organización Mundial de la Salud. International Conference on Harmonization (ICH) Harmonised Tripartite Gudeline, ICH Topic E6: Guideline for Good Clinical Practice.

- Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.
- Ley 03/2005 que modifica la Ley 03/2001 reguladora del consentimiento informado e historia clínica de los pacientes.
- Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios.
- La ORDEN SCO/256/2007, de 5 de febrero, por la que se establecen los principios y las directrices detalladas de buena práctica clínica y los requisitos para autorizar la fabricación o importación de medicamentos en investigación de uso humano.
- Ley Orgánica de Protección de Datos de Carácter Personal.
- El análisis estadístico se realizó siguiendo las normas de buena práctica en Biometría de la International Conference on Harmonization 6 (ICH 6).

Hoja de información y formulario de consentimiento

Se informó al paciente verbalmente y por escrito de los diferentes aspectos del estudio y las consecuencias de su aceptación a participar, para su conocimiento y se solicitó posteriormente su consentimiento informado según modelo recogido en anexo.

Los datos personales de los pacientes (nombre, apellidos, dirección y teléfono) quedaron bajo custodia del investigador y sólo se utilizaron para contactar con el sujeto según lo previsto en el protocolo.

Confidencialidad de los datos

Para garantizar la confidencialidad de los datos se asignó un código a cada sujeto en el momento de su inclusión en el estudio. La recogida, procesamiento y análisis de información se realizó de forma codificada y disociada en todo momento. Se garantizo así en todo momento la confidencialidad sobre los datos que identifican a los sujetos de estudio, custodiados por el equipo investigador.

Aprobación por Comité Ético de Investigación Clínica

El estudio fue evaluado por el Comité Ético de Investigación Clínica de Galicia, emitiéndose dictamen favorable con código AMG-EPI-2003-03 y registro del CEIC: 2004/042

COLABORACION INSTITUCIONAL

El estudio contó con la colaboración de las siguientes instituciones a las que se presentó el protocolo del estudio:

• Dirección General de Planificación Sanitaria del Ministerio de Sanidad y Consumo

• Consejerías de Salud de todas las CC.AA. del Estado, a través del Consejo Interterritorial de Salud

• Sociedad Española de Nefrología, promotor del estudio.

• Gerencias de los hospitales y de los CAP participantes en el estudio, quienes facilitaron la realización de los estudios de bioquímica no centralizados y la realización de las entrevistas epidemiológicas durante el trabajo de campo.

• Instituto Nacional de Estadística (INE).

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V. RESULTADOS

V.1 ARTICULO i

"Epidemiology of chronic renal disease in the Galician population: results of the pilot Spanish EPIRCE study"

Otero A, Gayoso P, García F, De Francisco AL.

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RESUMEN:

En este original se comunican los resultados del estudio epidemiologico transversal planteado como piloto del estudio EPIRCE que fue realizado en la submuestra de población seleccionada en la C.A. de Galicia por el Instituto Nacional de Estadistica. Ademas del analisis de situacion en Galicia, cumplio el objetivo de identificar los aspectos a mejorar en el plan de trabajo planteado, adaptandolo a los procedimientos mas eficientes para facilitar la participacion de todos los sujetos seleccionados y garantizar la correcta recogida y procesamiento de los datos y muestras biologicas.

ABSTRACT

Background. Chronic kidney disease (CKD) is a major social health problem because of the aging of the population, the high incidence of diabetes mellitus, and the epidemic of silent CKD resulting from inadequate diagnosis of early chronic renal insufficiency

Methods. The sociodemographic, baseline characteristics and CKD prevalence measured by the Modification of Diet in Renal Disease formula were studied in a randomly selected sample of people aged 20 years or older in the general population. We report the results of the analysis of the EPIRCE (Estudio Epidemiologico de la Insuficiencia Renal en España) pilot study performed in Galicia, Spain, in the last quarter of 2004.

Results. Baseline characteristics, sociodemographic characteristics, and results of a clinical examination and blood variables were collected from 237 patients who fulfilled the study's inclusion and exclusion criteria. The mean age of the sample was 49.58 years (95% confidence interval, 47.39-51.76). The prevalence of Kidney Disease Outcomes Quality Initiative grade 3 CKD was 5.1%, but the coexistence of an albumin/creatinine ratio >30 mg/g with grade 1 to 2 CKD raised the final rate to 12.7% in this population. We found a high prevalence of hypertension (31.5%), isolated systolic hypertension (20.1%), diabetes mellitus (8%), obesity (13.1%), smoking habit (22.7%), high atherogenic index (30.8%), and high alcohol intake (24%). Risk factors significantly associated with renal disease were age [P = 0.018; odds ratio (OR) 2.7], hypertension (P = 0.023; OR 2.13), pulse pressure (P = 0.04; OR 0.10), diabetes mellitus (P = 0.08; OR 4.48), obesity (P = 0.000; OR 7.7), and insulin resistance index (P = 0.04; OR 4.95).

Conclusion. The prevalence of CKD and conventional cardiovascular risk factors is high in this randomly selected sample of the general population. Secondary preventive measures are needed to detect chronic kidney impairment as early as possible and to reduce the incidence and mortality arising from the associated comorbidities.

Keywords: cardiovascular risk factors, chronic kidney disease, epidemiology.

INTRODUCTION

Chronic kidney disease (CKD) is a public health problem worldwide because of the increasing prevalence of type 2 diabetes mellitus and atherosclerosis-related renal disease. This creates an important health care problem because a high proportion of these patients will need renal replacement therapy. One of the barriers to early detection of CKD is the lack of a precise, reliable, and consistent measure of kidney function. In practice, the glomerular filtration rate (GFR) is usually evaluated with the serum plasma creatinine (SCr) concentration. However, SCr concentration varies by age, sex, muscle mass, and diet, and between laboratories. Moreover, SCr concentration can remain within the normal range despite significantly impaired renal function. The National Health and Nutrition Examination Survey III (NHANES III) study [1] reported that 11% of the United States population exhibits an abnormal SCr concentration, although we do not know whether these data also apply to Spain because such measurements are not always directly comparable. (Coresh et al. 2003; Simal et al. 2004; Otero, Abelleira, et al. 2005; Gorostidi et al. 2004)

In Spain, patients are referred to nephrology departments late in the course of the disease. The epidemiologic data should be viewed with caution because the Modification of Diet in Renal Disease (MDRD) equation underestimates GFR by 6.2% in patients with CKD and 29% in healthy persons (Rule et al. 2004), and the method selected to estimate renal function may affect the interpretation of the relation between cardiovascular risk factors and renal function. To study the relation between risk factors and renal function in large population studies, indirect estimates of renal function should be used with caution (Verhave et al. 2004). Nevertheless, the systematic evaluation of all patients and incorporation

of simplified definitions should improve the outcome in patients with kidney disease, and the MDRD formula is a useful method for studying large populations.

Cardiovascular disease is the most common cause of death in patients with (Muntner, He, L. L. Hamm, et al. 2002; Zanchetti et al. 1998; Anavekar & McMurray 2004), who should be considered in the highest risk group for cardiovascular disease. Traditional and non-traditional risk factors have been implicated in the high prevalence of cardiovascular disease associated with CKD. The inflammatory process starts in the early phases of CKD, as shown by a GFR of 50 to 60 mL/min (Stenvinkel et al. 2002), and accelerates vascular damage through an increase in insulin resistance, stimulation of the adhesion molecules, inhibition of nitric oxide synthesis, endothelial dysfunction, and arteriosclerosis. The proinflammatory cytokines and impaired synthesis of erythropoietin are implicated in the onset of anaemia, which contributes significantly to the development of left ventricular hypertrophy, a significant cause of mortality. Well-established therapeutic interventions that delay or prevent progressive kidney disease are incorporated into the widely disseminated clinical practice guidelines, which recommend aggressive treatment of traditional and non-traditional risk factors. These interventions also reduce the risk of cardiovascular disease and should be regarded as essential components in the care of patients with CKD.

For the reasons mentioned above, the Spanish Nephrology Society is studying the prevalence of CKD in Spain to provide useful information to identify the true population at risk and to increase the preventive measures aimed at reducing the incidence of renal failure, cardiovascular complications, and the progression

to renal sclerosis. This program is based on the concept that early detection and prevention can influence the outcomes of both renal insufficiency and cardiovascular morbidity and mortality.

This is the first study to investigate the prevalence of CKD in Spain. The Estudio Epidemiologico de la Insuficiencia Renal en España (EPIRCE) study investigated GFR, calculated by a simplified MDRD formula, in a randomly selected sample of the general population 20 years of age and older. We now report on the preliminary data obtained from the pilot study performed in Galicia, a region of Spain.

METHODS

The EPIRCE study is an epidemiologic, general population-based, transversal study that includes a randomly selected Spanish sample (N = 8400) aged 20 years or older. The sample was stratified by age, sex, and region, and is representative of all areas of Spain.

The initial sample results correspond to a pilot study performed in Galicia, one of the areas selected initially to identify potential difficulties before extending the study to all areas of Spain.

This first pilot study included a randomly selected sample of 574 residents of Galicia. Of the original sample of 574, 63 were excluded from the study, 107 were not contacted, and 165 refused to participate, leaving 239 who met the inclusion criteria.

The variables measured included anthropometric data (weight, height, body mass index) and baseline characteristics (obesity, history of hypertension, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia). Participants were interviewed to determine their smoking habits, alcohol consumption, and use of nephrotoxic drugs. After informed consent was provided, a blood sample was obtained from each individual for biochemical tests, which included serum creatinine concentration determined in the same reference laboratory for all samples.

GFR was calculated as an indicator of renal function with the simplified MDRD formula (Levey et al. 2000), and participants were classified according to the Kidney Disease Outcomes Quality Initiative guidelines. (Levey et al. 2003)

Statistical methods

Quantitative variables were summarized in terms of means and 95% confidence interval (CI); the comparison between CKD groups was performed by using a t test. Comparisons between categorical variables were performed with chi-square test. Univariate and multivariate logistic regression analyses were used to estimate the odds ratio (OR) and CIs comparing vascular risk factors on CKD occurrence. $P < 0.05$ was considered significant. Analyses were performed with SPSS (Chicago, IL, USA).

RESULTS

The pilot study analysed data for 237 participants or 41.6% of the initial sample of 574. This study sample was distributed similarly to the estimated sample size design (Table 1).

Table 1. Distribution of the sample size and the theoretical assignment in the protocol.

		Sample (%)	**Planned population (%)**
Age, years	20-39	33.76	36.5
	40-64	43.46	37.7
	> 65	22.78	25.8
Sex	Male	42.6	47.7
	Female	57.4	52.6
Habitat	Urban	65.0	66.1
	Rural	35.0	33.9

The mean age was 49.58 years (95% CI 47.39-51.76), and the prevalence of grade 3 CKD was 5% (Table 2). However, after the addition of participants classified as grade 1 or 2 CKD because they had an albumin/creatinine ratio >30 mg/g, the prevalence of CKD increased to 12.7%.

Table 2. Prevalence of CKD according to the degree of renal insufficiency and pathologic albumin/creatinine index

			Alb/Cr (> 30 mg/dL)	
GFR mL/min/1.73 m^2	**N**	**Prevalence**	**N**	**Prevalence**
>90	95	40.6	8	3.5
>60–89	127	54.3	8	3.5
>30–59	11	4.7	11	5.3
>15–29	1	0.4	1	0.4
<15	0	0	0	0
Total	234	100	28	12.5

CKD, chronic kidney disease; GFR, glomerular filtration rate: Alb/Cr, albumin/creatinine

The prevalence of associated cardiovascular risk factors was high for arterial hypertension (31.5%), isolated systolic hypertension (20.1%), pulse pressure (27.8%), obesity (13.1%), diabetes mellitus (8%), a high atherogenic index (30.8%), hypercholesterolemia (12.8%), hypertriglyceridemia (6.3%), elevated low-density lipoprotein-cholesterol complex (37.5%), low high-density lipoprotein-cholesterol complex (18.1%), smoking >10 cigarettes/day (22.7%), and high alcohol consumption >70 g/day (24%).

Table 3. Prevalence (%) of conventional VRF according to the stages of renal function (G1-G3)

VRF	G1	G2	G3	P
HT	4.2	5.6	9.9	0.107
ISHT	5.9	5.9	14.7	0.038
PP	3.2	7.9	11.1	0.01
Obesity	4	4	8	0.471
DM	16.7	0	16.7	ND
Hypercholesterolemia	0	3.4	10.3	ND
Hypertriglyceridemia	0	20	6.7	ND
Low HDL-C	4.8	4.8	9.5	0.505
High LDL-C	3.6	2.4	4.4	0.88
AI	4.3	5.8	10.1	0.08

VRF, vascular risks factors; G1, GFR <90; G2, GFR 60–89; G3, GFR 30–59; HT, hypertension (blood pressure >140/90 mm Hg); ISHT, isolated systolic HT (systolic blood pressure >140 and diastolic BP <90 mm Hg); PP, pulse pressure >60 mm Hg; obesity, BMI >29 kg/m^2; DM, diabetes mellitus (blood glucose concentration >126 mg/dL); hypercholesterolemia >240 mg/dL; hypertriglyceridemia >200 mg/dL; low HDL-C concentration <35 mg/dL; high LDL-C concentration >160 mg/dL; AI, atherogenic index (>4); ND, not determined.

The prevalence of cardiovascular risks factors increased in proportion to GFR (Table 3). Univariate analysis identified the independent variables that correlated significantly with GFR as age (OR 2.7), hypertension (OR 2.13), pulse pressure (OR 0.101), diabetes mellitus (OR 4.481), obesity (OR 7.7), and the insulin resistance index (OR 4.95) (Table 4). However, GFR was correlated significantly only with pulse pressure (P = 0.066; OR 5.74) and diabetes mellitus (P = 0.060; OR 6.95) in the multivariate analysis.

Table 4. Risk of CKD and atherosclerotic risk factors. Univariate logistic regression analysis.

Variable	P	OR	95% CI
Age	0.018	2.7	1.18, 6.31
HT	0.023	2.13	1.11, 4.11
ISHT	0.123	2.039	0.82, 5.04
PP	0.042	0.101	0.96, 3.90
DM	0.086	4.481	1.54, 13.04
Obesity	0.0000	7.7	2.65, 22.3
Hypercholesterolemia	0.11	2.08	0.84, 5.15
Hypertriglyceridemia	0.22	2.01	0.64, 6.29
High LDL-C concentration	0.230	1.437	0.77, 2.79
AI	0.70	1.845	0.95, 3.57
HOMA	0.04	4.95	1.07, 22.8
Smoking	0.26	0.73	0.43, 1.25
Alcohol	0.467	0.78	0.41, 1.50
Physical activity	0.92	1.03	0.50, 2.13

CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; hypertension (blood pressure >140/90 mm Hg); ISHT, isolated systolic hypertension (systolic blood pressure >140 and diastolic BP <90 mm Hg); PP, pulse pressure >60 mm Hg; DM, diabetes mellitus (blood glucose concentration >126 mg/dL); obesity, BMI >29 kg/m2; hypercholesterolemia >240 mg/dL; hypertriglyceridemia >200 mg/dL; high LDL-C concentration >160 mg/dL; AI, atherogenic index (>4); HOMA, blood insulin × glucose concentration/22.5; smoking >10 cigarettes/day; alcohol consumption >70 g/day.

DISCUSSION

This preliminary report of a pilot study of 237 randomly selected patients in Galicia is the first in a larger study of the prevalence of CKD in the general population in Spain. The larger study will include more than 8400 people and aims to investigate the prevalence of silent CKD in the Spanish population.

The approach to CKD and its management have changed recently based on new epidemiologic, clinical, and physiopathology evidence showing that, even in its early stages, CKD constitutes a significant risk factor for cardiovascular and global morbidity and mortality be-cause of the inflammatory state in the initial phases of renal failure. For these reasons, the Seventh Report of the Joint National Committee (Chobanian, Bakris & H. R. Black 2003) includes micro albuminuria and a GFR <60 mL/min as significant cardiovascular risk factors. The fundamental objective is to identify people at risk of developing cardiovascular complications among the apparently healthy and those already diagnosed with vascular disease or grade 1 or 2 CKD. Our data from the EPIRCE pilot study are relevant because of the high prevalence of conventional risk factors, CKD (12.7%), and a GFR <60 mL/min (5.7%) in a population with a mean age of 49.58 years.

The overall prevalence of CKD was 11% in the U.S.-based NHANES III study (Coresh et al. 2003) and 12.7% in our pilot study. The prevalence distribution pattern using the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative stages of CKD was 3.3% in NHANES III and 3.5% in our study for stage 1, 3.0% in NHANES III and 3.5% in our study for stage 2, 4.3% in NHANES III and 5.3% in our study for stage 3, 0.25% in NHANES III and 0.4% in our study for stage 4, and 0.2% in NHANES III and 0% in our study for stage 5 (end-stage renal failure); the latter value was very low because of the small sample size. Others have reported similar values. Anandarajah et al reviewed routinely collected data from 12 practices in 3 localities across the United Kingdom and found that 4.9% of the registered population had an estimated GFR of <60 mL/min/ 1.73 m2, which is equivalent to stages 3 to 5 CKD

(Anandarajah et al. 2005). We found a relatively high prevalence of asymptomatic CKD in the apparently healthy general population in Spain.

We found that age, arterial hypertension, isolated systolic hypertension, pulse pressure, diabetes mellitus, obesity, and the insulin resistance index were independent variables related to renal disease. All of these variables reflect it´s combined effects of inflammation and arteriosclerosis.

Prevention of CKD and its associated complications needs a clear understanding of the prevalence and outcome of renal disorders, the earlier stages of renal disease, the risk factors, and the appropriate treatment of populations at risk. In the study by Anandarajah et al (Anandarajah et al. 2005), although 5% of the population had stages 3 to 5 CKD, only a small proportion (8%) of these individuals had received a renal diagnosis or had been seen by a renal physician.

Earlier identification of CKD in primary care, better management of cardiovascular risk, the avoidance of medication that impairs renal function, and specialist referral where appropriate may improve long-term outcomes.

However, our understanding of this disease, its risk factors, and its impact on the public health system is incomplete, and no large epidemiologic studies have been performed in Europe. Future studies should focus on the prevalence and outcome of CKD and on the pathology of the interaction between the kidney and cardiovascular system to prevent the progression of renal dysfunction, which should have a beneficial effect in reducing the risk and prevalence of cardiovascular disease.

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V.2 ARTICULO 2

"Prevalence of chronic renal disease in Spain: Results of the EPIRCE study "

Otero A, Gayoso P, Garcia F, De Francisco AL. on behalf of the EPIRCE Study Group

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RESUMEN: En este original se recogen los resultados globales de prevalencia de Enfermedad Renal Crónica y factores de riesgo asociados en población general española mayor de 20 años, mediante el estudio de una muestra de 2746 individuos. Se utiliza para la estimacion de la tasa de filtrado glomerular la ecuación MDRD-4. Se aborda con estos resultados el objetivo especifico primero de esta Tesis de Doctorado.

ABSTRACT

Introduction: Chronic kidney disease (CKD) is an independent cardiovascular risk factor. The knowledge of prevalence in general population may help to early detection of CKD and prevent or delay its progression.

Methods: Sociodemographic, baseline characteristics, and CKD prevalence (measured by centralized serum creatinine and MDRD equation) were evaluated in a randomly selected sample of general population aged 20 years or older, collected in all Spanish regions and stratified by habitat, age and sex according to 2001 census (n = 2,746). Univariate and multivariate logistic regression analyses were used to evaluate associations with CKD risk factors.

Results: Mean age was 49.5 years. The overall prevalence of Kidney Disease Outcomes Quality Initiative grades 3-5 CKD was 6.8%, with a 95% confidence interval (CI) of 5.4 to 8.2 (3.3% for age 40-64 years and 21.4% for age >64 years). The prevalence estimates of CKD stages were: 0.99% for stage 1 (glomerular filtration rate [GFR] >_90 ml/min per 1.73 m2 with proteinuria); 1.3% for stage 2 (GFR 60-89); 5.4% for stage 3a (GFR 45-59); 1.1% for stage 3b (GFR 30-44); 0.27% for stage 4 (GFR 15-29); and 0.03% for stage 5 (GFR <15). An important prevalence of classical cardiovascular risk factors was observed: dyslipemia (29.3%), obesity (26.1%), hypertension (24.1%), diabetes (9.2%) and current smoking (25.5%). The independent predictor factors for CKD were age, obesity and previously diagnosed hypertension.

Conclusions: The prevalence of CKD at any stage in general population from Spain is relatively high, especially in the elderly, and similar to countries of the same geographical area. Independently of age, two modifiable risks factors, hypertension and obesity, are associated with an increased prevalence of CKD.

Key words: Cardiovascular risk factors. Chronic kidney disease. Epidemiology.

INTRODUCTION

Chronic kidney disease (CKD) is a major social health problem. In the last decade, it has been shown that early stages of CKD are associated with an inflammatory state (Stenvinkel et al. 2002) that implies an increased cardiovascular morbidity and mortality risk at long term (Sarnak et al. 2003; Ruggenenti et al. 2001), higher than the risk of progression to end stage renal disease (Sarnak et al. 2003; Mann et al. 2001). Cardiovascular events are the most common cause of death in these patients (Muntner, He, L. Hamm, et al. 2002). For this reason, micro albuminuria and reduced glomerular filtration rate (GFR) (<60 ml/min/1.73m^2) have been added to the list of non traditional cardiovascular risk factors (Chobanian, Bakris, H. R. Black, et al. 2003). In many patients, the concurrence of these markers with classical factors as diabetes, hypertension or obesity, predicts accelerated vascular damage and multiplies the associated risk (Sarnak et al. 2003; Ruggenenti et al. 2001).

Furthermore, the prevalence of CKD is growing worldwide due to the increase in related diseases as type 2 diabetes mellitus, obesity, hypertension or atherosclerosis (Perneger et al. 1994; Haroun et al. 2003). The asymptomatic nature of CKD makes its early detection more difficult, which could be important as the treatment in early stages may prevent or delay its progression (Locatelli et al. 2002). The knowledge of the prevalence of CKD might be useful to assess the level of its under diagnosis and estimate the impact of potential screening policies.

The 2002 practice guideline of the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) (Foundation 2002a) defined

CKD as either kidney damage or glomerular filtration rate (GFR) below 60 ml/min/1.73 m2 for three or more months. GFR is usually estimated from serum creatinine using one of the following equations: the Cockcroft-Gault (CG) (Cockcroft & Gault 1976) or the Modification of Diet in Renal Disease Study (MDRD) (Levey et al. 1999) equation. These indirect methods are currently considered to be the easiest way to estimate GFR in epidemiologic studies conducted in adult individuals (Verhave et al. 2003). The MDRD equation is more commonly used (Q. L. Zhang & Rothenbacher 2008), but it leads to a certain underestimation of GFR (6.2% in CKD patients and 29% in healthy persons) (Rule et al. 2004) compared to the CG equation. However, it seems that the MDRD equation provides a more accurate estimation in patients with GFR below 60 ml/min/1.73 m^2, with good performance among subgroups of age, sex, race, diabetes or body mass index (Lamb et al. 2005; L. A. Stevens et al. 2007).

In the last five years, more than 25 epidemiological studies have investigated CKD prevalence worldwide (Q. L. Zhang & Rothenbacher 2008), leading to a median prevalence of 7.2% in persons aged 30 years or older, and revealing ethnic-specific differences. In our country, the Spanish Society of Nephrology (S.E.N.) has initiated a program to identify the true population at risk for CKD, and to increase the preventive measures aimed at reducing the incidence of renal failure, cardiovascular complications, and progression to end stage renal failure (Martin de Francisco et al. 2009; de Francisco et al. 2007).

Within this program, the «Estudio Epidemiólogico de la Insuficiencia Renal en España» (EPIRCE) is the first epidemiological study at a national level designed

to describe the prevalence of CKD in the general Spanish population aged 20 years or older, using the simplified MDRD equation.

METHODS

The EPIRCE was an epidemiologic, general population based, cross-sectional study that included a randomly selected Spanish sample aged 20 years or older. The exclusion criteria were residence outside the recruiting municipality, or institutionalization at the time of the study. An ethics committee approved the protocol, and all enrolled patients provided informed consent.

The target sample were 13,013 individuals, stratified by age, sex, and habitat within each Spanish region, according to the 2001 Census. A total of 6,464 out of the initial list of 13,013 were finally contacted for the study. Census errors were the most important reason for the impossibility to contact individuals. The sample was recruited between January 2004 and January 2008 in 42 points (municipalities). The final completed interviews were 2,746, and the response rate was 42.5%.

Data were collected as follows. First, a letter describing the study was sent to each randomly selected individual. Next, a health professional contacted the potential respondents by phone to verify inclusion and exclusion criteria, ask for participation, and make appointments with those who volunteered. Minimums of three negative answers were required to discard a selected individual.

The collected variables included anthropometric and sociodemographic data (age, gender, ethnicity, weight, height, body mass index), blood pressure and

clinical history at study inclusion (obesity, hypertension, diabetes mellitus, dyslipemia, cardiovascular disease, gout, renal lithiasis, CKD, transplant). Participants were also interviewed to determine their smoking and exercise habits, alcohol consumption, drug abuse and use of nephrotoxic drugs. After informed consent was provided, a blood sample was obtained from each individual for biochemical tests. Serum creatinine concentration was determined in the same reference laboratory for all samples. GFR was calculated as an indicator of renal function with the simplified MDRD formula (Levey et al. 2000), and participants were classified according to the Kidney Disease Outcomes Quality Initiative guidelines (Foundation 2002a). Stage 3 was split into 3a (GFR 45-59 mL/min/1.73 m^2) and 3b (GFR 30-44 mL/min/1.73 m^2). Other analytical determinations included: glucose, urea, total cholesterol (C), triglycerides (Tg), HDL-C, LDL-C, insulin resistance index (HOMA), haemoglobin (Hb), ferritin, uric acid and urinary albumin to creatinine ratio.

Statistical methods

Adjustment weights were used to correct for non-response bias, with the age, gender and habitat distribution of survey respondents being equated to the population structure as determined from the 2001 census. All prevalence and mean estimates were calculated with the weighted sample, and asymptotic 95% confidence intervals (CI) were obtained. Univariate and multivariate logistic regression analyses, also weighted for non-response bias, were used to calculate the odds ratio (OR) and CIs for candidate CKD risk factors. P values < 0.05 were considered significant. Since there were 0.05 were considered

significant. Since there were statistically significant differences in the response rate between participating municipalities (data not shown), a sensitivity analysis was performed comparing the results between highly responding centres (>60% of response rate, n = 1,098) and the overall group, to assess for a possible non-response bias. All analyses were performed with SAS version 9.1.3 Service Pack 4 (SAS Institute Inc., Carey, North Caroline, USA).

RESULTS

Sociodemographic and clinical characteristics.

Tables 1 and 2 show the characteristics of the 2,746 respondents (weighted estimates). Mean age was 49.5 years, and about one quarter of individuals was older than 64 years (25.8%). As in the general Spanish population, the ratio male: female was 0.9, almost all were Caucasian (99.1%), and the residence was urban in two thirds of cases (66.1%).

Clinical history revealed an important prevalence of previously diagnosed dyslipemia (29.3%), obesity (26.1%), hypertension (24.1%) and diabetes (9.2%). Among cardiovascular events, peripheral vascular episodes were the most frequent (10.8%), followed by ischemic heart disease (5.1%) and cerebrovascular disease (1.7%). Current smoking habit and habitual alcohol intake were frequent (25.5% and 45.1%, respectively).

Table 1. Demographic and clinical characteristics of Spanish population aged 20 years or older based on the cohort collected in the EPIRCE study (n=2746).

	N	Prevalence in Spanish population *
Age, years, mean (SEM)	2746	49.5 (1.1)
20-39	885	36.5%
40-64	1283	37.7%
>64	578	25.8%
Sex, %		
Male	1148	47.4
Female	1598	52.6
Habitat, %		
Urban	1805	66.1
Rural	941	33.9
Ethnicity		
Caucasian	2669	99.1
African	13	0.46
Asian	1	0.04
Others	12	0.44
BMI, kg/m2, mean (SEM)		
Overweight (BMI 25-30 kg/m2)	1063	39.4
Obesity (BMI > 30 kg/m2)	723	26.1
Systolic blood pressure, mmHg	2737	132.3 (1.0)
Diastolic blood pressure, mm Hg	2736	78.8 (0.4)
Hypertension, %	1128	42.4
Previously diagnosed	640	24.1
Current hypertension (SBP/DBP>140/90 mmHg)	937	35.6

Isolated systolic hypertension	464	18.3
Pulse pressure>60 mmHg, %	658	26.2
Previous cerebrovascular disease, %	46	1.7
Previous ischaemic heart disease, %	123	5.1
Previous peripheral vascular disease, %	303	10.8
Previous gout,%	122	4.7
Previous diagnosis chronic kidney disease, %	11	0.4
Previous kidney transplant, %	1	0.04
Previous renal lithiasis,%	385	13.9
Glucose, mg/dl, mean (SEM)	2741	96.3 (0.8)
HOMA, mean (SEM)	2497	2.0 (0.03)
Diabetes, % Previously diagnosed diabetes, % Current glucose > 126 mg/dl, %	282 237 183	10.8 9.2 7.0
Total cholesterol, mg/dl, mean (SEM) > 200 mg/dl, %	2740 1414	202.2 (1.2) 49.6
Previously diagnosed dyslipemia, %	804	29.3
HDL-cholesterol, mg/dl, mean (SEM) < 35 mg/dl, %	2737 18	71.6 (0.9) 0.76
LDL-cholesterol, mg/dl, mean (SEM) > 160 mg/dl, %	2717 429	124.5 (1.1) 15.0
Triglycerides, mg/dl, mean (SEM) > 200 mg/dl, %	2739 56	107.7 (2.0) 2.2
Atherogenic index, mean (SEM) >4.5, %	2737 178	3.0 (0.05) 6.7
Haemoglobin, g/dl, mean (SEM) Anaemia (Hb<11 g/dl), %	2706 38	14.4 (0.07) 1.4
Ferritin, ng/ml, mean (SEM)	2532	117.7 (5.7)

Uric acid, mg/dl, mean (SEM)	2737	4.9 (0.07)
Serum urea, mg/dl, mean (SEM)	2734	37.2 (0.5)
Serum creatinine, mg/dl, mean (SEM)	2746	0.92 (0.01)
eGFR, ml/mn/1.73 m^2, mean (SEM)	2746	84.6 (0.7)
Albumin to creatinine ratio, mg/g, mean (SEM)	2244	9.7 (0.6)
Proteinuria (ACR > 30 mg/g), %	74	4.0%
Smoking habit, %		
Current	675	25.5%
Former	673	25.8%
Non smoker	1324	48.3%
Alcohol intake, %		
Habitual	1176	45.1%
Occasional	556	20.1%
Former consumer	210	8.3%
Never	750	26.5%
Substance abuse, %	70	3.0%
Physical inactivity, %	786	28.9%
Use of nephrotoxic drugs, %		
Ibuprofen		6.0%
Aspirin		5.5%
Captopril		1.0%
Sulfonylurea		1.0%
N-acetylcisteine		0.59%
Carvedilol		0.35%

*Frequency estimates calculated on weighted sample; blog (TG/HDL-C) with TG and HDL-C expressed in molar concentrations. SEM: standard error of the mean; HOMA: Homeostasis Model Assessment Index; ACR: urine albumin to creatinine ratio; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFR: glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Hb: haemoglobin.

CKD prevalence

The overall prevalence of CKD stages 3-5 (eGFR < 60 ml/min/1.73 m^2) was 6.83 %, with a 95% CI of 5.41 to 8.25 (3.33% for age 40-64 years and 21.42% for age >64 years). When the albumin to creatinine ratio was added to the diagnostic criteria, the prevalence rose to 9.16% (95% CI, 7.5 to 10.8). The prevalence estimates of CKD stages were: 0.99% for stage 1; 1.3% for stage 2; 5.4% for stage 3a; 1.1% for stage 3b; 0.27% for stage 4; and 0.03% for stage 5 (table 2). The prevalence of proteinuria (ACR>30 mg/g) in stage 3a was 5.9%, in stage 3b, 6.8%, and in stage 4, 36.7%

Table 2. Prevalence of chronic kidney disease in the Spanish population aged 20 years or older based on the cohort collected in the EPIRCE study (n=2746).

	Spanish Population		Prevalence of estimated GFR (ml/min per 1.73 m²) categories, % (95% CI)						
	N	% (95% CI)	Normal (≥90)	Stage 1 (≥90 with proteinuria)	Stage 2 (60-89)	Stage 3a (45-59)	Stage 3b (30-44)	Stage 4 (15-29)	Stage 5 (<15)
TOTAL	2,746		90.8 (89.1 to 92.5)	0.99 (0.57 to 1.4)	1.3 (0.84 to 1.8)	5.4 (4.3 to 6.6)	1.1 (0.65 to 1.5)	0.27 (0.06 to 0.48)	0.03 (0.00 to 0.08)
Age, years									
20-39	885	36.50 (34.60 to 38.40)	98.1 (96.8 to 99.3)	0.86 (0.15 to 1.6)	0.97 (0.18 to 1.8)	0.10 (0.00 to 0.30)	–	–	–
40-64	1,283	37.70 (35.50 to 39.90)	93.8 (92.1 to 95.5)	1.0 (0.32 to 1.7)	1.8 (0.90 to 2.8)	2.8 (1.8 to 3.9)	0.37 (0.04 to 0.69)	0.09 (0.00 to 0.27)	0.07 (0.00 to 0.22)
>64	578	25.80 (23.82 to 27.78)	76.3 (72.2 to 80.5)	1.1 (0.32 to 1.9)	1.1 (0.30 to 2.0)	16.8 (13.6 to 20.0)	3.7 (2.1 to 5.2)	0.92 (0.13 to 1.7)	-
Sex									
Male	1,148	47.40 (45.46 to 49.30)	91.4 (88.6 to 94.1)	1.4 (0.68 to 2.2)	1.3 (0.60 to 2.1)	4.7 (2.9 to 6.4)	0.79 (0.21 to 1.37)	0.39 (0.02 to 0.77)	-
Female	1,598	52.60 (50.66 to 54.54)	90.3 (88.2 to 92.5)	0.58 (0.16 to 1.00)	1.3 (0.65 to 2.0)	6.2 (4.5 to 7.8)	1.3 (0.69 to 2.0)	0.16 (0.00 to 0.38)	0.05 (0.00 to 0.16)
Habitat									
Urban	1,805	66.10 (63.54 to 68.66)	91.8 (89.6 to 94.1)	0.53 (0.21 to 0.86)	1.3 (0.63 to 1.9)	5.1 (3.5 to 6.7)	0.99 (0.40 to 1.6)	0.29 (0.01 to 0.57)	-
Rural	941	33.90 (31.34 to 36.46)	88.9 (85.8 to 92.0)	1.9 (0.77 to 3.0)	1.5 (0.70 to 2.3)	6.1 (3.9 to 8.4)	1.3 (0.59 to 1.9)	0.23 (0.00 to 0.56)	0.08 (0.00 to 0.24)

There were no patients with GFR<15 mg/ml/m2; GFR: glomerular filtration rate; prevalence estimates calculated on the weighted sample.

Risk factors in CKD

Table 3. Unadjusted associations between demographic or clinical characteristics and the presence of chronic kidney disease.

Category (reference)	OR (95% confidence
Age>64 years (vs. 20-39 years)	267.5 (37.5, 1909.1)
Age 40-64 years (vs. 20-39 years)	34.4 (5.8, 204.6)
Men (vs. women)	0.74 (0.5, 1.1)
Rural habitat (vs. urban)	1.2 (0.71, 2.1)
Overweight (vs. normal)	2.3 (1.4, 4.0)
Obesity (vs. normal)	3.5 (2.0, 6.0)
Hypertension (vs. absence)	6.2 (4.0, 9.6)
Previously diagnosed hypertension (vs. absence)	5.9 (4.0, 8.5)
Current hypertension (vs. absence)	3.1 (2.2, 4.4)
Isolated systolic hypertension (vs. absence)	3.3 (2.2, 4.6)
Pulse pressure >60 mm Hg(vs. ≤60)	3.8 (2.6, 5.5)
Previous cerebrovascular disease (vs. absence)	3.3 (1.4, 7.8)
Previous ischemic heart disease (vs. absence)	4.1 (2.6, 6.5)
Previous peripheral vascular disease (vs. absence)	2.1 (1.4, 3.1)
Previous gout (vs. absence)	2.2 (1.2, 4.2)
Diabetes (vs. absence)	2.0 (1.4, 2.8)
Previously diagnosed diabetes (vs. absence)	2.4 (1.7, 3.3)
Current glucose>126 md/dl (vs. ≤126)	2.2 (1.4, 3.5)
Total cholesterol>200 mg/dl (vs. ≤200)	1.2 (0.8, 1.7)
Previously diagnosed dyslipemia (vs. absence)	2.1 (1.4, 3.0)
HDL-cholesterol <35 mg/dl (vs. ≥35)	4.6 (0.8, 27.1)
LDL-cholesterol >160 mg/dl (vs. ≤160)	1.1 (0.7, 1.7)
Triglycerides >200 mg/dl (vs. ≤200)	1.1 (0.3, 3,5)
Atherogenic index >4.5 (vs. ≤4.5)	1.3 (0.7, 2.6)
Anaemia, Hb <11 mg/dl (vs. ≥11)	2.8 (1.0, 7.7)
Proteinuria, ACR >30 mg/dl (vs. ≤30)	2.1 (0.9, 4.5)
Former smoker (vs. non smoker)	16.4 (1.9, 143.2)
Habitual alcohol intake (vs. never)	0.43 (0.3, 0.6)
Occasional alcohol intake (vs. never)	0.37 (0.2, 0.6)
Former alcohol consumption (vs. never)	1.39 (0.8, 2.4)
Substance abuse (vs. non abuse)	0.15 (0.02, 1.1)
Physical inactivity (vs. regular)	1.2 (0.7, 2.1)

OR for predicting stages 4-5; for stages 3-5 the OR is 0.81 (95% IC: 0.55,1.2). HOMA: Homeostasis Model Assessment index; ACR: urine albumin to creatinine ratio; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFR: glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Hb: haemoglobin.

Table 3 shows the unadjusted associations between sociodemographic and clinical characteristics of the patients and CKD. The strongest predictor was age. The observed odds ratios (OR) were 34.4 for individuals between 40-64 years with respect to those between 20-39 years old and 267.5 for individuals above 64 years. Other strong predictor factors were hypertension, especially when previously diagnosed (OR 5.9), pulse pressure above 60 mmHg (OR 3.8), previous history of cardiovascular events (ORs 4.1 for ischemic heart disease, 3.3 for cerebrovascular disease and 2.1 for peripheral vascular disease), overweight or obesity (ORs of 2.3 and 3.5, respectively), diabetes (OR 2.4 for previously diagnosed patients), dyslipemia (OR 2.1 for previously diagnosed patients) and gout (OR 2.2).

In the multivariate analysis, the independent predictor factors that remained in the model were age, obesity and previously diagnosed hypertension (table 4).

Table 4. Adjusted associations between demographic or clinical characteristics and the presence of chronic kidney disease.

Predictor	OR (95% confidence	P value
Age years (for each year)	267.5 (37.5, 1909.1)	<0.0001
Obesity, BMI >39kg/m2 (vs. 30)	3.5 (2.0, 6.0)	0.0061
Previously diagnosed hypertension (vs. absence)	5.9 (4.0, 8.5)	0.0071

Sensitivity analyses

Individuals recruited at highly responding centres (>60% of response rate, n = 1,098) were healthier according to the following differences with respect to the overall sample: they were less obese (22.9% with BMI >30 kg/m2 versus 26.1% in the total population), less sedentary (25.4% versus 28.9%) and suffered less diabetes (5.2% of none previously diagnosed diabetes versus 7.0%). They also displayed more percentage of habitual alcohol consumption (49.7% versus 45.1%). Despite these findings, the prevalence of CKD stages 3-5 in this subgroup was equivalent to that found in the overall sample: 6.65 (95% CI of 4.66 to 8.64). The prevalence of proteinuria (ACR >30 mg/g) was slightly lower (3.6%, 95% CI 1.4 to 5.8), but not significantly different. No differences were observed either in the prevalence within age, gender or habitat categories or in the risk factors associated to CKD (data not shown).

DISCUSSION

The present study is the first epidemiological investigation of the prevalence of CKD in Spanish population aged 20 years or older at a national level. The recruited sample is representative of all regions, and has been adjusted to provide valid estimates of CKD prevalence in age, gender and habitat subgroups, according to the real distribution of Spanish population in 2001.

The prevalence of CKD found in our study (6.8%) is very similar to the median reported in a systematic review of 26 epidemiological studies around the world (7.2%) (Q. L. Zhang & Rothenbacher 2008). Since ethnic-specific differences have been reported (Q. L. Zhang & Rothenbacher 2008), the relevant comparisons with other European countries show that the prevalence in Spain remains within the range of previous studies that have used the MDRD equation: 4.7-8.1% in studies from Italy (Cirillo et al. 2006), Switzerland (Nitsch et al. 2006), Norway (S. I. Hallan et al. 2006) and Iceland (Viktorsdottir et al. 2005).

These estimates are also similar to those from the US National Health and Nutrition Examination Surveys (NHANES) (5.6% in 1988 through 1994 and 8.05% in 1999 through 2004) (Coresh, Selvin, L. A. Stevens & Van Lente 2007), despite the incidence of end stage renal disease (ESRD) in this country being much higher than in Europe (Lopez Revuelta et al. 2004). The epidemiological study from Norway (S. I. Hallan et al. 2006) investigated the progression rate from CKD stages 3 or 4 to ESRD in their cohort and found that the relative risk of progression in US Caucasian patients was 2.5 times higher than in Norwegian patients. Among the possible explanations for these differences they postulate a later referral to nephrologist and a higher presence of obesity and diabetes in the US population.

The addition of the albumin/creatinine ratio to the CKD diagnosis (stages 1 and 2) allowed detecting a further 2.3% of population at risk, which substantially improves diagnostic accuracy without losing predictive power. According to previous studies, referral based on current stages 3 to 4 CKD identifies

approximately only 70% of all individuals that progress to ESRD (S. I. Hallan et al. 2009).

We found a high prevalence of conventional risk factors, overweight and obesity, hypertension, diabetes, dyslipemia and smoking. All of them were significantly associated to CKD, which agrees with previous findings (Kronborg et al. 2008; Foley et al. 2005). With respect to smoking habit, we did not find a significant association with current smoking, but the ex-smoker status was related to a higher frequency of stage 4 CKD. A possible explanation is that, previous to the study entry, these patients had already suffered other health problems that compelled them to discontinue tobacco. Unexpectedly, the habitual alcohol intake was inversely associated to CKD, which partially agrees with the study of Kronborg et al., who found that alcohol consumption in men predicted an increase in eGFR (Kronborg et al. 2008; Foley et al. 2005). Red wine has been shown to improve surrogate markers for cardiovascular disease, such as nitric oxide release in the vessel wall. It also possesses anti-inflammatory and anti-oxidative properties, and inhibits platelet-derived growth factor-beta receptor phosphorylation (Bohm et al. 2004). However, it would be very difficult to perform prospective, randomized studies to demonstrate the benefits of moderate alcohol consumption, as the important secondary harmful effects (such as liver cirrhosis, blood pressure elevation, cancer or accidents) should be taken into account.

The three independent predictor factors for CKD were increasing age, obesity and history of hypertension, which suggests that these conditions predispose to renal impairment through different mechanisms.

The decline in GFR with age has been repeatedly described (Q. L. Zhang & Rothenbacher 2008). The prevalence of CKD in patients above 64 years found in the EPIRCE study (21.4%) is comparable to that reported in other European countries (15-25%21-24), usually with higher prevalence in older women (Nitsch et al. 2006; Viktorsdottir et al. 2005). The reduction starts progressively in the third decade of life, and becomes steeper after the age of 60, although it has not been observed in all individuals (Douville et al. 2009). There are several hypotheses to explain this phenomenon: it can be related to pathologic processes (cumulated immunologic, infectious, or toxic damage), progressive ischemia due to vascular aging, or cumulative changes in kidney structure due to hyper perfusion and hyper filtration with resultant glomerulosclerosis (Lamb et al. 2003; Lindeman 1990).

The contribution of sustained high blood pressure levels to renal function deterioration is well established: systemic and glomerular hypertension results in increased urinary excretion of proteins and accelerates renal function deterioration. Many studies have demonstrated that an adequate, or even intensified blood pressure control (less than 130/80 mmHg), can slow the progression of diabetic and non diabetic renal disease (Pisoni & Remuzzi 2000). Moreover, long-term studies indicate that the change in GFR may be minimal in well-controlled hypertensive patients, and that patients with non-malignant essential hypertension with early and good blood pressure control do not develop renal failure (Ljungman 1999). The relationship found in our cohort might be the result of inadequately controlled blood pressure levels in the individuals with current CKD.

The association between CKD and obesity was previously described in a prospective study of a large cohort (Gelber et al. 2005). The increase in body weight with time, even within normal BMI values, has also been independently associated with an increased risk for CKD (Ryu et al. 2008). One of the proposed mechanisms for the development of CKD in obese patients is the presence of an increased inflammation status. This is supported by the study of Bavbek et al., who found elevated serum C-reactive protein (CRP) levels in obese patients versus age-matched healthy controls, and a negative correlation between CRP levels and GFR (Bavbek et al. 2008). In morbidity obese patients who underwent very important weight reduction after biliopancreatic diversion all cardiovascular risk factors (hypertension, diabetes, hyperlipidaemia, pro-teinuria) improved during follow-up (Palomar et al. 2005).

An early identification of CKD in primary care is very important, as specialist referral at an appropriate timing may improve long-term outcomes. It has been reported that, in Spain, late referral to nephrologist is common in chronic diseases such as diabetes or hypertension (Perez-Garcia et al. 2009). Our results indicate that almost ten per cent of adult individuals may suffer some degree of renal impairment, and therefore, reveal the need for taking this disease into account. In addition, our findings suggest that the control of classical cardiovascular risk factors as obesity or hypertension in primary care setting might help preventing CKD development.

The main limitation of the study is its poor response rate. The sensitivity analysis excluding the centres with low participation revealed some non-response bias, which did not appear to introduce substantial bias into CKD and proteinuria prevalence estimates. Another limitation is the indirect GFR

estimation method, based on a single creatinine measurement, that should be used with caution (Verhave et al. 2004). Currently, the benefit of performing extensive screening of unselected populations with the intention to reduce the subsequent risk of cardiovascular events or progression to end-stage-renal disease remains unproven (Glassock & Winearls 2008). Although the MDRD equation is the most commonly used in epidemiological studies14, it underestimates the GFR15. Moreover, the cut-off value of 60 ml/min per 1.73 m2 for all ages leads to over diagnosis in elderly population. A new equation recently developed seems to improve the GFR estimation (Levey et al. 2009). Finally, the cross sectional design of the study does not allow inferring causal relationships between the risk factors and CKD.

Some strengths of our study are its large sample size, well representative of the different Spanish regions, and the random selection of the participants. The agreement with results from other European countries supports the external validity of our findings.

In conclusion, we found a relatively high prevalence of asymptomatic CKD (almost one of ten) in apparently healthy general population from Spain, especially in older, obese and hypertensive patients. Independently of age, many of the risks factors for CKD are modifiable: hypertension, diabetes mellitus, obesity, dyslipemia and smoking. Further studies should assess whether early detection of CKD in general population might avoid CKD progression and protect from associated cardiovascular risk factors.

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V.3 ARTICULO 3

"Insulin resistance index (HOMA-IR) levels in a general adult population: curves percentile by gender and age. The EPIRCE study"

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RESUMEN: En este original se analiza la distribución en población española no diabética mayor de 20 años de los niveles de HOMA-IR como marcador de resistencia a la insulina. Se dan por primera vez para población española los valores de la distribución percentil por edad, sexo y obesidad (analizada mediante el IMC y la circunferencia de cintura que recoge la distribución central de tejido adiposo). Se aborda con este análisis el segundo de los objetivos propuestos en la presente Tesis de Doctorado.

ABSTRACT

Objective. To describe the distribution of HOMA-IR levels in a general nondiabetic population, by gender and age, and its relationships with metabolic and lifestyles characteristics.

Design. Cross-sectional observational study.

Setting. Random Spanish population sample, stratified by age and gender.

Subjects. A total of 2246 nondiabetic adults.

Methods. Assessments included a structured interview, physical examination, and blood sampling. Generalized additive models (GAMs) were used to assess the effect of lifestyle habits and clinical and demographic measurements on HOMA-IR. Multivariate GAMs and quantile regression analyses of HOMA-IR were carried out separately in men and women.

Results

This study shows refined estimations of HOMA-IR levels by age, body mass index, and waist circumference in men and women. HOMA-IR levels were higher in men (2.06) than women (1.95) (P=0.047). We found a different effect of age on HOMA-IR levels in men and women. In women, but not men, HOMA-IR and age showed a significant non linear association (edf=2.78, P=0.006), with increased levels above fifty years of age. We estimated HOMA-IR curves percentile in men and women.

Conclusions. Age- and gender-adjusted HOMA-IR levels are reported in a representative Spanish adult non-diabetic population. There are gender-specific differences in serum HOMA-IR levels, with increased levels in women over fifty years of age that may be related with changes in body fat distribution after menopause.

Key words: Insulin-resistance, gender, lifestyles.

INTRODUCTION

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is widely used in large epidemiological studies and in clinical practice to estimate insulin resistance. Insulin resistance is a pathogenic factor for type 2 diabetes, and is associated with cardiovascular diseases, CVD (B. C. Martin et al. 1992)(H. N. Ginsberg 2000; Bertoni, Wong, Shea, et al. 2007). Other studies have showed that insulin resistance may be an important predictor of CVD risk (A. J. Hanley et al. 2002; Bonora et al. 2007).

Determining the distribution of HOMA-IR levels in general populations is important to help clinicians interpret its value. The common guidelines for the definition and determination of reference intervals in the clinical laboratory note that partitioning should be considered when there are significant differences among subgroups defined by age, gender, and common exposures such as smoking or alcohol consumption (National Committee for Clinical Laboratory Standards (NCCLS). 2000). HOMA-IR levels have been reported to be inversely associated with physical activity (Balkau et al. 2008). Moderate drinkers have lower HOMA-IR values (Rimm et al. 1999), but fewer studies have addressed the overall effects of smoking, physical activity, alcohol intake, and common metabolic abnormalities on insulin resistance.

On the other hand, IR has been proposed as a principal factor in initiating and perpetuating the pathologic manifestations of the metabolic syndrome (Lann & LeRoith 2007) and it is associated with inflammatory disease mechanisms (J. Chen, R. P. Wildman, et al. 2004). Obesity and metabolic syndrome, the

paradigms of metabolic abnormalities, are common in many populations, and their worldwide prevalence has risen dramatically over recent decades (Eckel et al. 2006).

To the best of our knowledge, no previous studies have focused on the possible combined associations between lifestyles (exercise, smoking, and alcohol consumption) and other common metabolic abnormalities with serum HOMA-IR levels in a nondiabetic population from an entire European country.

The aim of the present population-based study was to assess serum HOMA-IR levels in nondiabetic adults and its relationship with (i) demographic factors (age and gender); (ii) life style habits (exercise, alcohol consumption, and smoking); and (iii) common metabolic abnormalities, including the components of metabolic syndrome, in a nondiabetic population in Spain.

MATERIALS AND METHODS

Study population

The present study took advantage of a survey of the general adult population (EPIRCE) (Otero, Gayoso, et al. 2005). The EPIRCE is an epidemiologic, cross-sectional study that included a randomly selected sample of Spanish persons aged 20 years and older. The study was primarily intended to investigate the prevalence of chronic kidney disease (CKD) in the adult Spanish population.

A random sample, stratified by age, gender, and habitat, was drawn from the 2001 Spanish Census. The sample (n=13,013) was recruited between January 2004 and December 2007 in 42 municipalities. Because of census errors, a

total of 6,464 people were finally contacted. The response rate was 42.5%, with 2,746 completed interviews included. The recruited sample is representative of all regions, and was adjusted to provide valid estimates of age and gender according to the distribution of the Spanish population in 2001.

Data were collected using a standardized questionnaire administered during a structured interview, followed by a detailed physical examination and blood sample collection (Otero, Gayoso, et al. 2005; Otero et al. 2010).

People with diabetes, defined as a fasting plasma glucose ≥126 mg/dl and/or the current use of diabetes medications, were excluded (Mellitus. 2003). From the overall sample, 2246 nondiabetic individuals were selected. The median age was 47 years (range 20–92 years). A total of 1329 (59.2%) were women. All participants were Caucasians.

Lifestyle habits

Alcohol consumption was evaluated with standard drinking units (Gual et al. 1999), which sums the number of glasses of wine (~ 10 g), bottles of beer (~ 10 g), and units of spirits (~ 20 g) consumed regularly per week. Individuals with a usual alcohol consumption of 1–140 g/week (*n* = 1078, 48.2%) were considered light drinkers, those consuming 141–280 g/week (*n* = 191, 8.5%) were considered moderate drinkers, and those consuming ≥ 280 g/week (*n* = 127, 5.7%) were considered heavy drinkers. The alcohol abstainers or very occasional alcohol drinkers (*n* = 839, 37.5%) were combined in the same group. Those who consumed at least one cigarette per day were considered smokers (n=567, 28.5%). Subjects who had stopped smoking during the last 12 months after years of smoking were considered smokers.

Physical activity was evaluated by self-reported questionnaire, and categorized in one of the follow categories: sedentary (n=640, 29%), occasional exercise (moderate activity once a month, *n* = 1022, 47%), moderate exercise (moderate exercise once a week, *n* = 324, 14%), and intense exercise (moderate or intense physical activity more than twice a week, *n* = 225, 10%).

Anthropometric and clinical measurements

Subjects were considered to have hypertension if they had a mean systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or used antihypertensive medications.

Waist circumference and body weight and height were measured according to a standard protocol. The body mass index (BMI) was calculated as the weight (in kg) divided by the square of the height (in meters). Following standard criteria, individuals were classified as normal weight (< 25 kg/m^2), overweight (25–30 kg/m^2), or obese (> 30 kg/m^2).

Specific laboratory determinations

A blood sample was collected after an overnight fast of > 8 h. Plasma glucose levels were measured using a hexokinase enzymatic reference method. Fasting insulin levels were measured using a RIA method. Fasting lipids were analysed, and for the present study serum levels of cholesterol ≥ 5.172 mmol/l and triglycerides > 4.137 mmol/l were considered abnormally high.

A Homeostasis Model Assessment of Insulin Resistance (HOMA - IR) was used to evaluate insulin resistance, and was calculated with the following formula:

fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (D. R. Matthews et al. 1985).

Statistical Analyses

Baseline subject characteristics are expressed as the mean ± SD or as percentages. Age- and gender-adjusted HOMA-IR levels are reported as the median and percentile. Cross-tabulation significance levels were based on Pearson's chi-square test for categorical variables. Non-parametric tests were employed for comparison of quantitative variables.

The possible effects of lifestyles, clinical measurements, and anthropometric measurements on the HOMA-IR levels were assessed using Generalized Additive Models (GAM) [17-18]. Explicitly, in our study, the GAM can be expressed in the following manner: log (HOMA-IR) = a + $f_1(X_1)$ + $f_2(X_2)$ + . . . , where α is a constant, and $f_i(X_i)$ are smooth functions representing the partial effects of the explanatory variables X_i on the HOMA-IR.

Since HOMA-IR is a non negative response variable showing a positive skewness, the gamma distribution was assumed for this outcome in all the fitted GAMs, and the log function was considered as the link. As a first step in our analysis, independent GAMs were initially constructed for each explanatory variable, and duly adjusted by the age × gender interaction. The final multivariate GAM regression models included SBP, waist circumference, high-density lipoprotein (HDL), triglycerides (in log scale), educational level, physical activity, cigarette smoking, and alcohol consumption. As the BMI and waist circumference variables were used as indicators of obesity, they were not simultaneously included in the same model to prevent potential concurvity (the

analogue to the collinearity in parametric model) (Hastie & Tibshirani 1990). Since the GAM including the interaction between age and gender presented a better fit in terms of deviance explained, the multivariate GAMs where run separately in men and women.

For fitting the GAMs, penalized regression splines were used to estimate the smooth functions, $f_i(X_i)$ with optimal *effective degrees of freedom* (edf) chosen automatically by means of Generalized Cross Validation (GCV). A Bayesian approach to uncertainty estimation was used to obtain 95% confidence intervals for the effects (Wood 2006).

With regard to the quantile regression analysis of HOMA-IR, the methodology used relied on GAMLSS (Rigby & Stasinopoulos 2005) with gamma distribution and log link for both the mean and the variance. As in the previous GAM regression models, penalized regression splines were used as smoothers of the quantile curves and the analyses were carried out separately in men and women. All statistical analyses were performed using R software, version 2.9.1 (R 2009). GAMs were fitted using the mgcv package (Wood 2006) and quantile analysis was performed using the gamlss package (Rigby & Stasinopoulos 2005).

Ethical considerations

The Galician Health Service's Ethics Committee approved the protocol, and all enrolled subjects provided informed consent.

RESULTS

Men showed worse lifestyle habits than women. There were significant differences by gender with respect to smoking (28% of men were smokers vs. 21% of women, p < 0.0001); alcohol intake (75.7% men were current alcohol drinkers, with a median of 183 g/week vs. 50.2% women, with a median of 50 g/week, *P*<0.001); hypertension (49% of men were hypertensive vs. 36% of women, *P*<0.001) and obesity (76% of men had a BMI over 25 kg/m^2 vs. 61% of women, *P*<0.001). Triglycerides were higher (3.01 mmol/l in men vs. 2.34 mmol/l in women, *P*<0.001), and HDL cholesterol was lower (5.24 mmol/l in men vs. 5.32 mmol/l in women, *P*<0.001). However, there were more sedentary women (30.9%) than men (26.7%) (*P*= 0.004).

The overall distribution of HOMA-IR levels in the population by age and gender.

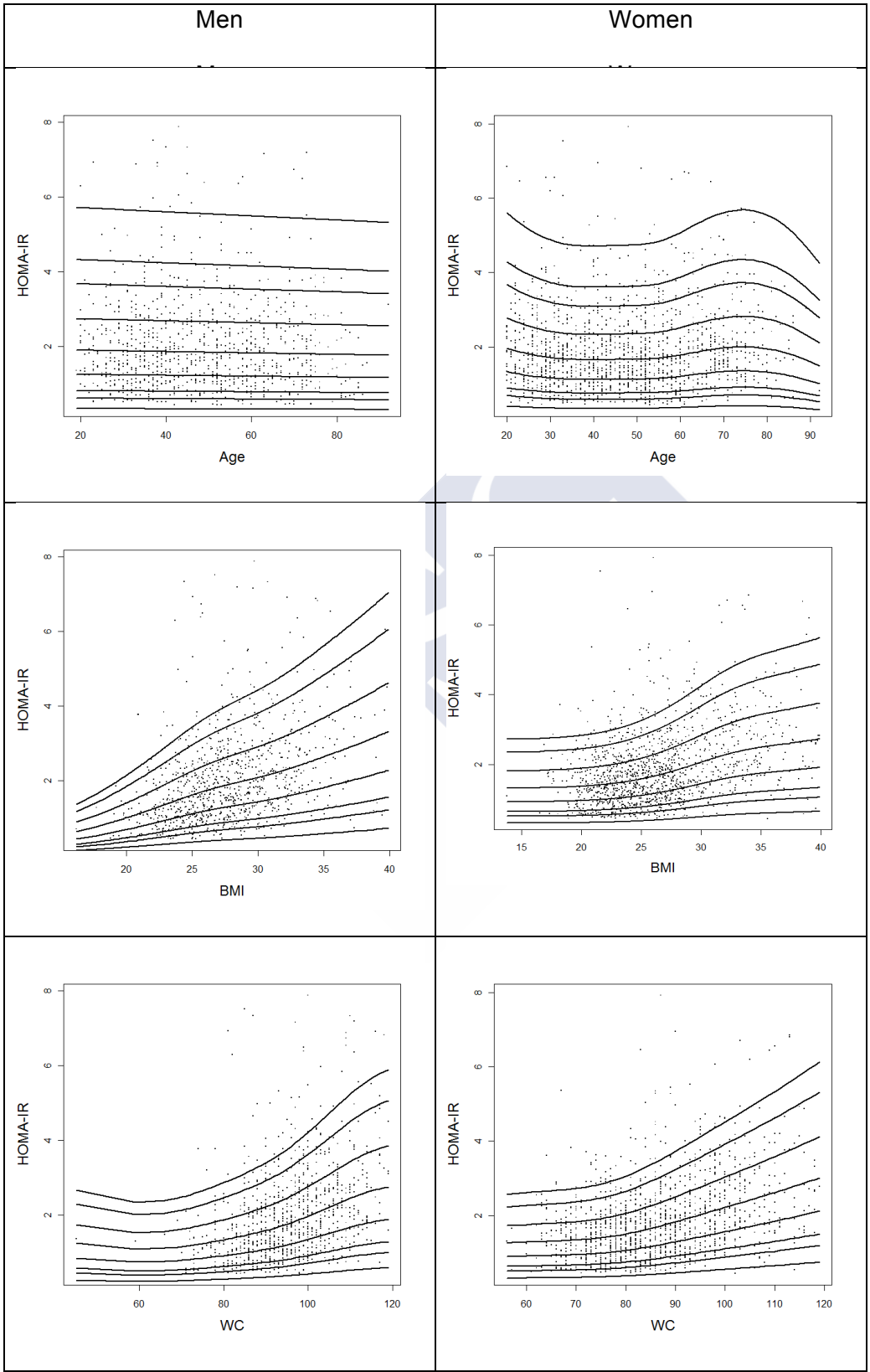
In the overall data set, mean HOMA-IR levels were higher in men than in women (2.06 vs. 1.93, respectively; *P*=0.047). Age- and gender-adjusted HOMA-IR levels are reported in Table 1.

Table 1. Observed and averaged smooth HOMA-IR percentiles, by gender and age group, among 2246 nondiabetic individuals.

	%	Median	P3	P5	P10	P25	P50	P75	P90	P95	P97
Observed HOMA-IR percentiles											
Total		1.73	0.55	0.63	0.80	1.17	1.73	2.48	3.46	4.14	4.72
Age group's men (P=0.35) *											
20–29	12.9	1.66	0.58	0.62	0.92	1.24	1.66	2.48	3.41	4.01	5.06
30–39	22.8	1.81	0.57	0.71	0.85	1.16	1.81	2.55	3.73	4.53	5.56
40–49	20.0	1.85	0.63	0.71	0.85	1.20	1.85	2.72	3.87	5.54	6.21
50–59	17.8	1.78	0.54	0.63	0.85	1.16	1.78	2.51	3.40	4.10	4.58
60–69	14.3	1.82	0.52	0.65	0.77	1.18	1.82	2.67	3.40	4.10	4.52
70–79	9.4	1.74	0.47	0.53	0.87	1.19	1.74	2.62	3.78	5.30	6.58
≥ 80	2.8	1.18	0.65	0.65	0.68	0.75	1.18	2.22	2.97	3.57	3.82
Age group's women (P=0.04)*											
20–29	15.5	1.79	0.59	0.68	0.89	1.27	1.79	2.49	3.44	4.05	4.18
30–39	19.3	1.63	0.55	0.56	0.68	1.05	1.63	2.21	3.05	3.63	4.67
40–49	20.6	1.58	0.53	0.58	0.83	1.15	1.59	2.30	3.21	3.94	4.38
50–59	19.3	1.64	0.51	0.55	0.75	1.10	1.64	2.37	3.31	3.94	4.31
60–69	14.1	1.91	0.57	0.66	0.88	1.23	1.91	2.46	3.49	4.50	4.74
70–79	9.0	1.91	0.79	0.90	1.10	1.45	1.91	2.77	3.93	4.48	5.06
≥ 80	2.2	1.69	0.61	0.61	0.64	1.02	1.69	2.82	3.55	3.69	3.76
Averaged smooth HOMA-IR percentiles											
Age group's men											
20–29		1.90	0.51	0.62	0.82	1.26	1.90	2.73	3.66	4.30	4.75
30–39		1.88	0.51	0.62	0.82	1.24	1.88	2.71	3.63	4.26	4.71
40–49		1.86	0.50	0.61	0.81	1.23	1.86	2.68	3.59	4.22	4.66
50–59		1.84	0.50	0.60	0.80	1.22	1.84	2.65	3.55	4.18	4.62
60–69		1.83	0.49	0.60	0.79	1.21	1.83	2.63	3.52	4.14	4.57
70–79		1.81	0.49	0.59	0.78	1.19	1.81	2.60	3.49	4.10	4.53
≥ 80		1.79	0.48	0.59	0.77	1.18	1.79	2.57	3.45	4.05	4.47
Age group's women											
20–29		1.84	0.54	0.65	0.84	1.24	1.84	2.59	3.43	4.00	4.40
30–39		1.67	0.49	0.59	0.76	1.13	1.67	2.36	3.12	3.65	4.02
40–49		1.66	0.49	0.58	0.76	1.12	1.66	2.34	3.10	3.62	3.98
50–59		1.70	0.50	0.60	0.78	1.15	1.70	2.40	3.18	3.71	4.08
60–69		1.88	0.55	0.66	0.85	1.27	1.88	2.65	3.50	4.09	4.50
70–79		1.98	0.58	0.70	0.91	1.34	1.98	2.80	3.71	4.33	4.76
≥ 80		1.76	0.51	0.62	0.80	1.19	1.76	2.48	3.28	3.83	4.21

P: percentile at the indicated numerical value. * The Jonckheere–Terpstra test for trends was employed for median comparisons. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance measured as fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5

Figure 1. Percentile curves showing HOMA-IR for age, body mass index (BMI) and waist circumference (waist circumference) among 2246 nondiabetic individuals in men and women separately.

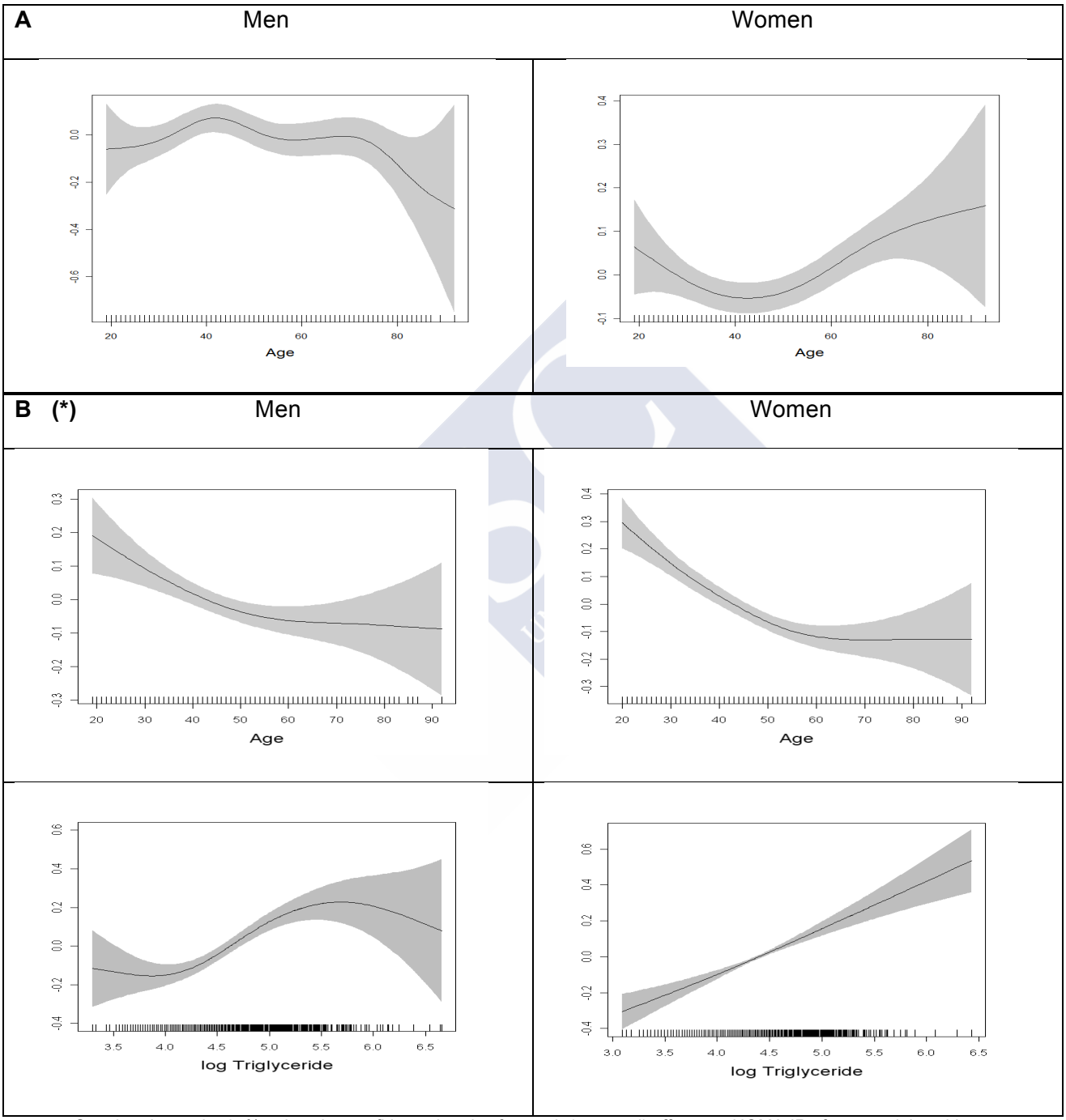


Values for the 1st, 5th, 10th, 25th,50th,75th,90th,95th and 99 th HOMA-IR percentiles with respect to age (in years), BMI (in kg/m^2), and waist circumference (WC), waist circumference (in cm) estimated by gender. The dots represent observed HOMA-IR values in the dataset.

The distribution of HOMA-IR levels by decades of age was different between men and women (Figure 1). HOMA-IR levels decreased with ageing in men, although the trend was not statistically significant (*P* for trend = 0.34). On the contrary, women aged over their fifth decade had significantly higher HOMA-IR levels (*P* for trend = 0.04).

This difference was also present when we analysed the HOMA-IR changes with age by GAM (Figure 2). Whereas in men there was no evidence to suggest an association between age and HOMA-IR (edf=4.88, *P*=0.07), women showed a significant non-linear association (edf=2.78, *P*=0.006) with an increase in levels in those aged fifty years and older.

Figure 2. Smooth (centered) effects of age on HOMA-IR in both men and women (A). Adjusted smooth (centered) effects of age and triglycerides (log scale) on HOMA-IR in men and women separately (B). Results are based on data from 2246 no diabetic individuals.



Grey bands are the 95% point-wise confidence bands of smooth (centered) effects on HOMA-IR of age or triglycerides.

(*)Model B both for men and women included age (years), physical activity (sedentary as reference), current smoking (never as reference), alcohol intake (non consumer as reference), educational level (no studies as reference), waist circumference (cm), systolic blood pressure SBP (mm Hg), triglycerides (mmol/l), and HDL-cholesterol (mmol/l) on HOMA-IR.

Table 2. HOMA-IR distribution by lifestyle habits, BMI, and waist circumference among 2246 nondiabetic individuals.

	%	HOMA–IR	p value
Physical activity			p < 0.001
Sedentary	29	1.58 (0.65, 4.47)	
Occasional	46	1.72 (0.69, 3.99)	
Moderate	15	1.64 (0.66, 4.18)	
Intense	10	1.53 (0.53, 4.03)	
Alcohol consumption			p = 0.022
None	37	1.79 (.065, 4.24)	
Occasional	48	1.67 (0.61, 4.06)	
Moderate	9	1.82 (0.65, 4.43)	
Heavy	6	1.78 (0.58, 3.83)	
Smoking habit			p = 0.024
Never	50	1.78 (0.68, 4.05)	
Former	26	1.75 (0.60, 4.29)	
Current	24	1.65 (0.59, 4.20)	
Educational level			p = 0.01
None	16	1.89 (0.65, 4.25)	
Primary	46	1.72 (0.62, 4.10)	
high school	21	1.72 (0.70, 4.25)	
University	17	1.33 (0.62, 4.09)	
BMI			p < 0.001
Normal weight	35	1.52 (0.53, 3.49)	
Overweight	40	1.75 (0.71, 4.12)	
Obese	25	2.34 (0.97, 5.01)	
waist circumference			p < 0.001
Lower than risk	71	1.56 (0.58, 3.65)	
Greater than risk	29	2.16 (0.91, 4.88)	

Relationship between HOMA-IR levels, metabolic characteristics and lifestyle habits (Table 2)

HOMA-IR levels decreased progressively with increasing physical activity (*P* for trend <0.001). HOMA-IR levels tended to be lower in parallel with alcohol consumption (*P* for trend=0.022). Accordingly, the lowest HOMA-IR levels were observed in heavy drinkers, who exhibited significantly lower HOMA-IR levels than those of abstainers (*P*<0.001). HOMA-IR levels were lower in smokers than in non-smokers, but the difference was not statistically significant (*P* for trend=0.236). HOMA-IR levels increased with waist circumference and BMI in both men and women. Figure 1.

Multivariate analyses of factors associated with HOMA-IR

The results of the independent GAM analyses on HOMA-IR, adjusted for age and gender, are presented in Table 3 (Model A). HOMA-IR levels showed a significant non-linear association with BMI (edf=3.48, *P*<0.001), waist circumference (edf=3.19, *P*<0.001), triglycerides (edf=5.08, *P*<0.001), systolic blood pressure (edf=2.65, *P*<0.001), and HDL-cholesterol (edf=3.23, *P*<0.001). GAM analysis showed a significant linear association between HOMA-IR and DBP (edf=1, *P*<0.001).

Table 3. Association between HOMA-IR and lifestyle habits, anthropometric, or metabolic characteristics. Multivariate models in 2246 nondiabetic individuals.

	Model A*			Model B (men)†			Model B(women) †		
Parametric terms	B	95% CI	p value	β	95%CI	p value	β	95% CI	p value
Physical activity									
Occasional	−0.099	−0.153, −0.045	<0.001	−0.069	−0.149, 0.011	0.093	−0.005	−0.066, 0.056	0.878
Moderate	−0.126	−0.199, −0.053	<0.001	−0.022	−0.127, 0.083	0.677	−0.005	−0.090, 0.080	0.905
Intense	−0.208	−0.291, −0.125	<0.001	−0.083	−0.198, 0.032	0.159	−0.102	−0.203, −0.001	0.047
Tobacco consume									
Former	−0.007	−0.053, 0.067	0.821	0.025	−0.054, 0.104	0.539	−0.018	−0.090, 0.054	0.630
Current	−0.051	−0.110, 0.008	0.092	−0.061	−0.146, 0.024	0.162	−0.043	−0.114, 0.028	0.239
Alcohol intake									
Light	−0.083	−0.134, −0.032	0.001	−0.074	−0.158, 0.010	0.086	−0.056	−0.111, 0.001	0.049
Moderate	−0.055	−0.146, 0.036	0.236	−0.100	−0.205, 0.005	0.063	−0.025	−0.186, 0.136	0.761
Heavy	−0.110	−0.218, −0.002	0.045	−0.149	−0.267, −0.031	0.014	−0.098	−0.354, 0.158	0.453
Educational level									
Elementary	−0.056	−0.127, 0.015	0.119	0.114	0.009, 0.219	0.034	−0.051	−0.127, 0.025	0.752
Middle / High	−0.061	−0.147, 0.025	0.168	0.126	0.002, 0.250	0.049	−0.008	−0.106, 0.090	0.362
University	−0.085	−0.176, 0.006	0.067	0.089	−0.046, 0.224	0.196	0.045	−0.056, 0.146	0.131
Non parametric terms	edf		p value	edf		p value	edf		p value
s (Age) men §	4.88		0.077	1.94		0.004			
s (Age) women §	2.78		0.006				2.48		<0.001
s (BMI)	3.48		<0.001						
s (waist circumference)	3.19		<0.001	1.00		<0.001	1.00		<0.001
s (HDL cholesterol)	3.23		<0.001	2.84		<0.001	1.00		0.003
s (LDL cholesterol)	1.01		0.464						
s(Triglycerides)	5.08		<0.001	4.01		<0.001	1.32		<0.001
s (SBP)	2.65		<0.001	1.00		0.448	1.48		0.063
s (DBP)	1.00		<0.001						

*Model A, adjusted for age (years), gender, physical activity (sedentary as reference), current smoking, alcohol intake (non consumer as reference), educational level (no studies as reference), waist circumference (cm), systolic blood pressure SBP (mm Hg), diastolic blood pressure DBP (mm HG), triglycerides (log scale), and LDL- and HDL-cholesterol (both in mmol/l) on HOMA-IR. † Model B included age, physical activity, current smoking, alcohol intake, waist circumference, systolic blood pressure (SBP), triglycerides and HDL-cholesterol.

Table 3 (Model B) shows the results of the multivariate GAM analysis for men and women separately. Since the multivariate model including waist circumference had a better fit (in terms of deviance explained) than the one including BMI (in both genders), we report the results for the waist circumference in this work.

Serum HOMA-IR levels decreased with ageing; they showed a non-linear association with age in both men (edf=1.94, *P*=0.004) and women (edf=2.47, *P*<0.001). Waist circumference showed a linear association with HOMA-IR (edf=1.00, *P*<0.001) in both genders. However, triglycerides showed a non

linear association (edf=2.84, *P*<0.001) with HOMA-IR levels in men, and an almost linear association (edf=1.31, *P*< 0.001) in women.

When we analysed lifestyle habits in multivariate models, we found a negative association between HOMA-IR levels and alcohol consumption in men but not women. HOMA-IR levels in heavy drinkers (more than 280 g/week) were lower than those in abstainers (β= –0.149, *P*=0.014). The significant positive association found between HOMA-IR and physical activity remained in women but not men in multivariate models. HOMA-IR levels were lower in women with intense physical activity than in sedentary women (β=-0.102, *P*=0.047).

DISCUSSION

In this comprehensive study in a general adult nondiabetic population, we found a different distribution of HOMA-IR levels between men and women related to age. In men, HOMA-IR decreased with ageing, but showed a U-shaped distribution in women, with significantly increasing HOMA-IR levels in women over fifty years of age.

However, when further adjusted for waist circumference, HDL, triglyceride levels, and lifestyles, we found an attenuation of these observed HOMA-IR differences by gender, with similar non-linear associations. We found a slight decrease of HOMA-IR levels with ageing in both men and women, probably because we had study a non-diabetic population.

The presence of visceral adipose tissue (VAT) is a risk factor for development of insulin resistance and obesity related diseases (S. H. Kim et al. 2004; Ritchie

& Connell 2007). Recent studies reported marked gender differences with regard to degrees of insulin resistance and body composition, and have showed that greater amounts of visceral and hepatic fat, in conjunction with the lack of the protective effect of oestrogens, may be related to higher insulin resistance in men than in women (Geer & Shen 2009). Gender differences in body composition may be due, at least in part, to the effect of gender hormones. The increase in insulin resistance with menopause suggests that oestrogens may play a role in the insulin sensitivity observed in women. The age and gender differences in HOMA-IR levels found in our study may reflect the effect of menopausal changes (decreased oestrogens levels and VAT increases) on insulin resistance.

When we evaluated HOMA-IR and lifestyles in a nondiabetic adult population, we found that HOMA-IR levels decreased progressively with increasing physical activity (*P* for trend <0.001), and this relationship remained after adjusting for age and gender. In the RISC Study, conducted in a population of men and women aged 30–64 years, total accumulated activity was the key parameter positively associated with insulin sensitivity (Rimm et al. 1999). In the Insulin Resistance Atherosclerosis Study, insulin sensitivity was positively associated with vigorous exercise and also with the energy expended in vigorous and no vigorous activities (Lann & LeRoith 2007).

The observed variations in HOMA-IR with alcohol consumption confirm those reported in previous studies (Rimm et al. 1999). HOMA-IR levels tended to decrease with alcohol consumption, being lower in heavy drinkers than in light-to-moderate drinkers and abstainers (Chung et al. 2003).

The strengths of this analysis include the use of a large, diverse, and well-characterized population-based sample of nondiabetic adults, and the consideration of lifestyle, clinical, and metabolic characteristics all together. The measure of insulin resistance utilized in this study, HOMA-IR, is a simple measure of insulin resistance derived from fasting glucose and insulin values, and correlates well with insulin sensitivity derived from the hyperinsulinemic-euglucemic techniques (Bonora et al. 2000).

To the best of our knowledge, this is the first study describing the effect of lifestyle, clinical measurements, and anthropometric measurements on insulin resistance (HOMA-IR) using flexible regression models like GAMs. These regression techniques have the advantage of not assuming a parametric form on the effects of continuous explanatory variables; instead, they assume only that these effects are additive and reasonably smooth. On the other hand, the regression percentile gives us a refined estimation of HOMA-IR levels by age, BMI, and waist circumference in a representative sample in a population of adult nondiabetics in Spain.

We acknowledge limitations to our approach as well. The cross-sectional nature of our study does not allow us to draw conclusions regarding causality between insulin resistance and lifestyle habits or cardio-metabolic risk factors. It should be also noted that the measurement of lifestyle habits using a self-administered questionnaire may be a limiting factor or a source of bias. Regardless, our hypothesis is consistent with a wide range of previous studies in both men and women.

In summary, with the current rise in the prevalence of obesity, the study of insulin resistance and body composition has become an important area of research in developed countries and a public health task. Because there are gender-specific differences in HOMA-IR levels and body composition, gender-tailored treatment of insulin resistance may be of benefit rather than a focus on visceral and hepatic adipose tissue, especially in postmenopausal women and the obese. For now, lifestyle changes, including weight loss and exercise, may be a more effective strategy to improve vascular health and limit insulin resistance.

V.4 ARTICULO 4

"Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age. EPIRCE cross-sectional study"

Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, Gonzalez-Quntela A.

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RESUMEN. En el siguiente original se estudia la capacidad de clasificación de riesgo cardiovascular que presenta el HOMA-IR en los individuos no diabéticos. Para ello, se ha tomado la definición de síndrome metabólico como criterio que permite identificar a los individuos con varios factores de riesgo cardiovascular. Mediante análisis de curvas ROC, se busca el punto de corte que mejor identifica a los individuos no diabéticos que reúnen criterios de síndrome metabólico. Con el objetivo de incrementar su utilidad clínica, se propone modificar el punto de corte de HOMA-IR utilizado para definir la presencia de resistencia a la insulina incorporando esta consideración de mejor clasificación de sujetos con riesgo cardiovascular. Se comprueba que esta consideración cambia el punto de corte respecto al propuesto usando únicamente el criterio de P90 de la distribución poblaciónal de HOMA-IR.

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ABSTRACT

Objective To describes the influence of age and gender in the estimation of HOMA-IR optimal cut-off values to identifying subjects with higher cardio metabolic risk in a general adult population.

Design Cross-sectional study.

Methods. It included 2459 adults in a random Spanish population sample. The effect of age on the accuracy of HOMA-IR was analyzed in individuals with and without diabetes mellitus separately. ROC regression methodology was used to evaluate the effect of age on HOMA-IR performance in classified cardio metabolic risk.

Results. In Spanish population the threshold value of HOMA-IR for IR drops from 3.46 using 90th percentile criteria to 2.05 take into account MetS components. In non-diabetic women, but no in men, we found a significant non-linear effect of age on the accuracy of HOMA-IR. In non-diabetic men, the HOMA-IR cut-off values were 1.85. All values are between 70th-75th percentiles of HOMA-IR levels in adult Spanish population.

Conclusions. We propose the addition of the components of MetS analysis as a criterion to establish the cut-off points of HOMA-IR to define IR instead of using a percentile of the population distribution. The consideration of the attendant risk of cardiovascular and metabolic diseases to establish this cut-off point would increase its clinical utility in identifying those patients in whom the presence of multiple metabolic risk factors imparts an increased metabolic and cardiovascular risk. The threshold HOMA-IR levels to define IR must be modified by age in non-diabetic women.

Keywords: insulin resistance, gender, cardio metabolic risk, metabolic syndrome,

INTRODUCTION

Insulin resistance (IR) is a feature of disorders such as type 2 diabetes and is also implicated in obesity, hypertension, cancer or autoimmune diseases (Rader 2007; Goodwin et al. 2009; Seriolo et al. 2008). Insulin resistance (IR) has been proposed, more than a primary cause, as a sort of final common pathway for negative environmental factors, which interact with the individual genetic background to cause metabolic and hemodynamic alterations and is associated with inflammation (J. Chen, R. Wildman, et al. 2004; Eckel et al. 2006).

Metabolic syndrome (MetS) definition is widely used as a practical tool to describe a cluster of clinical signs (central obesity, dyslipidemia, impaired glucose metabolism, and elevated blood pressure) that regardless of cause, identifies individuals at risk of atherosclerotic cardiovascular disease (CVD), and diabetes mellitus type 2 (DM2) (Kassi et al. 2011; Eckel et al. 2005; Alberti et al. 2009; Grundy et al. 2005). The worldwide prevalence of these factors has risen dramatically in recent decades (G. A. Bray & Bellanger 2006; Danaei, Finucane, Lu, et al. 2011; Finucane et al. 2011).

The Homeostasis Model Assessment of IR (HOMA-IR) has proved to be a robust tool for the surrogate assessment of IR (Lann & LeRoith 2007; Antuna-Puente et al. 2011). However, there is great variability in the threshold HOMA-IR levels to define IR. Population based studies for defining cut-off values of HOMA-IR for the diagnosis of IR had been conducted in different geographic areas (Hedblad et al. 2000; Sumner & Cowie 2008; B. Geloneze et al. 2006; A. Esteghamati et al. 2009)(Marques-Vidal et al. 2002; Do et al. 2010; Bonora et

al. 1998; Nakai et al. 2002). In most of cases the cutoff point's determination were made on the percentile criterion (80 or 90 according to studies) of values in the general population. However, in no case take into account the ability of classification proposed cutoff points are in terms of clinically relevant outcomes (Antuna-Puente et al. 2011).

In these studies the results have being reported without taking into account the possible effects of covariates on test results. However, it is well known that a biomarker's performance and, by extension, its discriminatory capacity can be affected by covariates (Pepe 2003).

In a previous study we showed that there are age and gender-specific differences in HOMA-IR levels, with increased levels in women over fifty years of age (Gayoso-Diz et al. 2011). On the other hand, the prevalence cardio metabolic diseases such as diabetes or central obesity, rises with age and shows gender differences (Danaei, Finucane, Lu, et al. 2011; Finucane et al. 2011). All these results suggest the possible effects of both age and gender on the accuracy of HOMA-IR to identify individuals with cardio metabolic risk.

The purpose of the present population-based study was to evaluate the change in defining cut-off values of HOMA-IR for the diagnosis of IR when cardio metabolic risk factors were considered. We currently assess the influence of age and gender on the performance of serum HOMA-IR levels to identifying cardio metabolic risk in an adult population, to better understand the relationship between insulin resistance and cardio metabolic risk.

MATERIALS AND METHODS

Subjects

The present study took advantage of a survey of the general adult population (EPIRCE) (Otero, Gayoso, et al. 2005; Otero et al. 2010). The EPIRCE is an observational, cross-sectional study that included a randomly selected sample of Spanish persons aged 20 years and older stratified by age, gender, and habitat. The study was primarily intended to investigate the prevalence of chronic kidney disease (CKD) in the adult Spanish population. Details of the study design were previously published (Otero et al. 2010).

For the present study, data analysis could not be performed in 249 individuals (9.1%) because of a lack of insulin level recording and in 38 (1.4%) individuals because of a lack of waist circumference recording. There were no statistically significant differences between individuals with or without missing data regarding age, sex, hypertension, alcohol intake, or physical activity. Finally, 2459 individuals were selected for study inclusion. People with diabetes (247, 10.0%), defined as a fasting plasma glucose ≥126 mg/dl and/or the current use of diabetes medications, were included. The average age was 49.4 ± 16.2 years (range 19–92 years). A total of 1436 (58.4%) were women. All participants were Caucasians.

Anthropometric and clinical measurements

Subjects were considered to have hypertension if they had a mean systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or used antihypertensive medications.

Waist circumference and body weight and height were measured according to a standard protocol. The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (meters). Following standard criteria, individuals were classified as normal weight (<25 kg/m^2), overweight (25–30 kg/m^2), or obese (>30 kg/m^2).

Specific laboratory determinations

A blood sample was collected after an overnight fast of >8 h. Plasma glucose levels were measured using a hexokinase enzymatic reference method. Fasting insulin levels were measured using a radioimmunoassay (RIA) method. Fasting lipids were analyzed, and for the present study serum levels of cholesterol ≥5.172 mmol l^{-1} and triglycerides ≥1.7 mmol l^{-1} were considered abnormal.

HOMA-IR was used to evaluate insulin resistance: (fasting serum insulin, μU/ml, × fasting plasma glucose, mmol l^{-1}) / 22.5 (D. R. Matthews et al. 1985).

Definition of metabolic syndrome

As an accurate indicator of cardio metabolic risk, MetS, both by the International Diabetes Federation (IDF) criteria and by the Adult Treatment Panel III (ATP III) criteria, were used. Under the IDF criteria, MetS ($MetS_{IDF}$) was defined as the presence of central obesity (waist circumference ≥94 cm for men and ≥80 for women) plus any two of the following risk factors:

HDL-cholesterol <1.03 mmol l^{-1} (males) and <1.29 mmol l^{-1} (females) or specific treatment for this lipid abnormality; systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg, or treatment of previously diagnosed hypertension; fasting plasma glucose ≥5.6 mmol l^{-1}, or previously diagnosed type 2 diabetes;

triglycerides ≥1.7 mmol l^{-1} or specific treatment for this lipid abnormality (Alberti et al. 2005).

According to ATPIII criteria, MetS ($MetS_{ATPIII}$) was defined as the presence of three or more of the following: HDL-cholesterol <1.03 mmol l^{-1} (males) and <1.30 mmol l^{-1} (females) or specific treatment for this lipid abnormality; blood pressure ≥130/85 mm Hg or treatment of previously diagnosed hypertension; fasting plasma glucose ≥5.6 mmol l^{-1}, or previously diagnosed type 2 diabetes; triglycerides ≥1.7 mmol l^{-1} or specific treatment for this lipid abnormality; waist circumference ≥102 cm for males and ≥88 cm for females (Expert panel on detection 2001).

Statistical Analyses

Baseline subject characteristics are expressed as the mean ± SD or as percentages. Cross-tabulation significance levels were based on Pearson's chi-square test for categorical variables. The Mann-Whitney U-test and Kruskall-Wallis test were employed for comparison of quantitative variables.

To analyze the effect of age on the accuracy of HOMA-IR when predicting the presence of cardio metabolic risk, a novel non-parametric extension (Rodriguez-Alvarez, Roca-Pardiñas, et al. 2011) of the induced ROC regression methodology (Pepe 2003; Faraggi 2003) was used. Since it well established that HOMA-IR values behave differently according to gender, the analyses were performed separately in men and in women. We evaluate the significant effect of age on the accuracy of HOMA-IR and P-values were obtained based on 200 bootstrap replications (Rodriguez-Alvarez, Tahoces, et al. 2011).

When the estimated effect of age on the mean of HOMA-IR probed to be linear, and the estimated variances probed to be constant (independent of age), we reanalyzed the data using the semi-parametric induced ROC regression.

Finally, in addition to the estimated (age-specific) ROC curve, the Area Under the Curve (AUC) and bootstrap-based confidence intervals was obtained, (b = 500 resamples). The (age-specific) threshold values were also computed based on two different criteria: (a) by setting the specificity at 0.7, and (b) by the Youden Index (YI). Insofar as the computation of the YI is concerned, in those situations where a significant effect of age was detected on the accuracy of HOMA-IR, a modification of the usual definition was used, which takes covariates into account. All statistical analyses were performed using R software, version 2.12.1 (R Development Core Team. R: A Language and Environment for Statistical Computing [article online], 2009. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, Available from http://www.R-project.org. Accessed 23 July 2012). ROC analyses were performed using the packages pROC (Robin et al. 2011), ROCRegression and npROCRegression. These last two packages can be obtained by contacting MX Rodriguez-Alvarez (maria.jose.rodriguez.alvarez2@sergas.es).

Ethical considerations

The Galician Ethical Committee for Clinical Research approved the study protocol. All patients provided informed consent.

RESULTS

Table 1 summarizes anthropometric, clinical, and biochemical characteristics of the study population.

Table 1. Anthropometric, clinical, and biochemical characteristics of patient sample: distribution by gender in diabetic (n=247) and non-diabetic (n=2212) individuals.

	Women (1308/128)	Men (904/119)	Total
Age (years)			
• Non-diabetic	47.6 ± 15.9	48.2 ± 16.0	47.9 ± 15.9
• Diabetic	64.4 ± 10.7	62.4 ± 10.8	63.4 ± 10.7
Waist Circumference (cm)			
• Non-diabetic***	86.8 ± 13.2	96.3 ± 11.3	90.6 ± 13.3
• Diabetic*	101.5 ± 13.5	105.0 ± 11.4	103.1 ± 12.5
BMI (kg/m^2)			
• Non-diabetic***	26.9 ± 5.4	27.8 ± 4.5	27.3 ± 5.1
• Diabetic***	32.2 ± 5.6	29.4 ± 4.4	31.1 ± 5.2
Systolic Blood Pressure (mmHg)			
• Non-diabetic***	125.4 ± 21.0	135.8 ± 19.0	129.6 ± 20.8
• Diabetic	145.9 ± 21.1	148.6 ± 21.2	147.3 ± 21.1
Diastolic Blood Pressure (mmHg)			
• Non-diabetic***	76.6 ± 11.0	81.1 ± 11.4	78.4 ± 11.4
• Diabetic	82.1 ± 11.7	82.1 ± 10.7	82.1 ± 11.2
Triglycerides (mmol l^{-1})			
• Non-diabetic***	1.0 ± 0.6	1.3 ± 0.9	1.1 ± 0.7
• Diabetic	1.5 ± 0.8	1.9 ± 1.9	1.7 ± 1.4
HDL-Cholesterol (mmol/L)			
• Non-diabetic***	2.0 ± 0.5	1.7 ± 0.4	1.9 ± 0.5
• Diabetic**	1.7 ± 0.4	1.6 ± 0.4	1.8 ± 0.4
Fasting Insulin (U/l)			
• Non-diabetic**	7.7 ± 4.6	8.5 ± 5.2	8.0 ± 4.9
• Diabetic	11.9 ± 6.2	10.9 ± 6.5	11.4 ± 6.3
Fasting Plasma Glucose (mmol l^{-1})			
• Non-diabetic***	4.9 ± 0.6	5.1 ± 0.6	5.0 ± 0.6
• Diabetic*	7.8 ± 2.4	8.1 ± 2.5	8.0 ± 2.5
HOMA-IR (units)			
• Non-diabetic	1.9 ± 1.0	2.1 ± 1.2	2.0 ± 1.1
• Diabetic*	1.9 ± 1.0	1.7 ± 1.1	1.9 ± 1.1
Metabolic syndrome			
ATPIII**	11.1%	14.9%	12.7%
• Non-diabetic**	7.6%	11.1%	9.0%
• Diabetic	46.9%	43.7%	45.3%
IDF***	12.1%	19.2%	15.0%
• Non-diabetic***	8.7 %	14.9 %	11.3%
• Diabetic	46.9 %	51.3 %	49.0 %

Data are presented as mean ± standard deviation, or percentages. BMI, body mass index; HOMA-IR, homeostasis model assessment of IR; ATPIII, Third Adult Treatment Panel; IDF, International Diabetes Federation
Contrast of characteristics by gender was done with the follow statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001

In non-diabetic individuals, but not in diabetic individuals, we found significant differences by gender in components of MetS (data no shown). The percentage of triglycerides, blood pressure, and glycaemia components were higher in men than in women (23% vs. 9.6% (P<0.001), 32% vs. 19% (P<0.001) and 21% vs. 13% (P<0.001)). Women had a significantly higher waist circumference component than men (43.6% vs. 29.8%, P<0.0001).

In the overall data set, the MetS prevalence was 15% for $MetS_{IDF}$ (19.2% in men vs. 12.1% in women, P<0.0001) and 12.7% for $MetS_{ATPIII}$ (14.9% in men vs. 11.1% in women, P=0.006).

Mean HOMA-IR levels significantly increased with rising number of MetS components from 1.7 (without MetS components) to 5.3 (with 5 components) (P<0.0001).

AUC values of HOMA-IR by gender and diabetes status

Regardless of diabetes status, the AUC values of HOMA-IR were slightly higher for $MetS_{ATPIII}$ than $MetS_{IDF}$ (Table 2).

The effect of age on the accuracy of HOMA-IR was analyzed in individuals with and without diabetes mellitus separately. As can be seen in Table 2, in non-diabetic women a significant non-linear effect of age on the accuracy of HOMA-IR in identifying MetS, both $MetS_{ATPIII}$ (P=0.012) and $MetS_{IDF}$ (P<0.001), was found.

Figure 1 shows the estimated AUC values by age, with the corresponding 95% point wise bootstrap confidence bands. The AUC presents a plateau with values greater than 0.7 until 50 years of age. From the age of 50, the AUC decreases progressively. For patients older than 70 years, the bootstrap confidence intervals for the AUC includes 0.5; thus there is no evidence suggesting that HOMA-IR can be used to classify non-diabetic older women with cardio metabolic risk.

Figure 1. Performance of HOMA-IR levels for classification of cardio metabolic risk in non-diabetic population. Influence of age and gender in the area under curve (AUC) distribution, ROC regression models.

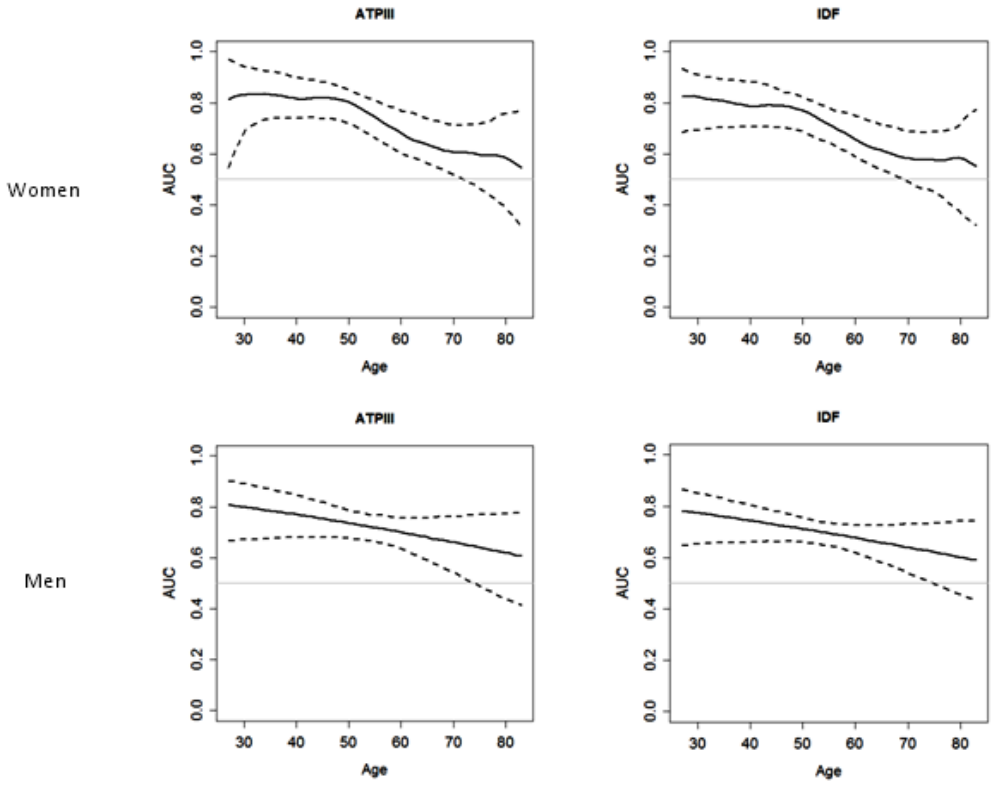


Table 2 shows the estimated AUC values for ages of 30, 50, and 70 years in our Spanish population. The AUC drops from 0.82 (age 30) to 0.58 (age 70). However, in non-diabetic men the AUC progressively decreases with age, without statistical significance (P=0.16, Figure 1). Thus AUC value, 0.69 (0.65, 0.74) for $MetS_{IDF}$ and 0.71 (0.66, 0.76) for $MetS_{ATPIII}$, was estimated without covariates (Table 2).

On the other hand, in diabetic individuals there was no statistically significant effect of age on the accuracy of HOMA-IR. The AUC show an acceptable performance of HOMA-IR in diabetic men, 0.7 (0.6, 0.8), but not in diabetic women 0.54 (0.44, 0.64) (Table 2).

Table 2. Performance of HOMA-IR values in the classification of cardio metabolic risk (both ATPIII MetS and IDF MetS definition), influence of age and gender. Areas under the ROC curves for non-diabetic (A) and diabetic (B) adults (n=2459).

		ROC coefficients*	P value	AUC (95% CI)
A	Males			
	IDF MetS			0.69 (0.65, 0.74)
	• Age	0.0102	0.1665	
	• Intercept	-1.1411	0.0048	
	ATPIII Mets			0.72 (0.67, 0.77)
	• Age	0.0117	0.1897	
	• Intercept	-1.2976	0.0089	
	Females **			
	IDF MetS			0.82 (0.71, 0.90)
	• Age 30 yr.		<0.001	0.77 (0.68, 0.82)
	• Age 50 yr.			
	• Age 70 yr.			0.58 (0.48, 0.68)
	ATPIII MetS			0.83 (0.71, 0.91)
	• Age 30 yr.		0.012	0.80 (0.71, 0.85)
	• Age 50 yr.			
	• Age 70 yr.			0.61 (0.52, 0.70)
B	Males			
	IDF MetS			0.68 (0.59, 0.78)
	• Age	-0.0113	0.8998	
	• Intercept	0.1406	0.5160	
	ATPIII MetS			0.72 (0.62, 0.81)
	• Age	-0.0029	0.8595	
	• Intercept	-0.4692	0.6515	
	Females			
	IDF MetS			0.54 (0.44, 0.64)
	• Age	-0.0010	0.9656	
	• Intercept	0.0173	0.9914	
	ATPIII MetS			0.54 (0.44, 0.64)
	• Age	-0.0010	0.9656	
	• Intercept	0.0173	0.9914	

AUC (95% CI), area under the ROC curve (95% Confidence Interval). *ROC regression models incorporating age as covariate. **The AUC was estimated for three ages (30, 50, and 70 years) to illustrate the performance of HOMA-IR.

Cut-off values of HOMA-IR

Table 3 shows gender distribution of HOMA-IR cut-off values, with their corresponding sensitivity and specificity.

Table 3. Gender distribution of HOMA-IR cut-off levels, with their corresponding sensitivity and specificity, for the IDF MetS and ATPIII MetS classify, in diabetic and non-diabetic individuals.

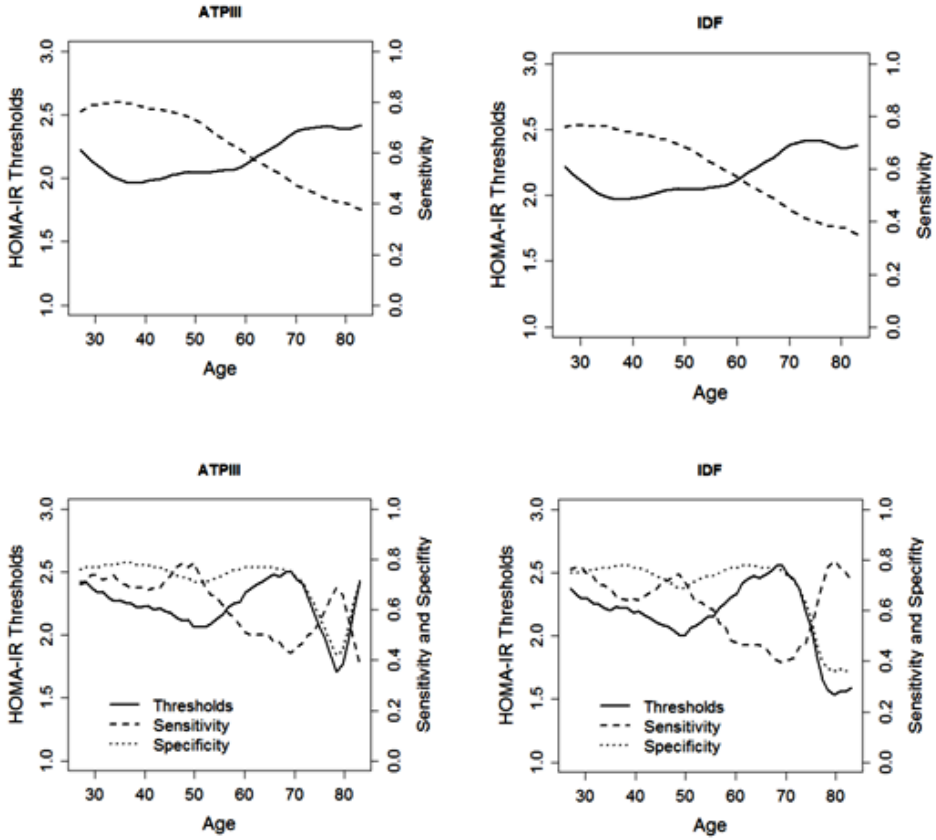
IDF Criteria						
Population	**Criterion of Specificity = 0.7**			**Youden Index Criterion**		
	Cut point	**Sensitivity**	**Specificity**	**Cut point**	**Sensitivity**	**Specificity**
Diabetic						
Men	1.55	0.60	0.70	1.60	0.59	0.74
Women	2.22	0.37	0.70	1.58	0.68	0.46
Non-diabetic						
Men	2.25	0.57	0.70	2.05	0.65	0.64
Women *						
30 years	2.11	0.77	0.70	2.31	0.71	0.76
50 years	2.05	0.69	0.70	2.05	0.69	0.70
70 years	2.38	0.45	0.70	2.53	0.40	0.75
ATP III Criteria						
Population	**Criterion of Specificity = 0.7**			**Youden Index Criterion**		
	Cut point	**Sensitivity**	**Specificity**	**Cut point**	**Sensitivity**	**Specificity**
Diabetic						
Men	1.57	0.64	0.70	1.60	0.63	0.73
Women	2.22	0.37	0.70	1.58	0.68	0.46
Non-diabetic						
Men	2.27	0.61	0.70	1.85	0.78	0.57
Women *						
30 years	2.12	0.79	0.70	2.36	0.73	0.77
50 years	2.05	0.73	0.70	2.07	0.72	0.71
70 years	2.37	0.48	0.70	2.47	0.44	0.74

*In non-diabetic females HOMA-IR cut-off values are estimated for 30, 50, and 70 years of age, because there is a non linear effect of age on test performance to classify IDF-defined MetS (P value < 0.001) and ATP III-defined MetS (P value = 0.012).

Figure 2 depicts the estimated HOMA-IR cut-off values by age in non-diabetic women for $MetS_{ATPIII}$ and $MetS_{IDF}$ respectively. For $MetS_{ATPIII}$ the optimal HOMA-IR cut-off values ranged from 2.07 (sensitivity, 0.72; specificity, 0.71) at 50 years to 2.47 (sensitivity, 0.44; specificity, 0.74) at 70 years when using YI criteria. Very similar values were found for $MetS_{IDF}$.

In non-diabetic men, for $MetS_{ATPIII}$ the optimal HOMA-IR cut-off was 1.85 (sensitivity, 0.78; specificity, 0.57) when YI criteria were used and 2.27 (sensitivity, 0.61) with fixed specificity criteria. Moreover, for $MetS_{IDF}$ the optimal HOMA-IR cut-off was higher, 2.05 (sensitivity, 0.65; specificity, 0.64), when YI criteria were used. In diabetic individuals the optimal HOMA-IR cut-off value for $MetS_{ATPIII}$ was 1.60 (sensitivity, 0.63; specificity, 0.73) in men and 1.58 (sensitivity, 0.68; specificity, 0.46) in women (YI criteria). All values are between 70^{nd} and 75^{nd} percentile of HOMA-IR levels in the Spanish adult population.

Figure 2. Optimal HOMA-IR cut point for classification of cardio metabolic risk in non-diabetic women. The top graphics show the results based on setting the specificity at 0.7, and the bottom graphics the results based on the generalization of the Youden Index. The ATPIII-defined criteria for metabolic syndrome were used on the left, and the IDF-defined criteria for metabolic syndrome on the right.



DISCUSSION

Overall, in non-diabetic individuals the best HOMA-IR cut-off levels ranged from 1.85 in men to 2.07 in women aged 50 years old for the diagnosis of IR take in account cardio metabolic risk. In women without diabetes, the optimal cutoff point should be estimated for each age group due to the non-linear effect of age on the accuracy of HOMA-IR. Even more, in women over 70 years there is no evidence suggesting that HOMA-IR can be used to classify individuals with or without cardio metabolic risk. All values are between the 70^{th}-75^{th} percentiles of HOMA-IR levels in the adult Spanish population (Gayoso-Diz et al. 2011).

We found lower cut-off values for diabetic than non-diabetic individuals (1.60 vs 2.05 for $MetS_{IDF}$ in men), probably because in the diabetic population there is an increased prevalence of hypertension, obesity, and dyslipidemia, thus lower HOMA-IR values identifies individuals with three or more MetS components.

In non-diabetic individuals AUC (95%IC) was 0.69 (0.64, 0.74) for $MetS_{IDF}$ and 0.72 (0.67, 0.77) for $MetS_{ATPIII}$ in men and 0.77 (0.68, 0.82) for $MetS_{IDF}$ and 0.80 (0.71, 0.85) for $MetS_{ATPIII}$ in women These results are similar to the study by Esteghamati that found an AUC of .0.65 (0.63, 0.67) for $MetS_{IDF}$ and 0.68 (0.66, 0.70 for $MetS_{ATPIII}$ (A. Esteghamati et al. 2010).

There is a significant effect of age on the diagnostic performance of HOMA-IR levels to identify cardio metabolic risk in non-diabetic women; however, there is no evidence of a significant effect in non-diabetic men. Meanwhile, in diabetic individuals we no found a statistically significant effect of age on the accuracy of HOMA-IR.

The AUC in non-diabetic women presents a plateau, with values greater than 0.7, until patients are in their fifties. Recent studies reported marked gender differences with regard to degrees of IR and body composition. The age effect found in non-diabetic women in our study may reflect the effect of menopausal changes (decreased estrogens levels and increased visceral adipose tissue, VAT) on HOMA-IR performance, with a higher utility to identify cardio metabolic risk below age 50.

IR increases atherogenesis and atherosclerotic plaque instability by inducing proinflammatory activities on vascular and immune cells (Bertoni, Wong & Shea 2007; Montecucco et al. 2008). HOMA-IR is a robust surrogate method to estimate IR in epidemiologic or clinical setting. However, there is great variability in their threshold levels; as can be seen in Table 4, usually the cut-off values of HOMA-IR were defined by population-based percentiles criteria. Furthermore, these cut-off values are different according to ethnicity, clinical methods of estimation, and metabolic conditions of populations studied (Antuna-Puente et al. 2011).

The consideration of the attendant risk of cardiovascular and metabolic diseases to establish this cut-off point would increase its clinical utility in identifying those patients in whom the presence of multiple metabolic risk factors imparts an increased metabolic and cardiovascular risk. In Spanish population the threshold value of HOMA-IR drops from 3.46 using 90^{th} percentile criteria to 2.05 take into account MetS components

Table 4. Summary of reports (sorted by sample size) on HOMA-IR cut-off in different populations

Study	Characteristics of study population	Threshold value	criteria
Hedblad,2000	N=4,816 Sweden, Population-based sample	≥ 2.0	75th percentile
Summer,2008	N=2804,U.S. NHANES population Age≥20 yr., normal BMI and fasting glucose	≥2.73	66th percentile
Geloneze,2006	N=1317 Brazilian, Age: 40 ± 12 yr, BMI: 34 ± 10 kg/m^2	≥ 2.77	90th percentile
Esteghamati,2009	N=1,276 Iranian, age: 38 ± 12 yr, non-diabetic, normotensive		
	IDF-MetS	≥1.80	ROC
	ATPIII-MetS	≥1.95	ROC
		≥1.6	75th percentile
		≥1.8	80th percentile
		≥ 2.3	90th percentile
Marques-Vidal,2002	N=1153, France Age 35-64 yr. population based sample	≥3.8	75th percentile
Do,2010	N=738 Thailand, Age: ≥35 yr, normal BMI and fasting glucose	1.55	90th percentile
Miccoli,2005	N=225 Italian, Age: 40 - 79 yr, healthy subjects	≥ 2.77	80th percentile
Taniguchi,1992	N=161 Japanese, Age: 41.6 ± 0.4 yr, healthy subjects	≥ 1.7	90th percentile
Ascaso,2001	N=140 Spanish, Age: 7 - 16 yr	3	ROC
Tome,2009	N=2860 Spanish, population based Age: 18-104 yr, BMI: 26.2 ± 4.9 kg/m^2	2	ROC

Our HOMA-IR cut-off levels are relatively low compared to those reported in a study of healthy Italian patients (Miccoli et al. 2005) with a value of 2.77, and in a Spanish non-diabetic population (Ascaso et al. 2001), with a value of 3.8. Both studies used the 80^{th} or 90^{th} percentile as cut-off selection criteria. On the other hand, our values are slightly higher than those reported in an Iranian population-based study with 1.77, using YI as cut-off selection criteria (A. Esteghamati et al. 2010), but in this case the value was estimated pooled in men and women.

The prevalence of MetS (15% for IDF and 12.7% for $MetS_{ATPIII}$) was quite similar to that found in northwest Spain (18.3 % for $MetS_{IDF}$ and 15.0% for $MetS_{ATPIII}$) (Tome et al. 2009) and in other European population-based studies (Bonora et al. 2003). On the other hand, it is significantly lower compared with the NHANES study (Ford et al. 2002), 23.7%, and SuRFNCD-2007 study (A. Esteghamati et al. 2010), 33.6%, probably because of the higher prevalence of obesity and other metabolic alterations in US and eastern Asia compared to the Spanish population (Danaei, Finucane, Lu, et al. 2011; Finucane et al. 2011).

The strengths of this study include the use of a large, diverse, and well-characterized population-based sample of adults. We used a novel non-parametric extension of the induced ROC regression methodology to analyze the effect of age on the accuracy of HOMA-IR when predicting the presence of cardio metabolic risk. The induced ROC regression methodology applied in this study is based on first evaluating the effect of covariates on the biomarker in healthy and diseased populations separately, and then computing the covariate effects on the associated ROC curve by deriving the induced form of the ROC curve.

We acknowledge limitations to our approach as well. The cross-sectional nature of our study does not allow us to draw conclusions regarding causality between IR and cardio metabolic risk. Furthermore the small sample size of diabetic patients does not allow us to draw conclusions about the performance of HOMA-IR in identifying cardio metabolic risk in diabetics. More prospective, population-based studies are needed to elucidate these concerns.

We propose the addition of the components of MetS analysis as a criterion to establish the cut-off points of HOMA-IR to define IR instead of using a percentile of the population distribution. The consideration of the attendant risk of cardiovascular and metabolic diseases to establish this cut-off point would increase its clinical utility in identifying those patients in whom the presence of multiple metabolic risk factors imparts an increased metabolic and cardiovascular risk.

In summary, with the increased prevalence of obesity and diabetes (Danaei, Finucane, Lu, et al. 2011; Finucane et al. 2011), the study of IR and body composition has become an important area of research in developed countries and a central public health task.

The effect of age and sex on the ability of HOMA-IR to identify subjects with cardio metabolic risk phenotype should be taken into account in the estimation of their values in different populations.

V.5 ARTICULO 5

"Strategy to estimate risk progression of chronic kidney disease (CKD), cardiovascular risk (CVR) and referral to nephrology. The EPIRCE Study proposal"

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RESUMEN. En este original se presentan los resultados de la reclasificación que se produce en las categorías de ERC cuando la estimación de filtrado glomerular se hace empleando la ecuación CKD-EPI en vez de MDRD. Se observa que la prevalencia de ERC se modifica, de forma variable en función de la edad. Asimismo para la estratificación de riesgo en pacientes con ERC, que permita una mejor priorización de actuaciones intensivas, se propone la aplicación de la metodología propuesta por Hallan et al. Se analiza la distribución de riesgo en población española mayor de 20 años mediante la citada metodología. Este trabajo responde al cuarto objetivo planteado en la presente Tesis de Doctorado.

ABSTRACT

Background: Although the prevalence of chronic kidney disease (CKD) is 10–14%, several prospective studies note a low rate of progression to end-stage renal disease (ESRD) in stages 3 and 4. A correct classification of risk of progression, based on demonstrated predictive factors, would allow better management of CKD. Recent studies have demonstrated the high predictive value of a classification that combines estimated (e) glomerular filtration rate (GFR) and albumin–creatinine ratio (ACR). We estimated the clinical risk of progression to ESRD and cardiovascular mortality predicted by the combined variable of eGFR and ACR in the Spanish general population.

Materials and Methods: This study was a cross-sectional evaluation in the EPIRCE sample, representative of Spanish population older than 20 years. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) and CKD-EPI formulas; microalbuminuria was considered to be an ACR 20–200 mg/g (men) or 30–300 mg/g (women) and macroalbuminuria was indicated beyond these limits. Population-weighted prevalence of risk of progression of CKD to ESRD was estimated.

Results: With MDRD, 1.4% of the adult Spanish population was at moderate risk of progression to ESRD, 0.1% at high risk, and 12.3% at low risk. With CKD-EPI, the moderate risk ratio rose to 1.7% and low risk to 12.6%, but high risk remained stable.

Conclusions: The addition of ACR to eGFR best classifies the population at risk for renal impairment relative to Kidney/Disease Outcomes Quality Initiative grades 3 and 4. Estimating GFR with CKD-EPI modifies the distribution of low and moderate risk.

Keywords: albuminuria, cardiovascular risk classification, chronic kidney disease, epidemiology, prognosis.

INTRODUCTION

Chronic kidney disease (CKD) is a growing health problem in developed countries because of its high prevalence, effect on quality of life, and high vascular-related mortality (Go et al. 2004), although its evaluation is imprecise. Classically, we assess the socioeconomic impact of CKD based on patients receiving renal replacement therapy (RRT) (Lysagrht 2002), but the real burden of CKD is 50–70 times higher than those because of RRT (Coresh et al. 2003; Cirillo et al. 2006), and patients in CKD stages 3–5 are at greater risk for cardiovascular disease (CVD) mortality than progression to end-stage renal disease (ESRD) (Keith et al. 2004; Sarnak et al. 2003).

The most frequently applied estimating formula, the Modification of Diet in Renal Disease (MDRD) equation (Levey et al. 1999), has been questioned because it underestimates GFR (Botev et al. 2009). The CKD-EPI creatinine equation is more accurate across various study populations and clinical conditions (Levey et al. 2009), and recent studies have shown an improved accuracy of CKD-EPI for estimating cardiovascular events and mortality risk (Montañes et al. 2010; Matsushita, Selvin, et al. 2010; White et al. 2010). Nevertheless, these methods remain inaccurate because the GFR itself is a poor indicator of renal function given that it does not exactly correlate with the rate of uremic toxin (Eloot et al. 2011).

Guidelines proposed in 2003 by the Kidney Disease Outcomes Quality Initiative (Levey et al. 2003) and adopted in 2005 by the Kidney Disease Improving Global Outcomes (KDIGO) for CKD defined it as the presence of a

GFR <60 mL/min/1.73 m^2 or kidney damage persistent for more than three months, regardless of cause.

In 2010, the Chronic Kidney Disease Prognosis Consortium (Levey et al. 2011), reported the results of the meta-analysis of the association using estimated (e) GFR and ACR with mortality in the general population (Matsushita, Van der Velde, et al. 2010), and in 2011, the results of the association with progression to ESRD (De Jong 2008; Gansevoort et al. 2011). In addition, this effect is present in people older and younger than 65 years, which again contradicts the belief that the prevalence of CKD increases with age (O'Hare et al. 2006); that belief is likely an artefact of the estimation formula, the retention of a renal functional reserve up to age 80 years (Fliser et al. 1993), and the fact that age is the seventh leading factor in RRT (Hsu et al. 2009). Furthermore, the association of eGFR-ACR with progression to ESRD is continuous and independent of other risk factors (Gansevoort et al. 2011).

CKD is otherwise a silent process in its early stages, linked to very early development of vascular lesions associated with micro inflammation and monocyte activation, with evidence to suggest a turning point for risk at GFR 75.6–89 mL/min (Van Biesen et al. 2007; Rogacev et al. 2011). Strategies to identify patients at risk would allow appropriate management programs of primary or secondary prevention aimed at not only changing the progression of CKD but also at decreasing the risk of CVD mortality. In 2009, Hallan et al. (S. I. Hallan et al. 2009; S. I. Hallan & P. E. Stevens 2010) proposed a new clinical risk classification system that combined all GFR levels with ACR measurement.

The aim of the current study was to estimate the clinical risk of progression to ESRD and cardiovascular mortality predicted by the combined variable of baseline eGFR and albuminuria in a Spanish general population. We also tested whether CKD-EPI eGFR modified the estimation of risk prediction compared to MDRD eGFR.

SUBJECTS AND METHODS

Study population

Our study population consisted of 2244 individuals who have enrolled in cross-sectional EPIRCE study with a urine albumin to creatinine ratio (ACR) estimation. In the Estudio Epidemiológico de la Insuficiencia Renal en España (EPIRCE) study, a random sample, stratified by age, sex, and location was drawn from the 2001 Spanish Census (Otero et al. 2010; Otero, Gayoso, et al. 2005). The recruited sample was adjusted to provide valid estimates of age and sex according to the distribution of the Spanish population in 2001. All participants were Caucasians.

Data collection

Data were collected using a standardized questionnaire administered during a structured interview, followed by a detailed physical examination and blood sample collection (Otero et al. 2010; Otero, Gayoso, et al. 2005). Serum creatinine concentration was determined in the same reference laboratory for all samples. GFR was calculated as an indicator of renal function with the MDRD-4

formula, $eGFR_{MDRD}$ (Levey et al. 1999), and the CKD-EPI formula, $eGFR_{CKD-EPI}$ (Levey et al. 2009). Participants were classified (eGFR categories: ≥90, 60–89, 45–59, 30–44, 15–29, <15 mL/min/1.73 m^2) according to the Kidney Disease Outcomes Quality Initiative guidelines (Foundation 2002b).

Patients were asked to deliver a spot urine sample, and ACR was used as an expression of albumin excretion. The ACR was measured in 2,244 individuals (81.7% overall sample). Microalbuminuria was defined as ACR 20 to 200 mg/g in men and 30 to 300 mg/g in women, and macroalbuminuria was defined as ACR >200 mg/g in men and >300 mg/g in women (De Jong 2006).

A new CKD classification system with four categories of eGFR (≥60, 45–59, 30–44, and 15–30 mL/min/1.73 m^2) complemented by three categories of albuminuria (normoalbuminuria, microalbuminuria, and macroalbuminuria) was used for the description of low, moderate, and high risk of progression to kidney failure (S. I. Hallan et al. 2009) and the relative risk for cardiovascular mortality (S. I. Hallan & P. E. Stevens 2010).

Statistical analyses

Baseline subject characteristics are expressed as the mean ± SD or as percentages. Age- and sex-adjusted eGFR levels are reported as percentages or medians and percentiles.

We cross-tabulated eGFR using clinically relevant categories (≥90, 60–89, 45–59, 30–44, 15–29, <15 mL/min/1.73 m^2) to evaluate the proportion of participants in each category of MDRD eGFR reclassified by the CKD-EPI

equation eGFR. Generalized additive models (GAMs) (Wood 2006) were used to evaluate the age and sex effect on eGFR categories, both $eGFR_{MDRD}$ and $eGFR_{CKD-EPI}$.

The main advantage of GAMs over traditional regression methods is that they do not impose a parametric form on the effects of continuous covariates on the response of interest. Instead, they assume only that these effects are additive and reasonably smooth. In this paper, penalized regression splines combined with thin plate splines as smoothers were used to estimate GAM regression models, and the estimation of the smoothing parameters was chosen automatically by means of a generalized cross validation criterion. A Bayesian approach to uncertainty estimation was used to obtain 95% confidence intervals for the estimated effects (Wood 2006). All statistical analyses were performed using R software, version 2.9.1; GAMs were fitted using the mgcv package (R 2009).

Ethical considerations

The Galician Ethical Committee for Clinical Research approved the study protocol. All participants provided informed consent.

RESULTS

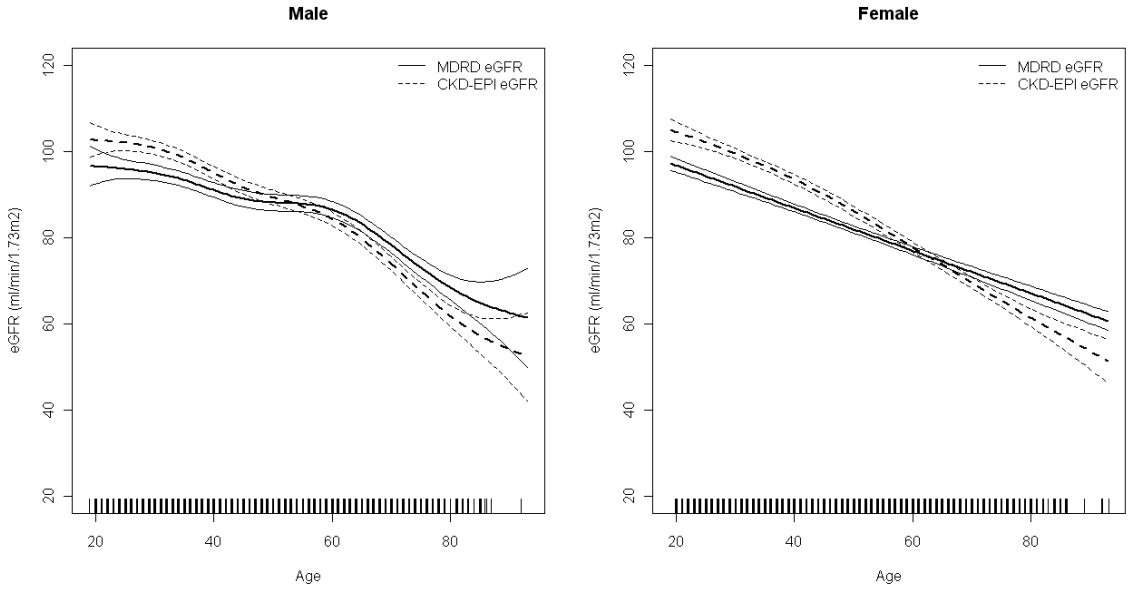
The mean population age was 49.5 years, 52.6% (1445) were women, 25.8% (709) were 65 years old, and 16.6% (457) were 70 years old or older. Their clinical characteristics and lifestyles have been described previously (24), highlighting a regular consumption of alcohol (45.1%), smoking (25.5%), and physical inactivity (28.9%). The population has a high prevalence of dyslipidemia (29.3%), obesity (26.1%), and hypertension (24.1%), and 9.2%

had a previous diagnosis of diabetes. Regarding previous cardiovascular events, peripheral vascular disease was the most frequent (10.8%), followed by ischemic heart disease (5.1%) and cerebrovascular disease (1.7%).

The prevalence of CKD stages 3 to 5 (eGFR <60 mL/min/1.73 m^2) in the general Spanish population was 6.8% with $eGFR_{MDRD}$ and 6.9% with $eGFR_{CKD-EPI}$; the prevalence of microalbuminuria/macroalbuminuria was 4.0%.

Population-weighted mean estimated GFR was higher when computed using the CKD-EPI equation (86.75 mL/min/1.73 m^2; 95% confidence interval [CI] 86.06, 87.44) compared to using the MDRD formula (84.64 mL/min/1.73 m2; 95% CI 83.96, 85.31; p<0.0001). We also analysed groups by age and sex for eGFR variation between the two methods. The MDRD underestimated GFR values relative to CKD-EPI, but for people over age 60 years, eGFR results were similar and even slightly higher with MDRD (Figure 1).

Figure 1. Distribution of estimated glomerular filtration rate (GFR) by age and sex. Differences by estimation equation in the EPIRCE Study.



CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease. Estimation and confidence intervals of estimated glomerular filtration rate computed by CKD-EPI equation (solid lines) and by MDRD equation (dotted lines), for males (left) and females (right), respectively.

When we analysed the variation in eGFR categories as computed using CKD-EPI compared with MDRD, we found that 13.3% (365) of the population was reclassified to a higher eGFR category and 3.3% (92) was reclassified to a lower eGFR category (Table 1).

Table 1. Reclassification across eGFR categories using the CKD-EPI equation from categories based on the MDRD equation: the EPIRCE study

		CKD-EPI Estimated GFR Categories						
		≥90	*60–89*	*45–59*	*30–44*	*15–29*	*<15*	*Total*
MDRD Estimated GFR Categories	*≥ 90*	870(31.7)	50 †(1.8)					920
	60–89	363‡(12.9)	1272(46.3)	29 †(1.1)				1654
	45–59		11 ‡(0.4)	116(4.2)	11†(0.4)			138
	30–44			1 ‡(0.03)	25(0.9)	1†(0.03)		27
	15–29					5 (0.2)	1†(0.03)	6
	<15						1 (0.03)	1
	Total	1223	1333	146	36	6	2	2746

CKD-EPI: Chronic Kidney Disease–Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease.

Values in each cell represent number (percent of overall) of subjects reclassified by CKD-EPI: up (‡) or down (†) GFR categories. In green, cell with not reclassified subjects.

Individuals reclassified to a lower category were older than those who were not reclassified (mean age 75.1±5.5 versus 49±17). When we analysed the subgroup of participants ages 65 years or older, we found that those reclassified to a lower category were older (75.5±5.1 vs. 72.6±5.2, p<0.001) and had more anaemia (6.1% vs. 1.6%, p=0.03), diabetes (41% vs. 23%, p=0.006) and a sedentary lifestyle (41% vs. 25%) compared to those who were not reclassified. Table 2 shows the risk categories of progression to ESRD in the EPIRCE sample.

Table 2. Distribution of risk of progression to kidney failure in EPIRCE study population.

		e GFR (MDRD)				
		≥ 60	45-59	30-44	15-29	Total
ACR	normoalbuminuria	1955 (87.1)	98 (4.4)	18 (0.8)	3 (0.1)	2074 (92.4)
	microalbuminuria	146 (6.5)	17 (0.8)	4 (0.2)	2 (0.1)	169 (7.5)
	macroalbuminuria	1 (0.5)	0	0	0	1 (0.05)
Total		2102 (93.7)	115 (5.1)	22 (1.0)	5 (0.2)	2244

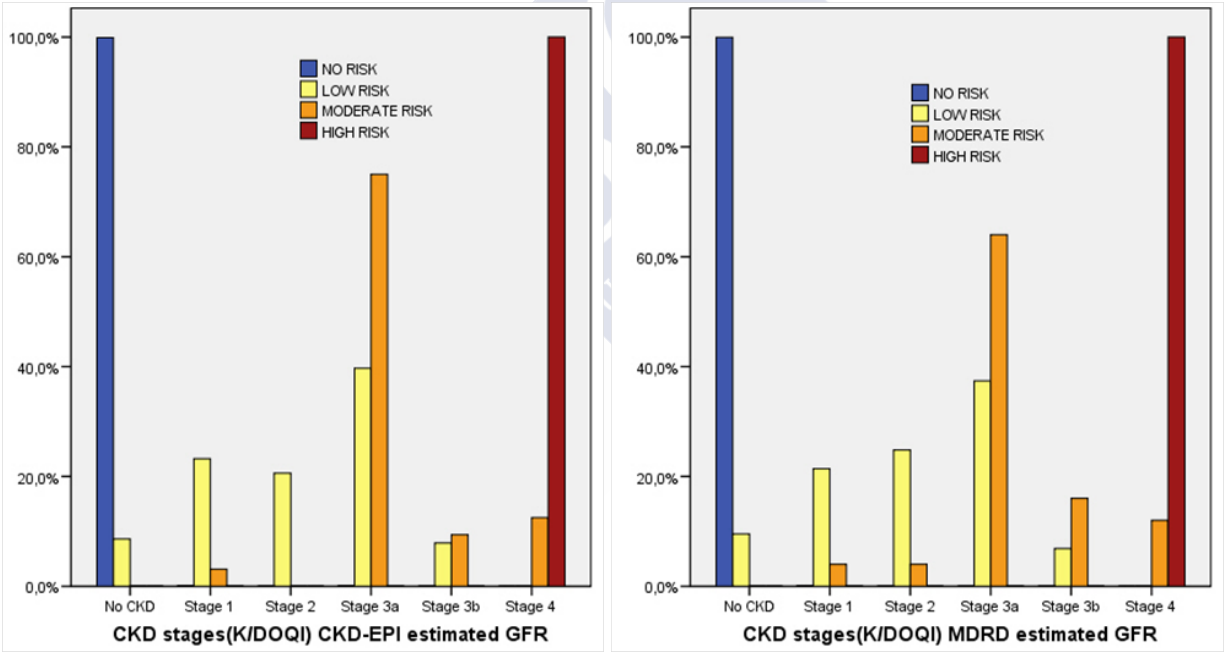
		e GFR (CKD-EPI)				
		≥ 60	45-59	30-44	15-29	Total
ACR	normoalbuminuria	1943 (86.6)	101 (4.5)	26 (1.2)	4 (0.2)	2074 (92.4)
	microalbuminuria	140 (6.2)	22	5 (0.2)	2 (0.1)	169 (7.5)
	macroalbuminuria	1 (0.5)	0	0	0	1 (0.05)
Total		2084 (92.9)	123 (5.5)	31 (1.4)	6 (0.3)	2244

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease.. ACR: albumin-to-creatinine ratio. Microalbuminuria was defined as ACR 20 to 200 mg/g in men and 30 to 300 mg/g in women, and macroalbuminuria was defined as ACR 200 mg/g in men and 300 mg/g in women. Values in each cell represent number (percent of overall). Shaded cells represent risk for progression of ESRD: low (green); moderate (orange); high (red).

The lower risk percentage was 11.7 with $eGFR_{MDRD}$ and 11.9 with $eGFR_{CKD\_EPI}$; the moderate risk percentages were 1.1 and 1.4, respectively; and the high-risk percentage was 0.1 with both eGFR equations. We also assessed the age- and sex-weighted percentages of low (12.3% vs. 12.6%), moderate (1.3% vs. 1.7%), and high risk (0.1%) of progression to ESRD in the general Spanish population based on eGFR with the MDRD and CKD-EPI equations, respectively.

When we analysed the risk of progression to ESRD by CKD stages using $eGFR_{CKD\text{-}EPI}$, we found that only 17.4% (15.0% with $eGFR_{MDRD}$) of participants in CKD stage 3 presented a moderate risk of progression to ESRD, compared with 66.7% (60.0% with $eGFR_{MDRD}$) in CKD stage 4 (Figure 2).

Figure 2. Risk of progression to ESRD categories by CKD stages using $eGFR_{CKD\text{-}EPI}$ (left) and $eGFR_{MDRD}$ (right); the EPIRCE Study.



CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease. Risk stratification of progression to ESRD categories: Hallan et al. proposal. No risk category: eGFR ≥60 and normoalbuminuria. Low risk category: normoalbuminuria with eGFR 30–59 or microalbuminuria with eGFR ≥60. Moderate risk: normoalbuminuria with eGFR <30 or microalbuminuria with eGFR 30–59 or macroalbuminuria with eGFR ≥60. High risk: microalbuminuria with eGFR<30 or macroalbuminuria with eGFR 30–59.

DISCUSSION

Using the stratification of risk of progression to ESRD given by Hallan et al (S. I. Hallan et al. 2009; S. I. Hallan & P. E. Stevens 2010; S. I. Hallan & Orth 2010), 12.6% of the Spanish population has a low risk of progression to ESRD while 1.7% has a moderate risk (with a hazard ratio [HR] of cardiovascular mortality between 2 and 3), and 0.1% a high risk (with a HR of cardiovascular mortality greater than 3). Although Hallan et al.'s proposal that CKD-EPI creatinine-based equation more accurately classifies individuals relative to risk for mortality and ESRD compared with MDRD, even after considering albuminuria (Matsushita et al. 2012; Shafi et al. 2012). We computed the risk stratification of ESRD in the EPIRCE population by using both equations. The results show a slight increase in low and moderate risk percentages with $eGFR_{CKD\text{-}EPI}$ (12.6% vs. 12.3% and 1.7% vs. 1.3%) and the same percentage of high risk (0.1%) in the Spanish adult population. These results are very similar to those reported by Hallan et al. from the HUNT 2 study: 12.6, 1.3, and 0.2%, respectively (S. I. Hallan & Orth 2010).

In previous studies, estimated GFR and ACR were the major predictors of future kidney failure, and adding age, sex, diabetes, hypertension, and other potential risk factors did not improve prediction (Matsushita, Selvin, et al. 2010; White et al. 2010)(Gansevoort et al. 2011). Risk stratification with a 12-category matrix (eGFR ≥60, 45–59, 30–44, and 15–29) subdivided by ACR into normoalbuminuria, microalbuminuria, and macroalbuminuria was more useful than the current CKD classification system (S. I. Hallan et al. 2009; S. I. Hallan & P. E. Stevens 2010; S. I. Hallan & Orth 2010; Hemmelgarn et al. 2010; White et al. 2010).

On the other hand, patients with CKD stage 1–3 have a 25 to 100 times higher risk of developing a cardiovascular event or death than of progressing to ESRD (Keith et al. 2004; de Jong et al. 2008), presumably because of subclinical atherosclerosis and/or vascular injury from early micro inflammation (Rogacev et al. 2011).

When CKD-EPI and MRDR estimation equations were compared in the current study, we found that MDRD underestimated GFR values relative to CKD-EPI, but over 60 years eGFR results were very similar and even slightly higher with MDRD. The AUSDIAB study found that in Australians age >25 years, the reference population-weighted eGFR values were similar for the population age ≥65 years, regardless of which equation (MDRD or CKD-EPI) was used, but that the CKD-EPI equation yielded significantly higher reference values in younger age groups (S. C. Chen et al. 2008). Carter et al, in the East Kent population, observed mean eGFR using CKD_EPI equation to be 11.2% higher than that estimated using the MDRD Study equation for individuals aged 40-49 years; this difference gradually diminished to 0.7% in the 70-79 years old; and in people older than 80 years, the MDRD equation gave a lower CKD prevalence than the CKD_EPI equation (Carter et al. 2011). Kilbride et al in European ancestry people older than 74 years found a mean lower eGFR using CKD-EPI equation than using MDRD equation (50.3 vs. 52.3 mL/min/1.73 m^2)

We analysed the variation in eGFR categories when computed using CKD-EPI compared with MDRD. We found that 13.3% (365 participants) were reclassified to a higher eGFR category and 3.3% (92 participants) were reclassified to a lower eGFR category. These results are quite similar to those found by the Chronic Kidney Disease Prognosis Consortium's recent meta-

analysis of 25 studies of population cohorts (Matsushita et al. 2012) but with a higher percentage of people reclassified to a lower level (3.3% vs. 0.6%). Just as Matsushita et al. reported in that analysis (Matsushita et al. 2012), in our population the individuals reclassified to a lower level were older than those who were not reclassified (mean age 75.1 versus 49 years in EPIRCE population; 77 vs. 49 years in the meta-analysis population). When we analysed the subgroup ages 65 years or older, we found that those reclassified to a lower level were older and had more anaemia and diabetes and sedentary lifestyles than those not reclassified.

We acknowledge limitations to our approach as well. The cross-sectional nature of the study does not allow to us to draw conclusions regarding causality between lower GFR and cardiovascular or progression to RRT risk. The data of seven years prospective follow-up of EPIRCE sample, actually in progress, allow us to analyse this topics in Spanish population. But considering the sample representativeness, to know the behaviour in Spanish population of different estimation equations and the consequences of risk stratification, as we proposal, could be of interest to clinicians and health policy makers.

Different studies have shown (De Jong et al. 2008; C. Jones et al. 2006; Martin de Francisco et al. 2009) that active disease management strategies can preserve kidney function and reduce CKD progression in CKD stage 3–5. Nevertheless, it remains unclear what the best clinically based criteria are that will result in more people benefiting from this approach. When considering the cost-effective use of health resources for the management of CKD, it is necessary to have instruments for selecting those patients in whom interventions are more efficient. A general practice and public health

perspective favours the estimated GFR using the CKD_EPI equation (Earley et al. 2012). One strategy to be developed jointly by nephrology and primary care clinicians (Martin de Francisco et al. 2009; P. E. Stevens et al. 2010; Richards et al. 2008) will be the establishment of consensus protocols to achieve this incorporation for the stratification of CKD patients. In the central area of Orense, we have initiated a program for early detection of CKD and associated cardiovascular risk based on these criteria. Systematically, the primary care provider receives, together with $eGFR_{CKD\text{-}EPI}$, an estimated risk of progression to ESRD according to risk stratification using ACR and eGFR. It will be necessary to assess the medium-term effectiveness of this program.

In conclusion, the proportion of the Spanish population with a high risk for progression to ESRD is low, but 1.7% is at moderate risk. The use of an instrument of "Risk Stratification of CKD Progression" employing the formula CKD-EPI+ACR would allow appropriate management not only in the early diagnosis of CKD but also as a tool for cardiovascular risk stratification and as criteria for referral from primary care to nephrology the patients at risk of progression.

VI. DISCUSION CONJUNTA

La ERC es una patología de elevada prevalencia en España. En población adulta el estudio EPIRCE halló una prevalencia de Insuficiencia renal crónica (IRC, filtrado glomerular estimado <60 mL/min/1.73 m^2) del 6.8% , utilizando MDRD 4, o 6.9%, utilizando CKD-EPI. Esta prevalencia es comparable a la del 7.2% de ERC en estadios 3-5 comunicada en la revisión sistemática de 26 estudios observacionales en población general realizada por Zhang y col. en 2008, y está dentro del rango de resultados de estudios de base poblacional en otros países europeos entre el 4.7% y 8.1% (Q. L. Zhang & Rothenbacher 2008). Por su parte, es inferior a la prevalencia del 8.05% comunicada en población de EE.UU., quizá en relación con una mayor prevalencia de obesidad y otros factores de riesgo en este país.

En los 25 estudios realizados en población general incluidos en The Chronic Kidney Disease Epidemiology Collaboration, la prevalencia conjunta de IRC fue del 6.3%, utilizando CKD-EPI, muy similar a la encontrada en nuestro estudio (Matsushita et al. 2012). Por otra parte, la prevalencia poblacional que estimamos en España es sensiblemente inferior a la prevalencia del 21.3% hallada en población española demandante de atención sanitaria seguida en centros de AP (De Francisco et al. 2007), como era esperable dada la selección de riesgos que se produce en la población habitualmente usuaria de servicios de salud.

La albuminuria, definida como un ACR superior a 30 mg/g, presenta una prevalencia poblacional de 4.0% en individuos mayores de 20 años en España.

Esta prevalencia es menor a la hallada en población noruega, 7.1%, o estadounidense, 6.8% en los estudios HUNT y NHANES respectivamente.

Al incorporar el cociente albumina creatinina (ACR) al filtrado glomerular se identificó una prevalencia de 2.3% para ERC en estadios I y II; individuos cuya patología renal no seria identificada de no realizar determinación de albuminuria, por lo que la tasa de infra diagnóstico potencial para estadios precoces de deterioro de función renal es del 2.3% en España.

Se estima que la prevalencia de ERC en población española mayor de 20 años, en cualquier estadio, es del 9.16% usando la ecuación MDRD y del 10.1% usando la ecuación CKD-EPI. Esta prevalencia es menor a la encontrada en poblaciones de similar edad en países como Australia del 13.8% con MDRD y 10.95% con CKD-EPI (White et al. 2010) y en población del National Health and Nutrition Examination Survey (NHANES) del 13.1% con MDRD y 11.5% con CKD-EPI (Levey et al. 2009). Es similar sin embargo a la prevalencia poblacional en Noruega del 10.2% utilizando MDRD (S. I. Hallan et al. 2006).

En la muestra objeto de estudio, únicamente 11 casos (0.4%) estaban diagnosticados de ERC, lo que representa una prevalencia poblacional de enfermedad renal crónica oculta del 7.7%, esto es 77.000 individuos pmp con algún grado de ERC no identificado en población española mayor de 20 años. Un 5.9% (estimando con CKD-EPI eGFR) o 5.2% (estimando con MDRD eGFR) de la población española mayor de 20 años presentan algún grado de

ERC con niveles de creatinina sérica en rango de normalidad (<1.1 mg/dl en mujeres y 1.2 mg/dl en varones), por tanto su alteración de función renal no se identificaría si en practica clínica se consideran únicamente los valores de creatinina plasmática no ajustados por edad, sexo y grupo étnico.

En la población de estudio se hallo una alta prevalencia de factores de riesgo cardiovascular. La prevalencia poblacional estimada fue de 26.1% para obesidad, 24.1% para hipertensión, 10.8% (9.2% previamente diagnosticada) para diabetes y 29.3% para dislipemia. Recientes estudios han estimado la prevalencia global estandarizada por edad, y referida a población de 2008 de: diabetes, 9.2% para mujeres y 9.8% en varones (Danaei, Finucane, Lu, et al. 2011); obesidad, 13.8% en mujeres y 9.8% en varones (Finucane et al. 2011); e hipertensión, 25% en mujeres y 29% en varones (Danaei, Finucane, J. K. Lin, et al. 2011). En estos estudios se observa en el entorno europeo una tendencia creciente en la prevalencia de obesidad y diabetes, mientras que la hipertensión muestra un descenso sostenido desde 1980 hasta 2008. Comparando estos resultados con los hallados en población española en el estudio objeto de esta Tesis Doctoral, se observa una mayor prevalencia de obesidad, siendo similar para diabetes e hipertensión.

En relación a estilos de vida, la población española presenta un elevado índice de sedentarismo, con una prevalencia poblacional estimada del 28.9%, casi uno de cada 3 sujetos. Un 25.5% refería ser fumador en el momento del estudio. Por su parte, el consumo habitual de alcohol estaba presente en un

45.1% de la población, con un consumo medio de 183 gr / semana en varones y 50 gr / semana en mujeres.

Considerando los criterios propuestos por la ATP III se estima en un 12.7 % (9.0% en no diabéticos) la prevalencia de síndrome metabólico en población española mayor de 20 años, siendo mayor en mujeres, 14.9% (11.1% en no diabéticos) que en varones, 11.1% (7.6% en no diabéticos) con el consiguiente aumento de riesgo cardiovascular. Esta prevalencia varia significativamente con la edad, con una tendencia creciente directamente proporcional al envejecimiento.

Los factores de riesgo asociados a la presencia de ERC fueron edad (OR-1.12), obesidad (OR-1.91), e hipertensión (OR-1.61) una vez controlado el efecto por otras posibles variables confusoras. Dado el progresivo envejecimiento de la población española y la elevada prevalencia tanto de obesidad como hipertensión, es esperable que la ERC presente una progresión de nuevos casos en los próximos años con el consiguiente incremento en la carga de enfermedad asociada a ella.

En relación a estilos de vida, tanto el sedentarismo (OR -1.2) como el consumo de tabaco (OR-16.4) presentaban asociación con la presencia de ERC, aunque al ajustar por otros factores, esta asociación no mantuvo su significación.

Las diferentes ecuaciones de estimación de filtrado glomerular presentan un rendimiento variable, por lo que su utilización produce modificaciones en la

prevalencia estimada de afectación renal y en la clasificación en estadios, sobre todo en los niveles próximos a 60 ml/min/1.73 m2(Glassock & Winearls 2008; Glassock 2009; Xie et al. 2008). Al comparar en población española los resultados utilizando la ecuación CKD-EPI respecto a MDRD, se encontró que un 13.3% (365) de sujetos fue reclasificado a una categoría de mayor eGFR mientras solo un 3.3% (92) fue reclasificado a categoría de menor eGFR. Estos últimos presentaban significativamente mayor edad que los no reclasificados (edad 75.1±5.5 versus 49±17 años). Al analizar específicamente el subgrupo de sujetos con edad ≥ 65 años, se observa que los sujetos reclasificados a categoría de menor eGFR son mayores (75.5±5.1 vs 72.6±5.2 años, $p<0.001$) y presentan mayor prevalencia de anemia (6.1% vs 1.6%, $p=0.03$), diabetes (41% vs 23%, $p=0.006$) y sedentarismo (41% vs 25%) que aquellos no reclasificados. Similares resultados fueron hallados tanto en el estudio Ausdiab como en la CKD-EPI Collaboration (White et al. 2010; Shafi et al. 2012).

Existe por tanto solida evidencia para recomendar al utilización sistemática de CKD-EPI como ecuación de estimación de filtrado glomerular en practica clínica.

La resistencia a la insulina, junto con la obesidad central son hechos comunes a la presencia de alteraciones metabólicas como dislipemia (hipertrigliceridemia, bajos niveles de HDL-colesterol), hiperglucemia e HTA. Todos ellos factores de riesgo cardiovascular. Recientes estudios prospectivos han mostrado la asociación entre síndrome metabólico, SM, y riesgo de

desarrollo de IRC (OR -1.5, IC 95% 1.34,1.79 , en el meta análisis realizado por Thomas el al en 2011) junto con un gradiente de incremento del riesgo al aumentar los componentes de SM presentes, OR desde 1.39 para 2 componentes de SM hasta 1.96 para 5 componentes respectivamente (Thomas et al. 2011).

En el trabajo objeto de esta Tesis Doctoral se ha hallado una elevada correlación entre obesidad visceral y resistencia a la insulina en población española. La distribución de valores poblacionales de HOMA-IR varia en relación tanto con IMC como con la circunferencia de cintura, con independencia de edad y sexo, mostrando mayores valores en sujetos con obesidad central.

En la población del NAHNES III se demostró que los marcadores de inflamación están directamente asociados a una mayor resistencia a la insulina (medida por HOMA-IR), siendo esta asociación independiente de otras características epidemiológicas ó clínicas (J. Chen, R. Wildman, et al. 2004). Además en sujetos no diabéticos, estar en el cuartil más alto de HOMA_IR suponía respecto al cuartil mas bajo, un OR de 2.65 (IC 95% 1.25, 5.62) para presentar IRC (GFR < 60 mL/min/1.73 m2) ajustado por variables potencialmente confusoras (J. Chen 2003).

Algunos estudios indican posibles causas genéticas que contribuyen a explicar la asociación existente entre tejido adiposo e inflamación crónica en ERC (Zoccali 2011). La resistencia a la insulina es importante como indicador de un

estado de inflamación crónica asociado etiopatológicamente a aterosclerosis y presente en la patogenia de patologías como diabetes mellitus tipo 2, obesidad y enfermedad cardiovascular.

En la toma de decisiones clínicas, disponer de criterios estables que definan la resistencia a la insulina resulta muy importante para una correcta clasificación de los pacientes atendidos y por tanto para la toma de decisiones. Existe una alta variabilidad en el valor establecido como punto de corte de HOMA-IR para identificar la resistencia a insulina.

En la tabla 4 del artículo 4 de esta Tesis Doctoral se recoge un resumen de los principales estudios publicados mostrando esta variabilidad en los puntos de corte propuestos. Variabilidad debida, como se observa, tanto a diferencias en las características de las poblaciones de estudio como en los criterios de estimación del punto de corte optimo. En muchos casos se establece utilizando el P90 o P80 de la distribución de HOMA-IR; en otros casos se realizó un análisis del comportamiento como prueba diagnostica mediante curvas ROC.

En el presente estudio se ha demostrado la variabilidad existente en la resistencia a la insulina en relación a sexo, edad y obesidad de predominio visceral.

Se aporta por otra parte evidencias de que el HOMA-IR presenta un buen comportamiento como marcador de riesgo cardio-metabólico. En población no diabética, niveles de HOMA-IR de 1.8 en varones y 2.1 en mujeres presentan un AUC superior a 0.7 para la identificación de sujetos con criterios de

síndrome metabólico. Es importante sin embargo señalar que en mujeres mayores de 70 años los resultados indican pérdida de esta capacidad de discriminación.

Perspectivas futuras en el manejo de la enfermedad renal crónica: cribado y abordaje multidisciplinar cooperativo.

El cribado sistemático para enfermedad renal crónica en la población general no se recomienda a la luz de la evidencia disponible. Sin embargo grupos de alto riesgo, como pacientes con diabetes mellitus, obesidad o hipertensión, junto con los sujetos mayores de 60 años deben tener una estimación de la tasa de filtración glomerular y de albuminuria.

Las evidencias apoyan la efectividad de algunas actuaciones en pacientes con ERC ya que retrasan la progresión del deterioro renal, reduciendo el riesgo de ECV y por tanto, pueden prevenir ó demorar la ocurrencia de complicaciones asociadas a una mayor morbilidad y frecuencia de ingresos hospitalarios. Por esta razón, la detección de ERC ha sido recomendada en los últimos años (Levey et al. 2003; Crowe et al. 2008). Sin embargo, los programas de detección de la ERC no son universalmente aceptados (Clase 2006; Glassock & Winearls 2008; McClellan et al. 2003). Los estudios que analizan estos programas son limitados, sobre todo en comparación con la evidencia existente en enfermedad cardiovascular ó diabetes, y hasta el momento no se dispone de ensayos clínicos que hayan evaluado la efectividad o utilidad de estrategias de cribado frente a no cribado. Pese a ello, numerosos programas de

prevención de ERC están desarrollándose en diferentes países (J. M. Smith et al. 2008).

El objetivo general de un programa de cribado es detectar la enfermedad en la fase preclínica de modo que el tratamiento puede producirse en una etapa anterior a la habitual, mejorando los resultados en salud de la intervención realizada. En 1968, Wilson y Jungner establecieron un conjunto de criterios que deben cumplirse para que un programa de cribado sea considerado beneficioso (Wilson & Jungner 1968).

En todo cribado, es importante evitar diagnósticos falsos positivos, que pueden conducir a consecuencias no deseadas tanto en términos económicos como médicos y psicológicos. En la ERC el resultado de interés, evolución a ERCT, tiene una incidencia baja, lo que subraya aún más la necesidad de identificar aquellas poblaciones con un alto riesgo y disponer de pruebas diagnósticas o sistemas de clasificación con una alta especificidad para la progresión a enfermedad renal crónica terminal.

Recientemente Hallan y col. comunicaron resultados sobre la capacidad predictiva de una matriz de clasificación que considera conjuntamente eGFR y ACR, estudiándolo en una cohorte poblacional de 65.123 sujetos seguidos durante 10 años (S. I. Hallan et al. 2009). Ciento veinte y cuatro individuos progresaron a enfermedad renal terminal o murieron a causa de enfermedad renal crónica con una tasa de filtrado documentado <15 ml / min por 1,73 m2. La tasa estimada de filtrado glomerular (eGFR) y el cociente

albumina/creatinina en orina (ACR) fueron los principales predictores de fallo renal, capacidad predictiva que no mejoró al añadir edad, sexo, presencia de diabetes, hipertensión y otros factores de riesgo. La estratificación de riesgo con una matriz de 12-categorías (TFG ≥ 60, 45-59, 30-44 y 15-29, subdividido por ACR en normoalbuminuria, microalbuminuria y macroalbuminuria) mostró mejor capacidad predictiva en comparación con el actual sistema de clasificación KDOQI de ERC; así utilizando como criterio de selección la clasificación de alto riesgo obtenida con la matriz de Hallan 66% de los futuros fallos renales fueron identificados, en comparación con un 69% identificado al usar la clasificación KDOQI, sin embargo la tasa de incorporación al programa de seguimiento intensivo fue de 14 frente a 47 por 1.000 sujetos cribados respectivamente.

En esta Tesis Doctoral se presentan los resultados hallados al aplicar la estratificación de riesgo propuesta por Hallan en población general española. La prevalencia poblacional de riesgo de progresión a ERCT, ajustada por edad y sexo, es de 12.6% (12.3%) para bajo riesgo, 1.7% (1.3%) para riesgo moderado y 0.1% para alto riesgo empleando CKD-EPI (MDRD) como ecuación de estimación del filtrado glomerular. En comparación con una estrategia consistente referir todos los casos de estadios 3-4 con ERC a una consulta especifica, la utilización de la matriz señalada para identificar los casos en alto riesgo susceptibles de atención específica permitiría detectar un número igual de casos con progresión severa, pero generaría muchos menos falsos positivos. Una intervención centrada en los individuos con riesgo alto o moderado de progresión, criterio recomendado, supondría actuar sobre el 1.7%

de la población mayor de 20 años, frente a la atención al 6.8% de población con una tasa de filtrado glomerular superior a 60 mL/min/1.73 m^2 si se sigue la recomendación del Documento de Consenso elaborado entre las sociedades científicas de Nefrología y Medicina de Familia que recoge un seguimiento conjunto, desde los servicios de atención primaria y de nefrología correspondientes al paciente, cuando el individuo presente una ERC en estadio III o superior (Alcázar et al. 2008).

Como toda patología crónica, una adecuada gestión de la ERC requiere establecer intervenciones complejas, con la participación coordinada de diferentes niveles asistenciales y con objetivos, centrados en el paciente, clínicamente relevantes en términos individuales (evitar eventos cardiovasculares ó mejorar la CVRS) y en términos de salud pública (gestión eficiente de enfermedades crónicas). La interacción entre los niveles de atención primaria y secundaria es imprescindible para la implementación de cualquier intervención de este tipo. Se han propuesto diferentes modelos de atención integrada a la ERC aunque su efectividad en términos de resultados clínicos no está aun demostrada (James MT 2010). El Documento de Consenso elaborado entre las sociedades científicas de Nefrología y Medicina de Familia (SEN y semFYC respectivamente) constituye un referente en nuestro país sobre el diagnostico y manejo de pacientes con ERC (Alcázar et al. 2008).

Varios estudios muestran que los pacientes atendidos en programas específicos alcanzan con mayor frecuencia los objetivos del tratamiento, en comparación con la atención habitual, con la consiguiente demora de

progresión en una significativa proporción de pacientes (C. Jones et al. 2006; Patwardhan et al. 2007). Por su parte, una preparación adecuada de la terapia renal sustitutiva disminuye tanto la morbilidad como la mortalidad asociadas (Stack 2003).

Los resultados de investigación fisiopatológica sugieren que fármacos dirigidos a contrarrestar los efectos de TGF-β u otros mediadores de inflamación podrían, potencialmente, detener la progresión de la glomerulosclerosis, atrofia tubular y fibrosis intersticial, que caracterizan la evolución de la ERC. Sin embargo mientras se espera el desarrollo de nuevas estrategias de tratamiento, una adecuada utilización de las opciones de tratamiento disponibles es importante. En la actualidad, la base del tratamiento es la reducción significativa de la presión arterial, junto con el control estricto de la glucemia en pacientes con diabetes mellitus. Tanto los inhibidores de la enzima convertidora de la angiotensina (IECA) como los antagonistas de los receptores de angiotensina II (ARA II) son grupos terapéuticos de elección por disminuir, junto a las cifras de TA, la excreción renal de albumina. Diferentes estudios han demostrado que sólo en el 20% de los pacientes con diabetes mellitus se monitorizan los niveles de HbA1C, y sólo el 30% son tratados con un IECA o ARA 2. Del mismo modo, únicamente entre un 30% y 50% de pacientes hipertensos alcanzan el objetivo de tratamiento de cifras inferiores a 140/90 mm Hg (Steinberg et al. 2008; Schaars et al. 2004). El tratamiento de los pacientes con ERC debe ser coste-efectivo y orientado a mejorar el pronóstico, estando disponible para todos los casos detectados. Algunos estudios han demostrado que una intervención multifactorial, es decir, el efecto conjunto de

varias opciones de tratamiento, es beneficiosa (Gaede et al. 2003). Por otra parte, los pacientes incluidos en protocolos de atención específicos presentan una reducción en la velocidad de progresión de la ERC (C. Jones et al. 2006). Sin embargo, sólo algunos estudios han evaluado la relación coste-eficacia del cribado de albuminuria y el tratamiento con IECA (Atthobari et al. 2006; Boulware et al. 2003). La mayoría de los estudios disponibles indican que el cribado es coste-efectivo en pacientes con diagnóstico de diabetes o hipertensión (Jaar et al. 2008) y algunos estudios muestran evidencias de que el cribado podría ser coste-efectivo en personas de más de 60 años sin diabetes ni hipertensión (Boulware et al. 2003).

El problema principal es cómo poner en práctica estas estrategias de detección y tratamiento de forma sostenible, considerando la organización de los sistemas sanitarios y las importantes cargas de trabajo ya existentes por la actividad asistencial habitual.

De acuerdo con lo expuesto anteriormente, la ERC es una patología prevalente, con severas consecuencias de salud. Además de factor de riesgo cardiovascular, causa morbimortalidad y deterioro de la CVRS. Su progresión, y la ocurrencia de eventos asociada, puede prevenirse / moderarse si se establece un diagnostico en fase tempranas y se realiza un adecuado manejo desde este momento.

Se hace necesario la identificación de estrategias de intervención multifactorial sostenibles en la organización del sistema sanitario, que permitan la identificación de sujetos en riesgo de progresión de ERC y su adecuado manejo.

Son precisos ensayos clínicos que evalúen el coste- efectividad y coste-utilidad de estrategias de cribado y tratamiento antes de generalizar su implementación.

Basándose en el conocimiento actual, el abordaje de la ERC plantea incertidumbres en el diagnostico: determinación del método de estimación de GFR más adecuado; puntos de corte que optimicen su clasificación para orientar el manejo de la enfermedad a los grupos de mayor riesgo.

En conclusión y para finalizar esta Tesis Doctoral, se ha estudiado el comportamiento en población general española de pruebas diagnósticas utilizadas en la valoración de ERC y resistencia a la insulina, dos trastornos de base inflamatoria, con elevada prevalencia en los países europeos y asociadas a la fisiopatología de la enfermedad cardiovascular. Se han analizado posibles fuentes de variabilidad en este comportamiento, entre las que destacan edad y sexo, para una mejor interpretación de los resultados obtenidos. Se estudian los puntos de corte para diagnostico de resistencia a la insulina tomando en consideración una adecuada clasificación de riesgo cardio metabólico. Finalmente se propone la utilización de una clasificación de la ERC que permita la priorización clínica basada en la identificación de mayor riesgo de eventos cardiovasculares y mortalidad. Con ello se cumplen los objetivos de esta Tesis Doctoral.

VII. CONCLUSIONES

A continuación se exponen las conclusiones de la presente Tesis Doctoral.

PRIMERA

La consideración de la capacidad de estratificación de riesgo de eventos clínicamente relevantes en el establecimiento de los puntos de corte en biomarcadores diagnósticos puede mejorar su utilidad clínica.

SEGUNDA

En población española mayor de 20 años, la prevalencia de Enfermedad Renal Crónica, en cualquier estadio, es del 9.16% y la de Insuficiencia renal crónica, (tasa de filtrado< 60 mL/min/1.73 m^2) es 6.9%. Por su parte, la prevalencia de albuminuria (cociente urinario albumina creatinina ≥30 mg/g) es del 4.0%.

TERCERA

Un 5.9% de la población española mayor de 20 años presentan algún grado de ERC con niveles de creatinina sérica en rango de normalidad (<1.1 mg/dl en mujeres y 1.2 mg/dl en varones). Por tanto si en practica clínica se consideran únicamente los valores de creatinina plasmática no ajustados por edad, sexo y grupo étnico, se produce un notable infra diagnostico.

CUARTA

Se establece la distribución percentil de HOMA-IR en población adulta española. La resistencia a la insulina varia con la edad, la distribución de grasa corporal y el sexo. En varones decrece con la edad, mientras en mujeres se incrementa significativamente en torno a los 50 años.

QUINTA

Se propone en población española un nivel de HOMA-IR de 2, en vez del valor del percentil 90, para una definición poblacional de resistencia a insulina que permita identificar los individuos con mayor riesgo cardio metabólico.

SEXTA

El método de estimación de filtrado glomerular con la ecuación CKD-EPI clasifica de forma más adecuada en población general a los sujetos en riesgo. Al comparar en población española los resultados utilizando la ecuación CKD-EPI respecto a MDRD, se encontró que un 13.3% (365) de sujetos fue reclasificado a una categoría de mayor eGFR mientras solo un 3.3% (92) fue reclasificado a categoría de menor eGFR. Estos últimos presentaban significativamente mayor edad, anemia y diabetes respecto a los no reclasificados.

SEPTIMA

Para conseguir una mejor adecuación en la atención a pacientes con Enfermedad Renal Crónica se propone la utilización en práctica clínica de una combinación de tasa de filtrado glomerular y cociente urinario albumina creatinina como instrumento de clasificación que permita identificar los sujetos en mayor riesgo de progresión y por tanto candidatos a derivación para seguimiento desde servicios de nefrología. En población general española se estima una prevalencia ponderada del 12.7% en bajo riesgo de progresión, 1.7% en riesgo moderado y 0.1% en alto riesgo.

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IX. ANEXOS

IX.1 Separata de cada uno de los artículos en su formato original.

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II. EPIDEMIOLOGY

Epidemiology of chronic renal disease in the Galician population: Results of the pilot Spanish EPIRCE study

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Epidemiology of chronic renal disease in the Galician population: Results of the pilot Spanish EPIRCE study.

Background. Chronic kidney disease (CKD) is a major social health problem because of the aging of the population, the high incidence of diabetes mellitus, and the epidemic of silent CKD resulting from inadequate diagnosis of early chronic renal insufficiency

Methods. The sociodemographic, baseline characteristics and CKD prevalence measured by the Modification of Diet in Renal Disease formula were studied in a randomly selected sample of people aged 20 years or older in the general population. We report the results of the analysis of the EPIRCE (Estudio Epidemiológico de la Insuficiencia Renal en España) pilot study performed in Galicia, Spain, in the last quarter of 2004.

Results. Baseline characteristics, sociodemographic characteristics, and results of a clinical examination and blood variables were collected from 237 patients who fulfilled the study's inclusion and exclusion criteria. The mean age of the sample was 49.58 years (95% confidence interval, 47.39-51.76). The prevalence of Kidney Disease Outcomes Quality Initiative grade 3 CKD was 5.1%, but the coexistence of an albumin/creatinine ratio >30 mg/g with grade 1 to 2 CKD raised the final rate to 12.7% in this population. We found a high prevalence of hypertension (31.5%), isolated systolic hypertension (20.1%), diabetes mellitus (8%), obesity (13.1%), smoking habit (22.7%), high atherogenic index (30.8%), and high alcohol intake (24%). Risk factors significantly associated with renal disease were age [$P = 0.018$; odds ratio (OR) 2.7], hypertension ($P = 0.023$; OR 2.13), pulse pressure ($P = 0.04$; OR 0.10), diabetes mellitus ($P = 0.08$; OR 4.48), obesity ($P = 0.000$; OR 7.7), and insulin resistance index ($P = 0.04$; OR 4.95).

Conclusion. The prevalence of CKD and conventional cardiovascular risk factors is high in this randomly selected sample of the general population. Secondary preventive measures are needed to detect chronic kidney impairment as early as possible and to reduce the incidence and mortality arising from the associated comorbidities.

Chronic kidney disease (CKD) is a public health problem worldwide because of the increasing prevalence of type 2 diabetes mellitus and atherosclerosis-related renal disease. This creates an important health care problem because a high proportion of these patients will need renal replacement therapy. One of the barriers to early detection of CKD is the lack of a precise, reliable, and consistent measure of kidney function. In practice, the glomerular filtration rate (GFR) is usually evaluated with the serum plasma creatinine (SCr) concentration. However, SCr concentration varies by age, sex, muscle mass, and diet, and between laboratories. Moreover, SCr concentration can remain within the normal range despite significantly impaired renal function. The National Health and Nutrition Examination Survey III (NHANES III) study [1] reported that 11% of the United States population exhibits an abnormal SCr concentration, although we do not know whether these data also apply to Spain because such measurements are not always directly comparable [2–4].

In Spain, patients are referred to nephrology departments late in the course of the disease. The epidemiologic data should be viewed with caution because the Modification of Diet in Renal Disease (MDRD) equation underestimates GFR by 6.2% in patients with CKD and 29% in healthy persons [5], and the method selected to estimate renal function may affect the interpretation of the relation between cardiovascular risk factors and renal function. To study the relation between risk factors and renal function in large population studies, indirect estimates of renal function should be used with caution [6]. Nevertheless, the systematic evaluation of all patients and incorporation of simplified definitions should improve the outcome in patients with kidney disease, and the MDRD formula is a useful method for studying large populations.

Cardiovascular disease is the most common cause of death in patients with CKD [7–9], who should be considered in the highest risk group for cardiovascular disease. Traditional and nontraditional risk factors have been implicated in the high prevalence of cardiovascular disease associated with CKD. The inflammatory process starts in the early phases of CKD, as shown by a GFR of 50 to

Key words: cardiovascular risk factors, chronic kidney disease, epidemiology.

60 mL/min [10], and accelerates vascular damage through an increase in insulin resistance, stimulation of the adhesion molecules, inhibition of nitric oxide synthesis, endothelial dysfunction, and arteriosclerosis. The proinflammatory cytokines and impaired synthesis of erythropoietin are implicated in the onset of anemia, which contributes significantly to the development of left ventricular hypertrophy, a significant cause of mortality. Well-established therapeutic interventions that delay or prevent progressive kidney disease are incorporated into the widely disseminated clinical practice guidelines, which recommend aggressive treatment of traditional and nontraditional risk factors. These interventions also reduce the risk of cardiovascular disease and should be regarded as essential components in the care of patients with CKD.

For the reasons mentioned above, the Spanish Nephrology Society is studying the prevalence of CKD in Spain to provide useful information to identify the true population at risk and to increase the preventive measures aimed at reducing the incidence of renal failure, cardiovascular complications, and the progression to renal sclerosis. This program is based on the concept that early detection and prevention can influence the outcomes of both renal insufficiency and cardiovascular morbidity and mortality. This is the first study to investigate the prevalence of CKD in Spain. The Estudio Epidemiológico de la Insuficiencia Renal en España (EPIRCE) study investigated GFR, calculated by a simplified MDRD formula, in a randomly selected sample of the general population 20 years of age and older. We now report on the preliminary data obtained from the pilot study performed in Galicia, a region of Spain.

METHODS

The EPIRCE study is an epidemiologic, general population-based, transversal study that includes a randomly selected Spanish sample ($N = 8400$) aged 20 years or older. The sample was stratified by age, sex, and region, and is representative of all areas of Spain.

The initial sample results correspond to a pilot study performed in Galicia, one of the areas selected initially to identify potential difficulties before extending the study to all areas of Spain.

This first pilot study included a randomly selected sample of 574 residents of Galicia. Of the original sample of 574, 63 were excluded from the study, 107 were not contacted, and 165 refused to participate, leaving 239 who met the inclusion criteria. The variables measured included anthropometric data (weight, height, body mass index) and baseline characteristics (obesity, history of hypertension, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia). Participants were interviewed to determine their smoking habits, alcohol consumption, and use of nephrotoxic drugs. After informed consent was provided, a blood sample was obtained from each individual for biochemical tests, which included serum creatinine concentration determined in the same reference laboratory for all samples. GFR was calculated as an indicator of renal function with the simplified MDRD formula [11], and participants were classified according to the Kidney Disease Outcomes Quality Initiative guidelines [12].

Table 1. Distribution of the sample size and the theoretical assignment described in the protocol

	Sample	Planned population
Age *years*	Percent	Percent
20–39	33.76	36.5
40–64	43.46	37.7
>64	22.78	25.8
Sex		
Male	42.6	47.4
Female	57.4	52.6
Habitat		
Urban	65.0	66.1
Rural	35.0	33.9

STATISTICAL METHODS

Quantitative variables were summarized in terms of means and 95% confidence interval (CI); the comparison between CKD groups was performed by using a *t* test. Comparisons between categorical variables were performed with chi-square test. Univariate and multivariate logistic regression analyses were used to estimate the odds ratio (OR) and CIs comparing vascular risk factors on CKD occurrence. $P < 0.05$ was considered significant. Analyses were performed with SPSS (Chicago, IL, USA).

RESULTS

The pilot study analyzed data for 237 participants or 41.6% of the initial sample of 574. This study sample was distributed similarly to the estimated sample size design (Table 1). The mean age was 49.58 years (95% CI 47.39-51.76), and the prevalence of grade 3 CKD was 5% (Table 2). However, after the addition of participants classified as grade 1 or 2 CKD because they had an albumin/creatinine ratio >30 mg/g, the prevalence of CKD increased to 12.7%. The prevalence of associated cardiovascular risk factors was high for arterial hypertension (31.5%), isolated systolic hypertension (20.1%), pulse pressure (27.8%), obesity (13.1%), diabetes mellitus (8%), a high atherogenic index (30.8%), hypercholesterolemia (12.8%), hypertriglyceridemia (6.3%), elevated low-density lipoprotein-cholesterol complex (37.5%), low high-density lipoprotein-cholesterol complex (18.1%), smoking >10 cigarettes/day (22.7%), and high alcohol consumption >70 g/day (24%).

Table 2. Prevalence of CKD according to the degree of renal insufficiency and the pathologic albumin/creatinine index

	Prevalence of CKD			
GFR mL/min/1.73 m^2	*N*	Prevalence	Alb/Cr >30 mg/dL	% Prevalence
>90	95	40.6	8	3.5
>60–89	127	54.3	8	3.5
>30–59	11	4.7	11	5.3
>15–29	1	0.4	1	0.4
<15	0	0	0	0
Total	234	100	28	12.5

Abbreviations are: CKD, chronic kidney disease; GFR, glomerular filtration rate; Alb/Cr, albumin/creatinine.

Table 3. Prevalence (%) of conventional VRF according to the stages of renal function (G1-G3)

VRF	G1	G2	G3	*P*
HT	4.2	5.6	9.9	0.107
ISHT	5.9	5.9	14.7	0.038
PP	3.2	7.9	11.1	0.01
Obesity	4	4	8	0.471
DM	16.7	0	16.7	ND
Hypercholesterolemia	0	3.4	10.3	ND
Hypertriglyceridemia	0	20	6.7	ND
Low HDL-C concentration	4.8	4.8	9.5	0.505
High LDL-C concentration	3.6	2.4	4.4	0.880
AI	4.3	5.8	10.1	0.08

Abbreviations are: VRF, vascular risks factors; G1, GFR <90; G2, GFR 60–89; G3, GFR 30–59; HT, hypertension (blood pressure >140/90 mm Hg); ISHT, isolated systolic HT (systolic blood pressure >140 and diastolic BP <90 mm Hg); PP, pulse pressure >60 mm Hg; obesity, BMI >29 kg/m^2; DM, diabetes mellitus (blood glucose concentration >126 mg/dL); hypercholesterolemia >240 mg/dL; hypertriglyceridemia >200 mg/dL; low HDL-C concentration <35 mg/dL; high LDL-C concentration >160 mg/dL; AI, atherogenic index (>4); ND, not determined.

The prevalence of cardiovascular risks factors increased in proportion to GFR (Table 3). Univariate analysis identified the independent variables that correlated significantly with GFR as age (OR 2.7), hypertension (OR 2.13), pulse pressure (OR 0.101), diabetes mellitus (OR 4.481), obesity (OR 7.7), and the insulin resistance index (OR 4.95) (Table 4). However, GFR was correlated significantly only with pulse pressure ($P = 0.066$; OR 5.74) and diabetes mellitus ($P = 0.060$; OR 6.95) in the multivariate analysis.

DISCUSSION

This preliminary report of a pilot study of 237 randomly selected patients in Galicia is the first in a larger study of the prevalence of CKD in the general population in Spain. The larger study will include more than 8400 people and aims to investigate the prevalence of silent CKD in the Spanish population.

The approach to CKD and its management have changed recently based on new epidemiologic, clinical, and physiopathologic evidence showing that, even in its early stages, CKD constitutes a significant risk factor for

Table 4. Risk of CKD and atherosclerotic risk factors. Univariate logistic regression analysis.

Variable	*P*	OR	95% CI
Age	0.018	2.7	1.18, 6.31
HT	0.023	2.13	1.11, 4.11
ISHT	0.123	2.039	0.82, 5.04
PP	0.042	0.101	0.96, 3.90
DM	0.086	4.481	1.54, 13.04
Obesity	0.0000	7.7	2.65, 22.3
Hypercholesterolemia	0.11	2.08	0.84, 5.15
Hypertriglyceridemia	0.22	2.01	0.64, 6.29
High LDL-C concentration	0.230	1.437	0.77, 2.79
AI	0.70	1.845	0.95, 3.57
HOMA	0.04	4.95	1.07, 22.8
Smoking	0.26	0.73	0.43, 1.25
Alcohol	0.467	0.78	0.41, 1.50
Physical activity	0.92	1.03	0.50, 2.13

Abbreviations are: CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; hypertension (blood pressure >140/90 mm Hg); ISHT, isolated systolic hypertension (systolic blood pressure >140 and diastolic BP <90 mm Hg); PP, pulse pressure >60 mm Hg; DM, diabetes mellitus (blood glucose concentration >126 mg/dL); obesity, BMI >29 kg/m^2; hypercholesterolemia >240 mg/dL; hypertriglyceridemia >200 mg/dL; high LDL-C concentration >160 mg/dL; AI, atherogenic index (>4); HOMA, blood insulin × glucose concentration/22.5; smoking >10 cigarettes/day; alcohol consumption >70 g/day.

cardiovascular and global morbidity and mortality because of the inflammatory state in the initial phases of renal failure. For these reasons, the Seventh Report of the Joint National Committee [13] includes microalbuminuria and a GFR <60 mL/min as significant cardiovascular risk factors. The fundamental objective is to identify people at risk of developing cardiovascular complications among the apparently healthy and those already diagnosed with vascular disease or grade 1 or 2 CKD. Our data from the EPIRCE pilot study are relevant because of the high prevalence of conventional risk factors, CKD (12.7%), and a GFR <60 mL/min (5.7%) in a population with a mean age of 49.58 years. The overall prevalence of CKD was 11% in the U.S.-based NHANES III study [1] and 12.7% in our pilot study. The prevalence distribution pattern using the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative stages of CKD was 3.3% in NHANES III and 3.5% in our study for stage 1, 3.0% in NHANES III and 3.5% in our study for stage 2, 4.3% in NHANES III and 5.3% in our study for stage 3, 0.25% in NHANES III and 0.4% in our study for stage 4, and 0.2% in NHANES III and 0% in our study for stage 5 (end-stage renal failure); the latter value was very low because of the small sample size. Others have reported similar values. Anandarajah et al reviewed routinely collected data from 12 practices in 3 localities across the United Kingdom and found that 4.9% of the registered population had an estimated GFR of <60 mL/min/1.73 m^2, which is equivalent to stages 3 to 5 CKD [14]. We found a relatively high prevalence of asymptomatic CKD in the apparently healthy general population in Spain.

We found that age, arterial hypertension, isolated systolic hypertension, pulse pressure, diabetes mellitus,

obesity, and the insulin resistance index were independent variables related to renal disease. All of these variables reflect the combined effects of inflammation and arteriosclerosis.

Prevention of CKD and its associated complications needs a clear understanding of the prevalence and outcome of renal disorders, the earlier stages of renal disease, the risk factors, and the appropriate treatment of populations at risk. In the study by Anandarajah et al [14], although 5% of the population had stages 3 to 5 CKD, only a small proportion (8%) of these individuals had received a renal diagnosis or had been seen by a renal physician. Earlier identification of CKD in primary care, better management of cardiovascular risk, the avoidance of medication that impairs renal function, and specialist referral where appropriate may improve long-term outcomes. However, our understanding of this disease, its risk factors, and its impact on the public health system is incomplete, and no large epidemiologic studies have been performed in Europe. Future studies should focus on the prevalence and outcome of CKD and on the pathology of the interaction between the kidney and cardiovascular system to prevent the progression of renal dysfunction, which should have a beneficial effect in reducing the risk and prevalence of cardiovascular disease.

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Prevalence of chronic renal disease in Spain: Results of the EPIRCE study

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is an independent cardiovascular risk factor. The knowledge of prevalence in general population may help to early detection of CKD and prevent or delay its progression. **Methods:** Sociodemographic, baseline characteristics, and CKD prevalence (measured by centralized serum creatinine and MDRD equation) were evaluated in a randomly selected sample of general population aged 20 years or older, collected in all Spanish regions and stratified by habitat, age and sex according to 2001 census (n = 2,746). Univariate and multivariate logistic regression analyses were used to evaluate associations with CKD risk factors. **Results:** Mean age was 49.5 years. The overall prevalence of Kidney Disease Outcomes Quality Initiative grades 3-5 CKD was 6.8%, with a 95% confidence interval (CI) of 5.4 to 8.2 (3.3% for age 40-64 years and 21.4% for age >64 years). The prevalence estimates of CKD stages were: 0.99% for stage 1 (glomerular filtration rate [GFR] ≥90 ml/min per 1.73 m2 with proteinuria); 1.3% for stage 2 (GFR 60-89); 5.4% for stage 3a (GFR 45-59); 1.1% for stage 3b (GFR 30-44); 0.27% for stage 4 (GFR 15-29); and 0.03% for stage 5 (GFR <15). An important prevalence of classical cardiovascular risk factors was observed: dyslipemia (29.3%), obesity (26.1%), hypertension (24.1%), diabetes (9.2%) and current smoking (25.5%). The independent predictor factors for CKD were age, obesity and previously diagnosed hypertension. **Conclusions:** The prevalence of CKD at any stage in general population from Spain is relatively high, especially in the elderly, and similar to countries of the same geographical area. Independently of age, two modifiable risks factors, hypertension and obesity, are associated with an increased prevalence of CKD.

Key words: Cardiovascular risk factors. Chronic kidney disease. Epidemiology.

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Prevalencia de la insuficiencia renal crónica en España: Resultados del estudio EPIRCE

RESUMEN

Introducción: *la insuficiencia renal crónica (IRC) constituye un factor de riesgo cardiovascular independiente. El conocimiento de su prevalencia en la población general puede contribuir a la detección precoz de esta enfermedad y de prevenir o retrasar su evolución.* ***Métodos:*** *se seleccionó una muestra aleatoria de población general española, con edad igual o superior a 20 años, distribuida por todo el territorio nacional y estratificada por hábitat, edad y sexo conforme al censo de 2001 (n = 2.746). Se recopilaron datos sociodemográficos y clínicos, y se evaluó la prevalencia de IRC mediante determinación centralizada de creatinina sérica y aplicación de la ecuación MDRD. Se llevaron a cabo análisis univariantes y multivariantes para evaluar la asociación entre la IRC y diversos factores de riesgo.* ***Resultados:*** *la edad media fue de 49,5 años. La prevalencia global de IRC en estadios 3-5, según la Kidney Disease Outcomes Quality Initiative, fue del 6,8%, con un intervalo de confianza del 95% (IC) de 5,4 a 8,2 (3,3% para edades 40-64 años y 21,4% para edades >64 años). Las prevalencias estimadas para cada uno de los estadios de IRC fueron: 0,99% para estadio 1 (tasa de filtrado glomerular [TFG] ≥90 ml/min por 1,73 m² con proteinuria); 1,3% para estadio 2 (TFG 60-89); 5,4% para estadio 3a (TFG 45-59); 1,1% para estadio 3b (TFG 30-44); 0,27% para estadio 4 (TFG 15-29), y 0,03% para estadio 5 (TFG <15). Se apreció una prevalencia considerable de factores de riesgo cardiovascular clásicos: dislipemia (29,3%), obesidad (26,1%), hipertensión (24,1%), diabetes (9,2%) y tabaquismo activo (25,5%). Los factores predictores independientes de IRC fueron la edad, la obesidad y la hipertensión previamente diagnosticada.* ***Conclusiones:*** *la prevalencia de IRC (en cualquier estadio) en la población general española es relativamente elevada, en especial en los individuos de edad avanzada, y similar a la de otros países del mismo entorno geográfico. Además de la edad, dos factores de riesgo modificables, la hipertensión y la obesidad, se asociaron con una mayor prevalencia de IRC.*

Palabras clave: *Factores de riesgo cardiovascular. Insuficiencia renal crónica. Epidemiología.*

INTRODUCTION

Chronic kidney disease (CKD) is a major social health problem. In the last decade, it has been shown that early stages of CKD are asociated with an inflammatory state[1] that

implies an increased cardiovascular morbidity and mortality risk at long term[2,3], higher than the risk of progression to end-stage renal disease[2,4]. Cardiovascular events are the most common cause of death in these patients[5]. For this reason, microalbuminuria and reduced glomerular filtration rate (GFR) (<60 ml/min) have been added to the list of non traditional cardiovascular risk factors[6]. In many patients, the concurrence of these markers with classical factors as diabetes, hypertension or obesity, predicts accelerated vascular damage and multiplies the associated risk[2,3].

Furthermore, the prevalence of CKD is growing worldwide due to the increase in related diseases as type 2 diabetes mellitus, obesity, hypertension or atherosclerosis[7,8]. The asymptomatic nature of CKD makes its early detection more difficult, which could be important as the treatment in early stages may prevent or delay its progression[9]. The knowledge of the prevalence of CKD might be useful to assess the level of its underdiagnosis and estimate the impact of potential screening policies.

The 2002 practice guideline of the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF)[10] defined CKD as either kidney damage or glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2 for three or more months. GFR is usually estimated from serum creatinine using one of the following equations: the Cockcroft-Gault (CG)[11] or the Modification of Diet in Renal Disease Study (MDRD)[12] equation. These indirect methods are currently considered to be the easiest way to estimate GFR in epidemiologic studies conducted in adult individuals[13]. The MDRD equation is more commonly used[14], but it leads to a certain underestimation of GFR (6.2% in CKD patients and 29% in healthy persons)[15], compared to the CG equation. However, it seems that the MDRD equation provides a more accurate estimation in patients with GFR below 60 ml/min/1.73 m^2, with good performance among subgroups of age, sex, race, diabetes or body mass index[16,17].

In the last five years, more than 25 epidemiological studies have investigated CKD prevalence worldwide[14], leading to a median prevalence of 7.2% in persons aged 30 years or older, and revealing ethnic-specific differences. In our country, the Spanish Society of Nephrology (S.E.N.) has initiated a program to identify the true population at risk for CKD, and to increase the preventive measures aimed at reducing the incidence of renal failure, cardiovascular complications, and progression to end stage renal failure[18,19].

Within this program, the «Estudio Epidemiólogico de la Insuficiencia Renal en España» (EPIRCE) is the first epidemiological study at a national level designed to describe the prevalence of CKD in the general Spanish population aged 20 years or older, using the simplified MDRD equation.

METHODS

The EPIRCE was an epidemiologic, general population-based, cross-sectional study that included a randomly selected Spanish sample aged 20 years or older. The exclusion criteria were residence outside the recruiting municipality, or institutionalization at the time of the study. The protocol was approved by an ethics committee, and all enrolled patients provided informed consent.

The target sample were 13,013 individuals, stratified by age, sex, and habitat within each Spanish region, according to the 2001 Census. A total of 6,464 out of the initial list of 13,013 were finally contacted for the study. Census errors were the most important reason for the impossibility to contact individuals. The sample was recruited between January 2004 and January 2008 in 42 points (municipalities). The final completed interviews were 2,746, and the response rate was 42.5%.

Data were collected as follows. First, a letter describing the study was sent to each randomly selected individual. Next, a health professional contacted the potential respondents by phone to verify inclusion and exclusion criteria, ask for participation, and make appointments with those who volunteered. A minimum of three negative answers were required to discard a selected individual.

The collected variables included anthropometric and sociodemographic data (age, gender, ethnicity, weight, height, body mass index), blood pressure and clinical history at study inclusion (obesity, hypertension, diabetes mellitus, dyslipemia, cardiovascular disease, gout, renal lithiasis, CKD, transplant). Participants were also interviewed to determine their smoking and exercise habits, alcohol consumption, drug abuse and use of nephrotoxic drugs. After informed consent was provided, a blood sample was obtained from each individual for biochemical tests. Serum creatinine concentration was determined in the same reference laboratory for all samples. GFR was calculated as an indicator of renal function with the simplified MDRD formula[20], and participants were classified according to the Kidney Disease Outcomes Quality Initiative guidelines[10]. Stage 3 was split into 3a (GFR 45-59 ml/min/1.73 m^2) and 3b (GFR 30-44 ml/min/1.73 m^2). Other analytical determinations included: glucose, urea, total cholesterol (C), tryglicerydes (Tg), HDL-C, LDL-C, insulin resistance index (HOMA), haemoglobin (Hb), ferritin, uric acid and urinary albumin to creatinine ratio.

Statistical methods

Adjustment weights were used to correct for non-response bias, with the age, gender and habitat distribution of survey respondents being equated to the population structure as

determined from the 2001 census. All prevalence and mean estimates were calculated with the weighted sample, and asymptotic 95% confidence intervals (CI) were obtained. Univariate and multivariate logistic regression analyses, also weighted for non-response bias, were used to calculate the odds ratio (OR) and CIs for candidate CKD risk factors. P values < 0.05 were considered significant. Since there were statistically significant differences in the response rate between participating municipalities (data not shown), a sensitivity analysis was performed comparing the results between highly responding centers (>60% of response rate, n = 1,098) and the overall group, to assess for a possible non-response bias. All analyses were performed with SAS version 9.1.3 Service Pack 4 (SAS Institute Inc., Carey, North caroline, USA).

RESULTS

Sociodemographic and clinical characteristics

Tables 1 and 2 show the characteristics of the 2,746 respondents (weighted estimates). Mean age was 49.5 years, and about one quarter of individuals were older than 64 years (25.8%). As in the general Spanish population, the ratio male:female was 0.9, almost all were caucasian (99.1%), and the residence was urban in two thirds of cases (66.1%).

Clinical history revealed an important prevalence of previously diagnosed dyslipemia (29.3%), obesity (26.1%), hypertension (24.1%) and diabetes (9.2%). Among cardiovascular events, peripheral vascular episodes were the most frequent (10.8%), followed by ischaemic heart disease (5.1%) and cerebrovascular disease (1.7%). Current smoking habit and habitual alcohol intake were frequent (25.5% and 45.1%, respectively).

CKD prevalence

The overall prevalence of CKD stages 3-5 (eGFR <60 ml/min) was 6.83 %, with a 95% CI of 5.41 to 8.25 (3.33% for age 40-64 years and 21.42% for age >64 years). When the albumin to creatinine ratio was added to the diagnostic criteria, the prevalence rose to 9.16% (95% CI, 7.5 to 10.8). The prevalence estimates of CKD stages were: 0.99% for stage 1; 1.3% for stage 2; 5.4% for stage 3a; 1.1% for stage 3b; 0.27% for stage 4; and 0.03% for stage 5 (table 2). The prevalence of proteinuria (ACR>30 mg/g) in stage 3a was 5.9%, in stage 3b, 6.8%, and in stage 4, 36.7%.

Risk factors for CKD

Table 3 shows the unadjusted associations between sociodemographic and clinical characteristics of the patients and CKD. The strongest predictor factor was age. The observed odds ratios (OR) were 34.4 for individuals between 40-64 years with respect to those between 20-39 years, and 267.5 for individuals above 64 years. Other strong predictor factors were hypertension, especially when previously diagnosed (OR 5.9), pulse pressure above 60 mmHg (OR 3.8), previous history of cardiovascular events (ORs 4.1 for ischaemic heart disease, 3.3 for cerebrovascular disease and 2.1 for peripheral vascular disease), overweight or obesity (ORs of 2.3 and 3.5, respectively), diabetes (OR 2.4 for previously diagnosed patients), dyslipemia (OR 2.1 for previously diagnosed patients) and gout (OR 2.2).

In the multivariate analysis, the independent predictor factors that remained in the model were age, obesity and previously diagnosed hypertension (table 4).

Sensitivity analyses

Individuals recruited at highly responding centers (>60% of response rate, n = 1,098) were healthier according to the following differences with respect to the overall sample: they were less obese (22.9% with BMI >30 kg/m^2 versus 26.1% in the total population), less sedentary (25.4% versus 28.9%) and suffered less diabetes (5.2% of non previously diagnosed diabetes versus 7.0%). They also displayed more percentage of habitual alcohol consumption (49.7% versus 45.1%). Despite these findings, the prevalence of CKD stages 3-5 in this subgroup was equivalent to that found in the overall sample: 6.65 (95% CI of 4.66 to 8.64). The prevalence of proteinuria (ACR >30 mg/g) was slightly lower (3.6%, 95% CI 1.4 to 5.8), but not significantly different. No differences were observed either in the prevalences within age, gender or habitat categories, nor in the risk factors associated to CKD (data not shown).

DISCUSSION

The present study is the first epidemiological investigation of the prevalence of CKD in Spanish population aged 20 years or older at a national level. The recruited sample is representative of all regions, and has been adjusted to provide valid estimates of CKD prevalence in age, gender and habitat subgroups, according to the real distribution of Spanish population in 2001.

The prevalence of CKD found in our study (6.8%) is very similar to the median reported in a systematic review of 26 epidemiological studies around the world (7.2%)[14]. Since ethnic-specific differences have been reported[14], the relevant comparisons with other European countries show that the prevalence in Spain remains within the range of previous studies that have used the MDRD equation (4.7-8.1% in studies from Italy[21], Switzerland[22], Norway[23] and Iceland[24]).

Table 1. Demographic and clinical characteristics of Spanish population aged 20 years or older based on the cohort collected in the EPIRCE study (n = 2,746).

	N of participants	Spanish populationa
Age, years, mean (SEM)	**2,746**	**49.5 (1.1)**
20-39, %	885	36.5
40-64, %	1,283	37.7
>64, %	578	25.8
Sex, %		
Male	1,148	47.4
Female	1,598	52.6
Habitat, %		
Urban	1,805	66.1
Rural	941	33.9
Ethnicity, %	**2,695**	
Caucasian	2,669	99.1
African	13	0.46
Asian	1	0.04
Other	12	0.44
Body mass index, kg/m², mean (SEM)	**2,738**	**27.4 (0.2)**
Overweight (BMI 25-30 kg/m²), %	1,063	39.4
Obesity (BMI >30 kg/m²), %	723	26.1
Systolic blood pressure, mmHg, mean (SEM)	2,737	132.3 (1.0)
Diastolic blood pressure, mmHg, mean (SEM)	2,736	78.8 (0.4)
Hypertension, %	**1,128**	**42.4**
Previously diagnosed hypertension, %	640	24.1
Current hypertension (SBP/DBP >140/90 mmHg), %	937	35.6
Isolated systolic hypertension, %	464	18.3
Pulse pressure >60 mmHg, %	**658**	**26.2**
Previous cerebrovascular disease, %	**46**	**1.7**
Previous ischaemic heart disease, %	**123**	**5.1**
Previous peripheral vascular disease, %	**303**	**10.8**
Previous gout, %	**122**	**4.7**
Previous diagnosis of chronic kidney disease, %	**11**	**0.4**
Previous kidney transplant, %	**1**	**0.04**
Previous renal lithiasis, %	**385**	**13.9**
Glucose, mg/dl, mean (SEM)	**2,741**	**96.3 (0.8)**
HOMA, mean (SEM)	**2,497**	**2.0 (0.03)**
Diabetes, %	**282**	**10.8**
Previously diagnosed diabetes, %	237	9.2
Current glucose >126 mg/d, %	183	7.0
Total cholesterol, mg/dl, mean (SEM)	**2,740**	**202.2 (1.2)**
>200, %	1,414	49.6
Previously diagnosed dyslipemia, %	**804**	**29.3**
HDL-cholesterol, mg/dl, mean (SEM)	**2,737**	**71.6 (0.9)**
< 35, %	18	0.76
LDL-cholesterol, mg/dl, mean (SEM)	**2,717**	**124.5 (1.1)**
>160, %	429	15.0
Triglycerides, mg/dl, mean (SEM)	**2,739**	**107.7 (2.0)**
>200, %	56	2.2
Atherogenic indexb, mean (SEM)	**2,737**	**3.0 (0.05)**
>4.5, %	178	6.7
Haemoglobin, g/dl, mean (SEM)	**2,706**	**14.4 (0.07)**
Anaemia (Hb <11 mg/dl), %	38	1.4
Ferritin, ng/ml, mean (SEM)	**2,532**	**117.7 (5.7)**
Uric acid, mg/dl, mean (SEM)	**2,737**	**4.9 (0.07)**

To be continued in the next page >>

Continuation

Table 1. Demographic and clinical characteristics of Spanish population aged 20 years or older based on the cohort collected in the EPIRCE study (n = 2,746)

Serum urea, mg/dl, mean (SEM)	**2,734**	**37.2 (0.5)**
Serum creatinine, mg/dl, mean (SEM)	**2,746**	**0.92 (0.01)**
eGFR, ml/min per 1.73 m², mean (SEM)	**2,746**	**84.6 (0.7)**
Albumin to creatinine ratio, mg/g, mean (SEM)	**2,244**	**9.7 (0.6)**
Proteinuria (ACR >30 mg/g) , %	74	4.0
Smoking habit, %		
Currently smoking	675	25.5
Exsmoker	673	25.8
Non smoker	1,324	48.3
Alcohol intake, %		
Habitual	1,176	45.1
Ocasional	556	20.1
Exalcohol consumer	210	8.3
Never	750	26.5
Substance abuse, %	70	3.0
Physical inactivity, %	786	28.9
Use of nephrotoxic drugs, %		
Ibuprofen		6.0
Aspirin		5.5
Captopril		1.0
Sulfonylurea		1.0
N-acetylcysteine		0.59
Carvedilol		0.35

[a] Frequency estimates calculated on the weighted sample; blog(TG/HDL-C), with TG and HDL-C expressed in molar concentrations.

SEM: Standard error of the mean; HOMA: Homeostasis Model Assessment index; ACR: urine albumin to urine creatinine ratio; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFR: glomerular filtration rate; HDL: high density lipoprotein-cholesterol; LDL: low density lipoprotein; Hb: haemoglobin.

These estimates are also similar to those from the US National Health and Nutrition Examination Surveys (NHANES) (5.6% in 1988 through 1994 and 8.05% in 1999 through 2004)[25], despite the incidence of end stage renal disease (ESRD) in this country being much higher than in Europe[26]. The epidemiological study from Norway[23] investigated the progression rate from CKD stages 3 or 4 to ESRD in their cohort and found that the relative risk of progression in US caucasian patients was 2.5 times higher than in Norwegian patients. Among the possible explanations for these differences they postulate a later referral to nephrologist and a higher presence of obesity and diabetes in the US population.

The addition of the albumin/creatinine ratio to the CKD diagnosis (stages 1 and 2) allowed to detect a further 2.3% of population at risk, which substantially improves diagnostic accuracy without losing predictive power. According to previous studies, referral based on current stages 3 to 4 CKD identifies approximately only 70% of all individuals that progress to ESRD[27].

We found a high prevalence of conventional risk factors, overweight and obesity, hypertension, diabetes, dyslipemia and smoking. All of them were significantly associated to CKD, which agrees with previous findings[28,29]. With respect to smoking habit, we did not find a significant association with current smoking, but the ex-smoker status was related to a higher frequency of stage 4 CKD. A possible explanation is that, previous to the study entry, these patients had already suffered other health problems that compelled them to discontinue tobacco. Unexpectedly, the habitual alcohol intake was inversely associated to CKD, which partially agrees with the study of Kronborg et al., who found that alcohol consumption in men predicted an increase in eGFR[28,29]. Red wine has been shown to improve surrogate markers for cardiovascular disease, such as nitric oxid release in the vessel wall. It also possesses anti-inflammatory and anti-oxidative properties, and inhibits platelet-derived growth factor-beta receptor phosphorylation[30]. However, it would be very difficult to perform prospective, randomized studies to demonstrate the benefits of moderate alcohol consumption, as the important secondary harmful effects (such as liver cirrhosis, blood pressure elevation, cancer or accidents) should be taken into account.

Table 2. Prevalence of chronic kidney disease in the Spanish population aged 20 years or older based on thee cohort collected in the EPIRCE study (n = 2,746).

	Spanish Population		Prevalence of estimated GFR (ml/min per 1.73 m²) categoriesa,b % (95% CI)						
	N	% (95% CI)	Normal (≥90)	Stage 1 (≥90 with proteinuria)	Stage 2 (60-89)	Stage 3a (45-59)	Stage 3b (30-44)	Stage 4 (15-29)	Stage 5 (<15)
TOTAL	2,746		90.8 (89.1 to 92.5)	0.99 (0.57 to 1.4)	1.3 (0.84 to 1.8)	5.4 (4.3 to 6.6)	1.1 (0.65 to 1.5)	0.27 (0.06 to 0.48)	0.03 (0.00 to 0.08)
Age, years									
20-39	885	36.50 (34.60 to 38.40)	98.1 (96.8 to 99.3)	0.86 (0.15 to 1.6)	0.97 (0.18 to 1.8)	0.10 (0.00 to 0.30)	–	–	–
40-64	1,283	37.70 (35.50 to 39.90)	93.8 (92.1 to 95.5)	1.0 (0.32 to 1.7)	1.8 (0.90 to 2.8)	2.8 (1.8 to 3.9)	0.37 (0.04 to 0.69)	0.09 (0.00 to 0.27)	0.07 (0.00 to 0.22)
>64	578	25.80 (23.82 to 27.78)	76.3 (72.2 to 80.5)	1.1 (0.32 to 1.9)	1.1 (0.30 to 2.0)	16.8 (13.6 to 20.0)	3.7 (2.1 to 5.2)	0.92 (0.13 to 1.7)	-
Sex									
Male	1,148	47.40 (45.46 to 49.30)	91.4 (88.6 to 94.1)	1.4 (0.68 to 2.2)	1.3 (0.60 to 2.1)	4.7 (2.9 to 6.4)	0.79 (0.21 to 1.37)	0.39 (0.02 to 0.77)	-
Female	1,598	52.60 (50.66 to 54.54)	90.3 (88.2 to 92.5)	0.58 (0.16 to 1.00)	1.3 (0.65 to 2.0)	6.2 (4.5 to 7.8)	1.3 (0.69 to 2.0)	0.16 (0.00 to 0.38)	0.05 (0.00 to 0.16)
Habitat									
Urban	1,805	66.10 (63.54 to 68.66)	91.8 (89.6 to 94.1)	0.53 (0.21 to 0.86)	1.3 (0.63 to 1.9)	5.1 (3.5 to 6.7)	0.99 (0.40 to 1.6)	0.29 (0.01 to 0.57)	-
Rural	941	33.90 (31.34 to 36.46)	88.9 (85.8 to 92.0)	1.9 (0.77 to 3.0)	1.5 (0.70 to 2.3)	6.1 (3.9 to 8.4)	1.3 (0.59 to 1.9)	0.23 (0.00 to 0.56)	0.08 (0.00 to 0.24)

[a]There were no patients with eGFR <15 ml/min per 1.73 m²; GFR: glomerular filtration rate; [b] Prevalence estimates calculated on the weighted sample.

The three independent predictor factors for CKD were increasing age, obesity and history of hypertension, which suggests that these conditions predispose to renal impairment through different mechanisms.

The decline in GFR with age has been repeatedly described[14]. The prevalence of CKD in patients above 64 years found in the EPIRCE study (21.4%) is comparable to that reported in other European countries (15-25%[21-24]), usually with higher prevalences in older women[22,24]. The reduction starts progressively in the third decade of life, and becomes steeper after the age of 60, although it has not been observed in all individuals[31]. There are several hypotheses to explain this phenomenon: it can be related to pathologic processes (cumulated immunologic, infectious, or toxic damage), progressive ischemia due to vascular aging, or cummulative changes in kidney structure due to hyperperfusion and hyperfiltration with resultant glomerulosclerosis[32,33].

The contribution of sustained high blood pressure levels to renal function deterioration is well established: systemic and glomerular hypertension results in increased urinary excretion of proteins and accelerates renal function deterioration. Many studies have demonstrated that an adequate, or even intensified blood pressure control (less than 130/80 mmHg), can slow the progression of diabetic and non diabetic renal disease[34]. Moreover, long-term studies indicate that the change in GFR may be minimal in well-controlled hypertensive patients, and that patients with nonmalignant essential hypertension with early and good blood pressure control do not develop renal failure[35]. The relationship found in our cohort might be the result of inadequately controlled blood pressure levels in the individuals with current CKD.

The association between CKD and obesity was previously described in a prospective study of a large cohort[36]. The increase in body weight with time, even within normal BMI values, has also been independently associated with an increased risk for CKD[37]. One of the proposed mechanisms for the development of CKD in obese patients is the presence of an increased inflammation status. This is supported by the study of Bavbek et al., who found elevated

Table 3. Unadjusted associations between demographic or clinical characteristics and the presence of chronic kidney disease (eGFR <60 ml/min per 1.73 m²)

Category (reference)	OR (95% confidence interval)
Age >64 years (vs. 20-39 years)	267.5 (37.5 to 1,909.1)
Age 40-64 years (vs. 20-39 years)	34.4 (5.8 to 204.6)
Men (vs. women)	0.74 (0.50 to 1.1)
Rural habitat (vs. urban)	1.2 (0.71 to 2.1)
Overweight, BMI 25-30 kg/m² (vs. normal, 18.5-25 kg/m²)	2.3 (1.4 to 4.0)
Obesity, BMI >30 kg/m² (vs. normal, 18.5-25 kg/m²)	3.5 (2.0 to 6.0)
Hypertension (vs. absence)	6.2 (4.0 to 9.6)
Previously diagnosed hipertensión (vs. absence)	5.9 (4.0 to 8.5)
Current hypertension (vs. absence)	3.1 (2.2 to 4.4)
Isolated systolic hipertensión (vs. absence)	3.3 (2.2 to 4.6)
Pulse pressure >60 mmHg (vs. ≤60)	3.8 (2.6 to 5.5)
Previous cerebrovascular disease (vs. absence)	3.3 (1.4 to 7.8)
Previous ischaemic heart disease (vs. absence)	4.1 (2.6 to 6.5)
Previous peripheral vascular disease (vs. absence)	2.1 (1.4 to 3.1)
Previous gout (vs. absence)	2.2 (1.2 to 4.2)
Diabetes (vs. absence)	2.0 (1.4 to 2.8)
Previously diagnosed diabetes (vs. absence)	2.4 (1.7 to 3.3)
Current glucose>126 mg/d (vs. ≤126)	2.2 (1.4 to 3.5)
Total colesterol >200 mg/dl (vs. ≤200)	1.2 (0.8 to 1.7)
Previously diagnosed dyslipemia (vs. absence)	2.1 (1.4 to 3.0)
HDL-cholesterol <35 mg/dl (vs. ≤35)	4.6 (0.8 to 27.1)
LDL-cholesterol >160 mg/dl (vs. ≤60)	1.1 (0.70 to 1.7)
Triglycerides >200 mg/dl (vs. ≤200)	1.1 (0.37 to 3.5)
Atherogenic index >4.5 (vs. ≤4.5)	1.3 (0.68 to 2.6)
Anaemia, Hb <11 mg/dl (vs. ≥11)	2.8 (1.0 to 7.7)
Proteinuria, ACR>30 mg/g (vs. ≤30)	2.1 (0.98 to 4.5)
Exsmoker (vs. non smoker)[a]	16.4 (1.9 to 143.2)
Habitual alcohol intake (vs. never)	0.43 (0.28 to 0.66)
Ocasional alcohol intake (vs. never)	0.37 (0.22 to 0.64)
Exalcohol consumption (vs. never)	1.39 (0.80 to 2.40)
Substance abuse (vs. non abuse)	0.15 (0.02 to 1.1)
Physical inactivity (vs. regular)	1.2 (0.7 to 2.1)

[a] OR for predicting stages 4-5; For stages 3-5, the OR is 0.81 (95% CI: 0.55 to 1.2).

HOMA: Homeostasis Model Assessment index; ACR: urine albumin to urine creatinine ratio; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFR: glomerular filtration rate; HDL: high density lipoprotein-cholesterol; LDL: low density lipoprotein; Hb: haemoglobin.

serum C-reactive protein (CRP) levels in obese patients versus age-matched healthy controls, and a negative correlation between CRP levels and GFR[38]. In morbidity obese patients who underwent very important weight reduction after biliopancreatic diversion all cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, proteinuria) improved during follow-up[39].

An early identification of CKD in primary care is very important, as specialist referral at an appropriate timing may improve long-term outcomes. It has been reported that, in Spain, late referral to nephrologist is common in chronic diseases such as diabetes or hypertension[40]. Our results indicate that almost ten percent of adult individuals may suffer some degree of renal impairment, and therefore, reveal the need for taking this disease into account. In addition, our findings suggest that the control of classical cardiovascular risk factors as obesity or hypertension in primary care setting might help preventing CKD development.

The main limitation of the study is its poor response rate. The sensitivity analysis excluding the centers with low participation revealed some non-response bias, which did not appear to introduce substantial bias into CKD and proteinuria prevalence estimates. Another limitation is the indirect GFR estimation method, based on a single creatinine measurement, that should be used with caution[41]. Currently, the benefit of performing extensive screening of unselected

Table 4. Independent predictors of chronic kidney disease (eGFR <60 ml/min per 1.73 m²) in the multivariate logistic regression model

Predictor	OR (95% confidence interval)	P value
Age, years (for each year)	1.12 (1.10 to 1.14)	<0.0001
Obesity, BMI >30 kg/m² (vs ≤30)	1.91 (1.20 to 3.03)	0.0061
Previously diagnosed hipertensión (vs. absence)	1.61 (1.14 to 2.28)	0.0071

BMI: body mass index; GFR: glomerular filtration rate.

populations with the intention to reduce the subsequent risk of cardiovascular events or progression to end-stage-renal disease remains unproven[42]. Although the MDRD equation is the most commonly used in epidemiological studies[14], it underestimates the GFR[15]. Moreover, the cut-off value of 60 ml/min per 1.73 m² for all ages leads to over diagnosis in elderly population. A new equation recently developed seems to improve the GFR estimation[43]. Finally, the cross-sectional design of the study does not allow inferring causal relationships between the risk factors and CKD.

Some strenghts of our study are its large sample size, well representative of the different Spanish regions, and the random selection of the participants. The agreement with results from other European countries supports the external validity of our findings.

In conclusion, we found a relatively high prevalence of assymptomatic CKD (almost one of ten) in apparently healthy general population from Spain, especially in older, obese and hypertensive patients. Independently of age, many of the risks factors for CKD are modifiable: hypertension, diabetes mellitus, obesity, dyslipemia and smoking. Further studies should assess whether early detection of CKD in general population might avoid CKD progression and protect from associated cardiovascular risk factors.

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Insulin resistance index (HOMA-IR) levels in a general adult population: Curves percentile by gender and age. The EPIRCE study

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ABSTRACT

Aims: To describe the distribution of HOMA-IR levels in a general nondiabetic population and its relationships with metabolic and lifestyles characteristics.
Methods: Cross-sectional study. Data from 2246 nondiabetic adults in a random Spanish population sample, stratified by age and gender, were analyzed. Assessments included a structured interview, physical examination, and blood sampling. Generalized additive models (GAMs) were used to assess the effect of lifestyle habits and clinical and demographic measurements on HOMA-IR. Multivariate GAMs and quantile regression analyses of HOMA-IR were carried out separately in men and women.
Results: This study shows refined estimations of HOMA-IR levels by age, body mass index, and waist circumference in men and women. HOMA-IR levels were higher in men (2.06) than women (1.95) ($P = 0.047$). In women, but not men, HOMA-IR and age showed a significant nonlinear association ($P = 0.006$), with increased levels above fifty years of age. We estimated HOMA-IR curves percentile in men and women.
Conclusions: Age- and gender-adjusted HOMA-IR levels are reported in a representative Spanish adult non-diabetic population. There are gender-specific differences, with increased levels in women over fifty years of age that may be related with changes in body fat distribution after menopause.

1. Introduction

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is widely used in large epidemiological studies and in clinical practice to estimate insulin resistance. Insulin resistance is a pathogenic factor for type 2 diabetes, and is associated with cardiovascular diseases (CVD) [1–5]. Other studies have showed that insulin resistance (IR) may be an important predictor of CVD risk [6–8].

Determining the distribution of HOMA-IR levels in general populations is important to help clinicians interpret its value.

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The common guidelines for the definition and determination of reference intervals in the clinical laboratory note that partitioning should be considered when there are significant differences among subgroups defined by age, gender, and common exposures such as smoking or alcohol consumption [9]. HOMA-IR levels have been reported to be inversely associated with physical activity [10]. Moderate drinkers have lower HOMA-IR values [11], but fewer studies have addressed the overall effects of smoking, physical activity, alcohol intake, and common metabolic abnormalities on insulin resistance in general population.

On the other hand, IR has been proposed as a principal factor in initiating and perpetuating the pathologic manifestations of the metabolic syndrome [12,13] and it is associated with inflammatory disease mechanisms [14]. Obesity and metabolic syndrome, the paradigms of metabolic abnormalities, are common in many populations, and their worldwide prevalence has risen dramatically over recent decades [15].

To the best of our knowledge, no previous studies have focused on the serum HOMA-IR levels quantile distribution in general population, and the possible combined associations of lifestyles (exercise, smoking, and alcohol consumption) and other common metabolic abnormalities with serum HOMA-IR levels in a nondiabetic population from an entire European country.

The aim of the present population-based study was to assess serum HOMA-IR levels in nondiabetic adults and its relationship with (i) demographic factors (age and gender); (ii) life style habits (exercise, alcohol consumption, and smoking); and (iii) common metabolic abnormalities, including the components of metabolic syndrome, in a nondiabetic population in Spain.

2. Subjects, materials and methods

2.1. Subjects

The present study took advantage of a survey of the general adult population (EPIRCE) [16]. The EPIRCE is an epidemiologic, cross-sectional study that included a randomly selected sample of Spanish persons aged 20 years and older. The study was primarily intended to investigate the prevalence of chronic kidney disease (CKD) in the adult Spanish population.

A random sample, stratified by age, gender, and habitat, was drawn from the 2001 Spanish Census. The sample (n = 13,013) was recruited between January 2004 and December 2007 in 42 municipalities. Because of census errors, a total of 6464 people were finally contacted. The response rate was 42.5%, with 2746 completed interviews included. The recruited sample is representative of all regions, and was adjusted to provide valid estimates of age and gender according to the distribution of the Spanish population in 2001.

Data were collected using a standardized questionnaire administered during a structured interview, followed by a detailed physical examination and blood sample collection [16,17].

People with diabetes (n = 282, 10.8%), defined as a fasting plasma glucose ≥126 mg/dl and/or the current use of diabetes medications, were excluded [18]. Data analysis could not be performed in 218 (8.8%) of the 2464 nondiabetics because of a lack of insulin level recording. There were no statistically significant differences between nondiabetics with or without missing data regarding age, sex, hypertension, alcohol intake, or physical activity (data not shown). Finally, 2246 nondiabetic individuals were selected. The median age was 47 years (range 20–92 years). A total of 1329 (59.2%) were women. All participants were Caucasians.

2.2. Lifestyle habits

Alcohol consumption was evaluated with standard drinking units [19], which sums the number of glasses of wine (~10 g), bottles of beer (~10 g), and units of spirits (~20 g) consumed regularly per week. Individuals with a usual alcohol consumption of 1–140 g/week (n = 1078, 48.2%) were considered light drinkers, those consuming 141–280 g/week (n = 191, 8.5%) were considered moderate drinkers, and those consuming ≥280 g/week (n = 127, 5.7%) were considered heavy drinkers. The alcohol abstainers or very occasional alcohol drinkers (n = 839, 37.5%) were combined in the same group. Those who consumed at least one cigarette per day were considered smokers (n = 567, 28.5%). Subjects who had stopped smoking during the last 12 months after years of smoking were considered smokers.

Physical activity was evaluated with a self-reported structured questionnaire. Subjects were asked to record their level of physical activity at home and at work. We also recorded their work status (the categories were low, moderate, high, and intense physical activity), and the amount of time for sports undertaken during their leisure time (categories were low if none; moderate if less than once weekly; high if once or twice weekly; and intense if more than twice weekly). Physical activity was then recorded and categorized in one of the following categories: sedentary (n = 640, 29%), occasional exercise (moderate activity once a month, n = 1022, 47%), moderate exercise (moderate exercise once weekly, n = 324, 14%), and intense exercise (moderate or intense physical activity more than once weekly, n = 225, 10%).

2.3. Anthropometric and clinical measurements

Subjects were considered to have hypertension if they had a mean systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or used antihypertensive medications [20].

Waist circumference and body weight and height were measured according to a standard protocol. The body mass index (BMI) was calculated as the weight (in kg) divided by the square of the height (in m). Following standard criteria, individuals were classified as normal weight (<25 kg/m^2), overweight (25–30 kg/m^2), or obese (>30 kg/m^2).

2.4. Specific laboratory determinations

A blood sample was collected after an overnight fast of >8 h. Plasma glucose levels were measured using a hexokinase enzymatic reference method. Fasting insulin levels were measured using a RIA method. Fasting lipids were analyzed, and for the present study serum levels of cholester-

ol ≥ 5.172 mmol/l and triglycerides > 2.26 mmol/l were considered abnormally high.

A Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was used to evaluate insulin resistance, and was calculated with the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 [21].

2.5. Statistical analyses

Baseline subject characteristics are expressed as the mean ± SD or as percentages. Age- and gender-adjusted HOMA-IR levels are reported as the median and percentile. Cross-tabulation significance levels were based on Pearson's chi-square test for categorical variables. The Mann–Whitney U-test, Kruskall–Wallis test, and the Jonckheere–Terpstra test (for trend analyses) were employed for comparison of quantitative variables.

The possible effects of lifestyles, clinical measurements, and anthropometric measurements on the HOMA-IR levels were assessed using generalized additive models (GAMs) [18,19]. Explicitly, in our study, the GAM can be expressed in the following manner: log (HOMA-IR) = $\alpha + f_1(X_1) + f_2(X_2) + \ldots$, where α is a constant, and $f_i(X_i)$ are smooth functions representing the partial effects of the explanatory variables X_i on the HOMA-IR.

Since HOMA-IR is a nonnegative response variable showing a positive skewness, the gamma distribution was assumed for this outcome in all the fitted GAMs, and the log function was considered as the link. As a first step in our analysis, independent GAMs were initially constructed for each explanatory variable, and duly adjusted by the age × gender interaction. The final multivariate GAM regression models included SBP, waist circumference, high-density lipoprotein (HDL), triglycerides (in log scale), educational level, physical activity, cigarette smoking, and alcohol consumption. As the BMI and waist circumference variables were used as indicators of obesity, they were not simultaneously included in the same model to prevent potential concurvity (the analogue to the

Table 1 – Observed and averaged smooth HOMA-IR percentiles, by gender and age group, among 2246 nondiabetic individuals.

	%	Median	P3	P5	P10	P25	P50	P75	P90	P95	P97
Observed HOMA-IR percentiles											
Total		1.73	0.55	0.63	0.80	1.17	1.73	2.48	3.46	4.14	4.72
Age group's men (P = 0.35)[a]											
20–29	12.9	1.66	0.58	0.62	0.92	1.24	1.66	2.48	3.41	4.01	5.06
30–39	22.8	1.81	0.57	0.71	0.85	1.16	1.81	2.55	3.73	4.53	5.56
40–49	20.0	1.85	0.63	0.71	0.85	1.20	1.85	2.72	3.87	5.54	6.21
50–59	17.8	1.78	0.54	0.63	0.85	1.16	1.78	2.51	3.40	4.10	4.58
60–69	14.3	1.82	0.52	0.65	0.77	1.18	1.82	2.67	3.40	4.10	4.52
70–79	9.4	1.74	0.47	0.53	0.87	1.19	1.74	2.62	3.78	5.30	6.58
≥80	2.8	1.18	0.65	0.65	0.68	0.75	1.18	2.22	2.97	3.57	3.82
Age group's women (P = 0.04)[a]											
20–29	15.5	1.79	0.59	0.68	0.89	1.27	1.79	2.49	3.44	4.05	4.18
30–39	19.3	1.63	0.55	0.56	0.68	1.05	1.63	2.21	3.05	3.63	4.67
40–49	20.6	1.58	0.53	0.58	0.83	1.15	1.59	2.30	3.21	3.94	4.38
50–59	19.3	1.64	0.51	0.55	0.75	1.10	1.64	2.37	3.31	3.94	4.31
60–69	14.1	1.91	0.57	0.66	0.88	1.23	1.91	2.46	3.49	4.50	4.74
70–79	9.0	1.91	0.79	0.90	1.10	1.45	1.91	2.77	3.93	4.48	5.06
≥80	2.2	1.69	0.61	0.61	0.64	1.02	1.69	2.82	3.55	3.69	3.76
Averaged smooth HOMA-IR percentiles											
Age group's men											
20–29		1.90	0.51	0.62	0.82	1.26	1.90	2.73	3.66	4.30	4.75
30–39		1.88	0.51	0.62	0.82	1.24	1.88	2.71	3.63	4.26	4.71
40–49		1.86	0.50	0.61	0.81	1.23	1.86	2.68	3.59	4.22	4.66
50–59		1.84	0.50	0.60	0.80	1.22	1.84	2.65	3.55	4.18	4.62
60–69		1.83	0.49	0.60	0.79	1.21	1.83	2.63	3.52	4.14	4.57
70–79		1.81	0.49	0.59	0.78	1.19	1.81	2.60	3.49	4.10	4.53
≥80		1.79	0.48	0.59	0.77	1.18	1.79	2.57	3.45	4.05	4.47
Age group's women											
20–29		1.84	0.54	0.65	0.84	1.24	1.84	2.59	3.43	4.00	4.40
30–39		1.67	0.49	0.59	0.76	1.13	1.67	2.36	3.12	3.65	4.02
40–49		1.66	0.49	0.58	0.76	1.12	1.66	2.34	3.10	3.62	3.98
50–59		1.70	0.50	0.60	0.78	1.15	1.70	2.40	3.18	3.71	4.08
60–69		1.88	0.55	0.66	0.85	1.27	1.88	2.65	3.50	4.09	4.50
70–79		1.98	0.58	0.70	0.91	1.34	1.98	2.80	3.71	4.33	4.76
≥80		1.76	0.51	0.62	0.80	1.19	1.76	2.48	3.28	3.83	4.21

P: percentile at the indicated numerical value.
HOMA-IR: Homeostasis Model Assessment of Insulin Resistance measured as fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5.
[a] The Jonckheere–Terpstra test for trends was employed for median comparisons.

collinearity in parametric model) [22]. Since the GAM including the interaction between age and gender presented a better fit in terms of deviance explained, the multivariate GAMs where run separately in men and women.

For fitting the GAMs, penalized regression splines were used to estimate the smooth functions, $f_i(X_i)$ with optimal *effective degrees of freedom* (edf) chosen automatically by means of Generalized Cross Validation (GCV). A Bayesian approach to uncertainty estimation was used to obtain 95% confidence intervals for the effects [23].

With regard to the quantile regression analysis of HOMA-IR, the methodology used relied on GAMLSS [24] with gamma distribution and log link for both the mean and the variance. As in the previous GAM regression models, penalized regression splines were used as smoothers of the quantile curves and the analyses were carried out separately in men and women.

All statistical analyses were performed using R software, version 2.12.1 [25]. GAMs were fitted using the MGCV package, version 1.7-6 [22] and quantile analysis was performed using the GAMLSS package, version 4.4-0 [24].

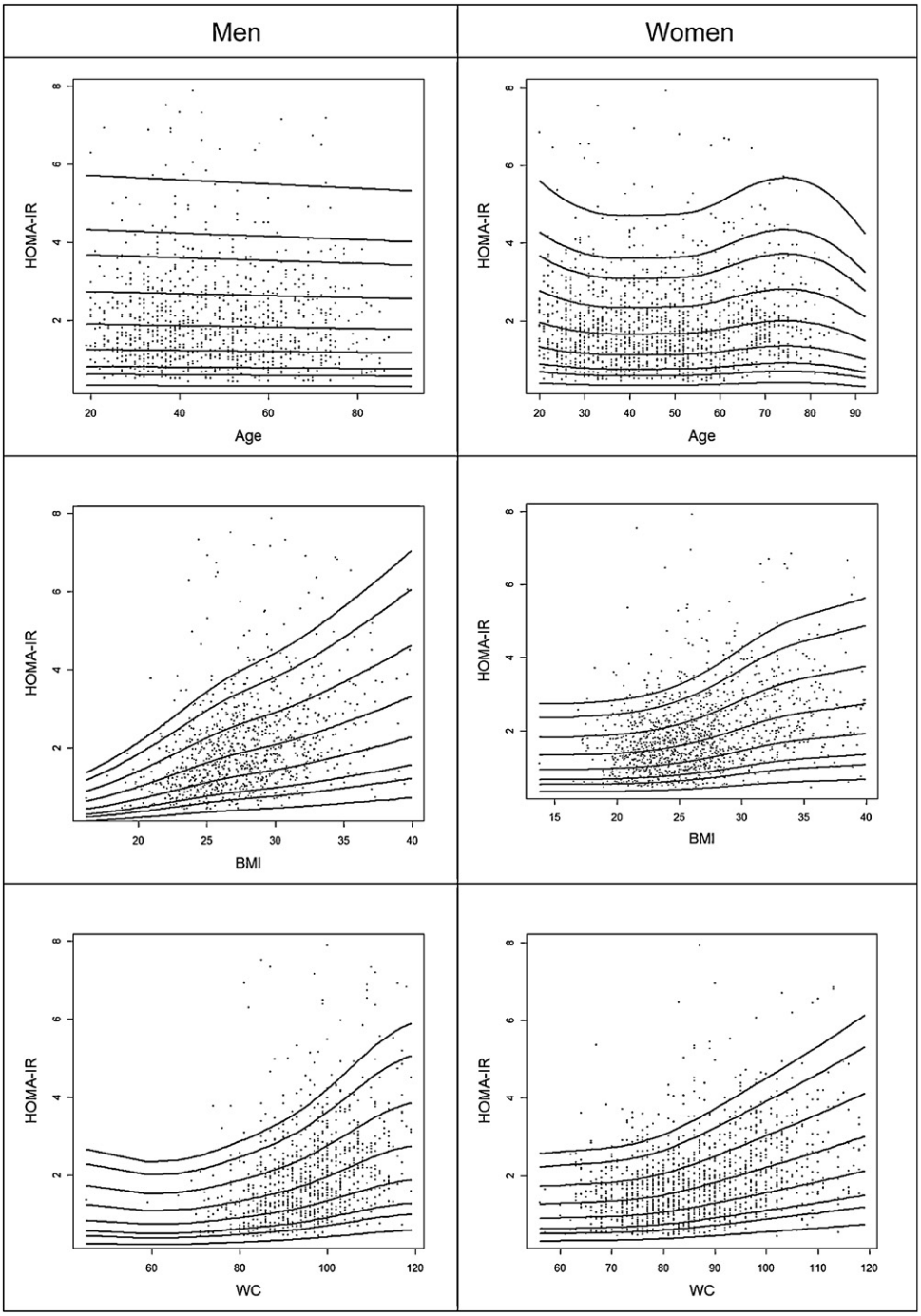

Fig. 1 – Percentile curves showing HOMA-IR for age, body mass index (BMI), and waist circumference (WC) among 2246 nondiabetic individuals in men and women separately.

2.6. Ethical considerations

The protocol was approved by the Ethics Committee, and all enrolled subjects provided informed consent.

3. Results

3.1. General characteristics

Men showed worse lifestyle habits than women. There were significant differences by gender with respect to smoking (28% of men were smokers vs. 21% of women, $P < 0.0001$); alcohol intake (75.7% men were current alcohol drinkers, with a median of 183 g/week vs. 50.2% women, with a median of 50 g/week, $P < 0.001$); hypertension (49% of men were hypertensive vs. 36% of women, $P < 0.001$) and obesity (27% of men vs. 23% of women had a BMI > 30 kg/m^2, $P < 0.001$). Triglycerides were higher (3.01 mmol/l in men vs. 2.34 mmol/l in women, $P < 0.001$), and HDL cholesterol was lower (1.69 mmol/l in men vs. 2.05 mmol/l in women, $P < 0.001$). However, there were more sedentary women (30.9%) than men (26.7%) ($P = 0.004$).

3.2. The overall distribution of HOMA-IR levels in the population by age and gender

In the overall data set, mean HOMA-IR levels were higher in men than in women (2.06 vs. 1.93, respectively; $P = 0.047$). Age- and gender-adjusted HOMA-IR levels are reported in Table 1. The distribution of HOMA-IR levels by decades of age was different between men and women (Fig. 1). Women aged over their fifth decade had significantly higher HOMA-IR levels (P for trend = 0.04). This difference was also present when we analyzed the HOMA-IR changes with age by GAM (Fig. 2).

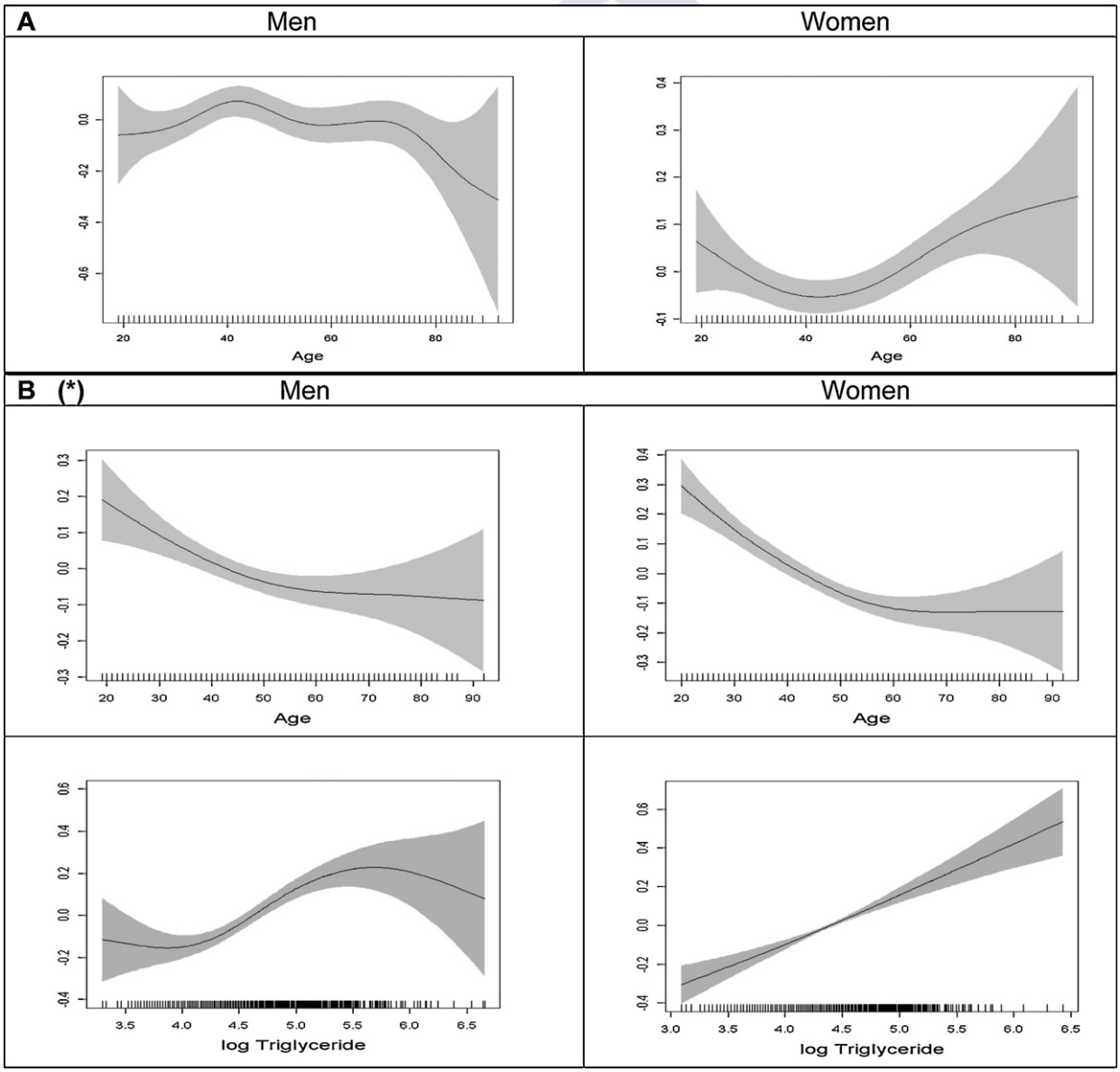

Fig. 2 – Smooth (centered) effects of age on HOMA-IR in both men and women (A). Adjusted smooth (centered) effects of age and triglycerides (log scale) on HOMA-IR in men and women separately (B). Results are based on data from 2246 nondiabetic individuals.

Whereas in men there was no evidence to suggest an association between age and HOMA-IR (edf = 4.88, $P = 0.14$), women showed a significant nonlinear association (edf = 2.78, $P = 0.006$) with an increase in levels in those aged fifty years and older.

3.3. *Relationship between HOMA-IR levels, metabolic characteristics and lifestyle habits (Table 2)*

HOMA-IR levels decreased progressively with increasing physical activity (P for trend < 0.001). HOMA-IR levels tended to be lower in parallel with alcohol consumption (P for trend = 0.022). Accordingly, the lowest HOMA-IR levels were observed in heavy drinkers, who exhibited significantly lower HOMA-IR levels than those of abstainers ($P < 0.001$). HOMA-IR levels were lower in smokers than in non-smokers, but the difference was not statistically significant (P for trend = 0.236). HOMA-IR levels increased with waist circumference and BMI in both men and women (Fig. 1).

3.4. *Multivariate analyses of factors associated with HOMA-IR*

The results of the independent GAM analyses on HOMA-IR, adjusted for age and gender, are presented in Table 3 (Model A). HOMA-IR levels showed a significant nonlinear association with BMI (edf = 3.48, $P < 0.001$), waist circumference (edf = 3.19, $P < 0.001$), triglycerides (edf = 5.08, $P < 0.001$), systolic blood pressure (edf = 2.65, $P < 0.001$), and HDL-cholesterol (edf = 3.23, $P < 0.001$). GAM analysis showed a significant linear association between HOMA-IR and DBP (edf = 1, $P < 0.001$).

Table 3 (Model B) shows the results of the multivariate GAM analysis for men and women separately. Since the multivariate model including waist circumference had a better fit (in terms of deviance explained) than the one including BMI (in both genders), we report the results for the waist circumference in this work. Serum HOMA-IR levels decreased with ageing; they showed a nonlinear association with age in both men (edf = 1.94, $P = 0.004$) and women (edf = 2.47, $P < 0.001$). Waist circumference showed a linear association with HOMA-IR (edf = 1.00, $P < 0.001$) in both genders. However, triglycerides showed a nonlinear association (edf = 2.84, $P < 0.001$) with HOMA-IR levels in men, and an almost linear association (edf = 1.31, $P< 0.001$) in women.

When we analyzed lifestyle habits in multivariate models, we found a negative association between HOMA-IR levels and alcohol consumption in men but not women. HOMA-IR levels in heavy drinkers (more than 280 g/week) were lower than those in abstainers ($\beta = -0.149$, $P = 0.014$). The significant positive association found between HOMA-IR and physical activity remained in women but not men in multivariate models. HOMA-IR levels were lower in women with intense physical activity than in sedentary women ($\beta = -0.102$, $P = 0.047$).

Table 2 – HOMA-IR distribution by lifestyle habits, BMI, and waist circumference among 2246 nondiabetic individuals.

	%	HOMA–IR	P value
Physical activity			$P < 0.001$
Sedentary	29	1.58 (0.65, 4.47)	
Occasional	46	1.72 (0.69, 3.99)	
Moderate	15	1.64 (0.66, 4.18)	
Intense	10	1.53 (0.53, 4.03)	
Alcohol consumption			$P = 0.022$
None	37	1.79 (.065, 4.24)	
Light	48	1.67 (0.61, 4.06)	
Moderate	9	1.82 (0.65, 4.43)	
Heavy	6	1.78 (0.58, 3.83)	
Smoking habit			$P = 0.024$
Never	50	1.78 (0.68, 4.05)	
Former	26	1.75 (0.60, 4.29)	
Current	24	1.65 (0.59, 4.20)	
Educational level			$P = 0.01$
None	16	1.89 (0.65, 4.25)	
Primary	46	1.72 (0.62, 4.10)	
High school	21	1.72 (0.70, 4.25)	
University	17	1.33 (0.62, 4.09)	
BMI			$P < 0.001$
Normal weight	35	1.52 (0.53, 3.49)	
Overweight	40	1.75 (0.71, 4.12)	
Obese	25	2.34 (0.97, 5.01)	
Waist circumference			$P < 0.001$
Lower than risk	71	1.56 (0.58, 3.65)	
Greater than risk	29	2.16 (0.91, 4.88)	

Data are median (P5, P95); HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.
The Jonckheere–Terpstra test for trends was employed for median comparisons.
Normal weight, body mass index (BMI) < 25 kg/m^2; overweight, BMI 25–30 kg/m^2; obese, BMI > 30 kg/m^2.
Individuals with alcohol consumption of 1–140 g/week were considered light drinkers, those with alcohol consumption of 140–280 g/week were considered moderate drinkers and those with alcohol consumption >280 g/week were considered heavy drinkers. Alcohol abstainers and very occasional alcohol drinkers were considered in the same category.

4. Discussion

In this comprehensive study in a general population of adult nondiabetic subjects, we describe the HOMA-IR levels by gender and age group. We also analyzed the effect of lifestyle, clinical measurements, and anthropometric measurements on insulin resistance (HOMA-IR) using flexible regression models like GAMs. On the other hand, the regression percentile provides a refined estimate of HOMA-IR levels by age, BMI, and waist circumference in a general population of adult nondiabetics in Spain. These estimates are a useful tool to properly study adults at risk of obesity and metabolic syndrome.

We found a different distribution of HOMA-IR levels between men and women related to age. HOMA-IR showed a significantly increasing HOMA-IR level in women over fifty years of age. However, when further adjusted for waist circumference, HDL-cholesterol, triglyceride levels, and lifestyles, we found an attenuation of these observed HOMA-IR differences by gender, with similar nonlinear associations in men and women.

We found a slight decrease of HOMA-IR levels with ageing, in both men and women, probably because we had studied a nondiabetic population. Some authors believe that age is the most powerful predictor of insulin resistance [26]. The

Table 3 – Association between HOMA-IR and lifestyle habits, anthropometric, or metabolic characteristics. Multivariate models in 2246 nondiabetic individuals.

Parametric terms	Model A[a]			Model B (men)[b]			Model B (women)[b]		
	B	95% CI	P value	β	95%CI	P value	β	95% CI	P value
Physical activity									
Occasional	−0.099	−0.153, −0.045	<0.001	−0.069	−0.149, 0.011	0.093	−0.005	−0.066, 0.056	0.878
Moderate	−0.126	−0.199, −0.053	<0.001	−0.022	−0.127, 0.083	0.677	−0.005	−0.090, 0.080	0.905
Intense	−0.208	−0.291, −0.125	<0.001	−0.083	−0.198, 0.032	0.159	−0.102	−0.203, −0.001	0.047
Tobacco consume									
Former	−0.007	−0.053, 0.067	0.821	0.025	−0.054, 0.104	0.539	−0.018	−0.090, 0.054	0.630
Current	−0.051	−0.110, 0.008	0.092	−0.061	−0.146, 0.024	0.162	−0.043	−0.114, 0.028	0.239
Alcohol intake									
Light	−0.083	−0.134, −0.032	0.001	−0.074	−0.158, 0.010	0.086	−0.056	−0.111, 0.001	0.049
Moderate	−0.055	−0.146, 0.036	0.236	−0.100	−0.205, 0.005	0.063	−0.025	−0.186, 0.136	0.761
Heavy	−0.110	−0.218, −0.002	0.045	−0.149	−0.267, −0.031	0.014	−0.098	−0.354, 0.158	0.453
Educational level									
Elementary	−0.056	−0.127, 0.015	0.119	0.114	0.009, 0.219	0.034	−0.051	−0.127, 0.025	0.752
Middle/high	−0.061	−0.147, 0.025	0.168	0.126	0.002, 0.250	0.049	−0.008	−0.106, 0.090	0.362
University	−0.085	−0.176, 0.006	0.067	0.089	–0.046, 0.224	0.196	0.045	−0.056, 0.146	0.131
Nonparametric terms	edf		P value	edf		P value	edf		P value
s (Age) men[c]	4.88		0.140	1.94		0.004			
s (Age) women[c]	2.78		0.006				2.48		<0.001
s (BMI)	3.48		<0.001						
s (waist circumference)	3.19		<0.001	1.00		<0.001	1.00		<0.001
s (HDL cholesterol)	3.23		<0.001	2.84		<0.001	1.00		0.003
s (LDL cholesterol)	1.01		0.390						
s (Triglycerides)	5.08		<0.001	4.01		<0.001	1.32		<0.001
s (SBP)	2.65		<0.001	1.00		0.448	1.48		0.091
s (DBP)	1.00		<0.001						

s (covariate): smooth (centered) effect of the covariate. edf: effective degrees of freedom.

[a] Model A, adjusted for age (years), gender, physical activity (sedentary as reference), current smoking, alcohol intake (nonconsumer as reference), educational level (no studies as reference), waist circumference (cm), systolic blood pressure SBP (mm Hg), diastolic blood pressure DBP (mm HG), triglycerides (log scale), and LDL- and HDL-cholesterol (both in mmol/l) on HOMA-IR.

[b] Model B included age, physical activity, current smoking, alcohol intake, waist circumference, systolic blood pressure (SBP), triglycerides and HDL-cholesterol.

[c] The results in Model A are those for the GAM including only the age-by-gender interaction.

relationship between age and insulin resistance is often confounded by the fact that prevalent diseases, such as diabetes, obesity, and essential hypertension all increase with age and, at same time, insulin resistance may also increase [27]. In a retrospective analysis of the EGIR Study database (1146 healthy men and women aged 18–85 years in whom insulin action was determined by the euglycemic clamp technique), Ferrannini showed that in healthy Europeans, age per se is not a significant cause of insulin resistance to glucose metabolism or lipolysis [28]. Esteghamati, in a population-based cross-sectional study in Iran [29], reported a slight decrease in HOMA-IR levels in subjects aged greater than 50 years (90th percentile, 3.1 in those over 50 years vs. 3.5 in those aged 31–49 years, and 3.2 in those aged ≤ 30 years). Values for older nondiabetic adults would probably be lower than those documented in younger nondiabetic adults; this could be relevant in clinical setting management of HOMA-IR levels in elderly nondiabetic patients.

The presence of visceral adipose tissue (VAT) is a risk factor for development of insulin resistance and obesity related diseases [30–32]. Recent studies reported marked gender differences with regard to degrees of insulin resistance and body composition, and have showed that greater amounts of visceral and hepatic fat, in conjunction with the lack of the protective effect of estrogens, may be related to higher insulin resistance in men than in women [33]. Gender differences in body composition may be due, at least in part, to the effect of gender hormones. The increase in insulin resistance with menopause suggests that estrogens may play a role in the insulin sensitivity observed in women. The age and gender differences in HOMA-IR levels found in our study may reflect the effect of menopausal changes (decreased estrogens levels and VAT increases) on insulin resistance.

When we evaluated HOMA-IR and lifestyles in a nondiabetic adult population, we found that HOMA-IR levels decreased progressively with increasing physical activity (P for trend < 0.001), and this relationship remained after adjusting for age and gender. In the RISC Study, conducted in a population of men and women aged 30–64 years, total accumulated activity was the key parameter positively associated with insulin sensitivity [11]. In the Insulin Resistance Atherosclerosis Study, insulin sensitivity was positively associated with vigorous exercise and also with the energy expended in vigorous and no vigorous activities [12]. Do et al. found a higher insulin resistance in obese than normal weight Thai adults [34].

The observed variations in HOMA-IR with alcohol consumption confirm those reported in previous studies [11]. HOMA-IR levels tended to decrease with alcohol consumption, being lower in heavy drinkers than in light-to-moderate drinkers and abstainers [35].

HOMA-IR may serve as a surrogate measure of the insulin-resistant phenotype, because it identifies a proportion of subjects with insulin resistance without directly measuring insulin action [36]. In Supplementary Table 1, we summarize the available population-based studies of insulin-resistance using HOMA-IR. As can be seen, very few studies report the distribution of HOMA-IR levels beyond one or two measures, which differ according to the studies [37]. Furthermore, ethnic factors are known to be significant in the etiology of insulin resistance, which limits inter-population comparisons. Additionally, the HOMA-IR level differences probably reflect the different clinical methods and diversity of populations studied in terms of ethnicity, with lower levels in Asiatic and multiethnic populations [4,34,38,39], and in clinical characteristics, with higher levels in diabetic and nondiabetic or obese [40] populations and lower levels in populations with no metabolic abnormalities.

In our population, HOMA-IR levels were similar to those found in southeastern Spain [41] and in a nondiabetic Iranian population [29]. However, two studies in a population in northwest Spain report slightly different HOMA-IR values. Ascaso report higher levels in populations with no metabolic abnormalities but who were younger compared with the EPIRCE study [42]. Tomé found the same median HOMA-IR values, but with a 7.8% of diabetic individuals [43].

Our HOMA-IR levels were higher than those reported in a nondiabetic population in the Malmo Study [44]. Other European population-based studies included diabetic and nondiabetic subjects, and reported HOMA-IR levels higher than expected [45,46]. On the other hand, our levels are relatively low compared with the NHANES study in a nondiabetic population, probably because of the multiethnic composition of the NHANES study subjects [47]. For these reasons, it is necessary to determine the HOMA-IR values for each nondiabetic population, and the HOMA-IR level differences by age group and gender.

The strengths of this analysis include the use of a large, diverse, and well characterized population-based sample of nondiabetic adults, with a significant-sized (more than 10% aged greater than 70 years) older-age group, and the consideration of lifestyle, clinical, and metabolic characteristics all together. The measure of insulin resistance utilized in this study, HOMA-IR, is a simple measure of insulin resistance derived from fasting glucose and insulin values, and correlates well with insulin sensitivity derived from the hyperinsulinemic–euglucemic techniques [36]. We used flexible models in our analysis, because regression techniques have the advantage of not assuming a parametric form on the effects of continuous explanatory variables; instead, they assume only that these effects are additive and reasonably smooth.

We acknowledge limitations to our approach as well. The cross-sectional nature of our study does not allow us to draw conclusions regarding causality between insulin resistance and lifestyle habits or cardio-metabolic risk factors. It should be also noted that the measurement of lifestyle habits using a self-administered questionnaire may be a limiting factor or a source of bias. Regardless, our hypothesis is consistent with a wide range of previous studies in both men and women.

In summary, with the current rise in the prevalence of obesity, the study of insulin resistance and body composition has become an important area of research in developed countries and a public health task. One important point for management of HOMA-IR in the clinical setting is to know the distribution HOMA-IR levels by gender and age for each population, or at least in similar populations. More prospective population-based studies are needed to elucidate the clinical value of HOMA-IR for use in management or clinical prediction of metabolic disorders.

On the other hand, because there are gender-specific differences in HOMA-IR levels and body composition, gender-tailored treatment of insulin resistance may be of benefit rather than a focus on visceral and hepatic adipose tissue, especially in postmenopausal women and the obese [48]. For now, lifestyle changes, including weight loss and exercise, may be a more effective strategy to improve vascular health and limit insulin resistance.

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Conflict of interest

All the authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.diabres.2011.07.015.

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Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age. EPIRCE cross-sectional study

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ABSTRACT

Backgrund To describes the influence of age and gender in the estimation of HOMA-IR optimal cut-off values to identifying subjects with higher cardio metabolic risk in a general adult population.

Methods. It included 2459 adults in a random Spanish population sample. The effect of age on the accuracy of HOMA-IR was analyzed in individuals with and without diabetes mellitus separately. ROC regression methodology was used to evaluate the effect of age on HOMA-IR performance in classified cardio metabolic risk.

Results. In Spanish population the threshold value of HOMA-IR for IR drops from 3.46 using 90th percentile criteria to 2.05 take into account MetS components. In non-diabetic women, but no in men, we found a significant non-linear effect of age on the accuracy of HOMA-IR. In non-diabetic men, the HOMA-IR cut-off values were 1.85. All values are between 70th-75th percentiles of HOMA-IR levels in adult Spanish population.

Conclusions. We propose the addition of the components of MetS analysis as a criterion to establish the cut-off points of HOMA-IR to define IR instead of using a percentile of the population distribution. The consideration of the attendant risk of cardiovascular and metabolic diseases to establish this cut-off point would increase its clinical utility in identifying those patients in whom the presence of multiple metabolic risk factors imparts an increased metabolic and cardiovascular risk. The threshold HOMA-IR levels to define IR must be modified by age in non-diabetic women.

Keywords: insulin resistance, gender, cardio metabolic risk, metabolic syndrome,

BACKGROUND

Insulin resistance (IR) is a feature of disorders such as type 2 diabetes and is also implicated in obesity, hypertension, cancer or autoimmune diseases [1-3]. Insulin resistance (IR) has been proposed, more than a primary cause, as a sort of final common pathway for negative environmental factors, which interact with the individual genetic background to cause metabolic and hemodynamic alterations and is associated with inflammation [4,5].

Metabolic syndrome (MetS) definition is widely used as a practical tool to describe a cluster of clinical signs (central obesity, dyslipidemia, impaired glucose metabolism, and elevated blood pressure) that regardless of cause, identifies individuals at risk of atherosclerotic cardiovascular disease (CVD), and diabetes mellitus type 2 (DM2) [6-9]. The worldwide prevalence of these factors has risen dramatically in recent decades [10-12].

The Homeostasis Model Assessment of IR (HOMA-IR) has proved to be a robust tool for the surrogate assessment of IR [13, 14]. However, there is great variability in the threshold HOMA-IR levels to define IR. Population based studies for defining cut-off values of HOMA-IR for the diagnosis of IR had been conducted in different geographic areas [15-22]. In most of cases the cutoff point's determination were made on the percentile criterion (80 or 90 according to studies) of values in the general population. However, in no case take into account the ability of classification proposed cutoff points are in terms of clinically relevant outcomes [14].

In these studies the results have being reported without taking into account the possible effects of covariates on test results. However, it is well known that a biomarker's performance and, by extension, its discriminatory capacity can be affected by covariates [23].

In a previous study we showed that there are age and gender-specific differences in HOMA-IR levels, with increased levels in women over fifty years of age [24]. On the other hand, the prevalence cardio metabolic diseases such as diabetes or central

obesity, rises with age and shows gender differences [11, 12]. All these results suggest the possible effects of both age and gender on the accuracy of HOMA-IR to identify individuals with cardio metabolic risk.

The purpose of the present population-based study was to evaluate the change in defining cut-off values of HOMA-IR for the diagnosis of IR when cardio metabolic risk factors were considered. We currently assess the influence of age and gender on the performance of serum HOMA-IR levels to identifying cardio metabolic risk in an adult population, to better understand the relationship between insulin resistance and cardio metabolic risk.

METHODS

Setting

The present study took advantage of a survey of the general adult population (EPIRCE) [25,26]. The EPIRCE is an observational, cross-sectional study that included a randomly selected sample of Spanish persons aged 20 years and older stratified by age, gender, and habitat. The study was primarily intended to investigate the prevalence of chronic kidney disease (CKD) in the adult Spanish population. Details of the study design were previously published [26].

For the present study, data analysis could not be performed in 249 individuals (9.1%) because of a lack of insulin level recording and in 38 (1.4%) individuals because of a lack of waist circumference recording. There were no statistically significant differences between individuals with or without missing data regarding age, sex, hypertension, alcohol intake, or physical activity. Finally, 2459 individuals were selected for study inclusion. People with diabetes (247, 10.0%), defined as a fasting plasma glucose ≥126 mg/dl and/or the current use of diabetes medications, were included. The average age

was 49.4 ± 16.2 years (range 19–92 years). A total of 1436 (58.4%) were women. All participants were Caucasians.

Anthropometric and clinical measurements

Subjects were considered to have hypertension if they had a mean systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or used antihypertensive medications.

Waist circumference and body weight and height were measured according to a standard protocol. The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (meters). Following standard criteria, individuals were classified as normal weight (<25 kg/m^2), overweight (25–30 kg/m^2), or obese (>30 kg/m^2).

Specific laboratory determinations

A blood sample was collected after an overnight fast of >8 h. Plasma glucose levels were measured using a hexokinase enzymatic reference method. Fasting insulin levels were measured using a radioimmunoassay (RIA) method. Fasting lipids were analyzed, and for the present study serum levels of cholesterol ≥5.172 mmol l^{-1} and triglycerides ≥1.7 mmol l^{-1} were considered abnormal.

HOMA-IR was used to evaluate insulin resistance (fasting serum insulin (μU/ml) × fasting plasma glucose (mmol l^{-1})/22.5) [27].

Definition of metabolic syndrome

As an accurate indicator of cardio metabolic risk, MetS, both by the International Diabetes Federation (IDF) criteria and by the Adult Treatment Panel III (ATP III) criteria, were used. Under the IDF criteria, MetS ($MetS_{IDF}$) was defined as the presence of central obesity (waist circumference ≥94 cm for men and ≥80 for women) plus any two of the following risk factors: HDL-cholesterol <1.03 mmol l^{-1} (males) and <1.29

mmol l^{-1} (females) or specific treatment for this lipid abnormality; systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg, or treatment of previously diagnosed hypertension; fasting plasma glucose ≥5.6 mmol l^{-1}, or previously diagnosed type 2 diabetes; triglycerides ≥1.7 mmol l^{-1} or specific treatment for this lipid abnormality [28]. According to ATPIII criteria, MetS ($MetS_{ATPIII}$) was defined as the presence of three or more of the following: HDL-cholesterol <1.03 mmol l^{-1} (males) and <1.30 mmol l^{-1} (females) or specific treatment for this lipid abnormality; blood pressure ≥130/85 mm Hg or treatment of previously diagnosed hypertension; fasting plasma glucose ≥5.6 mmol l^{-1}, or previously diagnosed type 2 diabetes; triglycerides ≥1.7 mmol l^{-1} or specific treatment for this lipid abnormality; waist circumference ≥102 cm for males and ≥88 cm for females [29].

Statistical Analyses

Baseline subject characteristics are expressed as the mean ± SD or as percentages. Cross-tabulation significance levels were based on Pearson's chi-square test for categorical variables. The Mann-Whitney U-test and Kruskall-Wallis test were employed for comparison of quantitative variables.

To analyze the effect of age on the accuracy of HOMA-IR when predicting the presence of cardio metabolic risk, a novel non-parametric extension [30] of the induced ROC regression methodology [23, 31] was used. Since it well established that HOMA-IR values behave differently according to gender, the analyses were performed separately in men and in women. We evaluate the significant effect of age on the accuracy of HOMA-IR and P-values were obtained based on 200 bootstrap replications [32].

When the estimated effect of age on the mean of HOMA-IR probed to be linear, and the estimated variances probed to be constant (independent of age), we reanalyzed the data using the semi-parametric induced ROC regression [31].

Finally, in addition to the estimated (age-specific) ROC curve, the Area Under the Curve (AUC) and bootstrap-based confidence intervals was obtained, (b = 500 resamples). The (age-specific) threshold values were also computed based on two different criteria: (a) by setting the specificity at 0.7, and (b) by the Youden Index (YI). Insofar as the computation of the YI is concerned, in those situations where a significant effect of age was detected on the accuracy of HOMA-IR, a modification of the usual definition was used, which takes covariates into account.

All statistical analyses were performed using R software, version 2.12.1 [33]. ROC analyses were performed using the packages pROC [34], ROCRegression and npROCRegression. These last two packages can be obtained by contacting MX Rodriguez-Alvarez (maria.jose.rodriguez.alvarez2@sergas.es).

Ethical considerations

The Galician Ethical Committee for Clinical Research approved the study protocol. All patients provided informed consent.

RESULTS

Table 1 summarizes anthropometric, clinical, and biochemical characteristics of the study population. In non-diabetic individuals, but not in diabetic individuals, we found significant differences by gender in components of MetS (data no shown). The percentage of triglycerides, blood pressure, and glycemia components were higher in men than in women (23% vs. 9.6% (P<0.001), 32% vs. 19% (P<0.001) and 21% vs. 13% (P<0.001)). Women had a significantly higher waist circumference component than men (43.6% vs. 29.8%, P<0.0001).

In the overall data set, the MetS prevalence was 15% for $MetS_{IDF}$ (19.2% in men vs. 12.1% in women, P<0.0001) and 12.7% for $MetS_{ATPIII}$ (14.9% in men vs. 11.1% in women, P=0.006).

Mean HOMA-IR levels significantly increased with rising number of MetS components from 1.7 (without MetS components) to 5.3 (with 5 components) (P<0.0001).

AUC values of HOMA-IR by gender and diabetes status

Regardless of diabetes status, the AUC values of HOMA-IR were slightly higher for $MetS_{ATPIII}$ than $MetS_{IDF}$ (Table 2).

The effect of age on the accuracy of HOMA-IR was analyzed in individuals with and without diabetes mellitus separately. As can be seen in Table 2, in non-diabetic women a significant non-linear effect of age on the accuracy of HOMA-IR in identifying MetS, both $MetS_{ATPIII}$ (P=0.012) and $MetS_{IDF}$ (P<0.001), was found. Figure 1 shows the estimated AUC values by age, with the corresponding 95% point wise bootstrap confidence bands. The AUC presents a plateau with values greater than 0.7 until 50 years of age. From the age of 50, the AUC decreases progressively. For patients older than 70 years, the bootstrap confidence intervals for the AUC includes 0.5; thus there is no evidence suggesting that HOMA-IR can be used to classify non-diabetic older women with cardio metabolic risk . Table 2 shows the estimated AUC values for ages of 30, 50, and 70 years in our Spanish population. The AUC drops from 0.82 (age 30) to 0.58 (age 70).

However, in non-diabetic men the AUC progressively decreases with age, without statistical significance (P=0.16, Figure 1). Thus AUC value, 0.69 (0.65, 0.74) for $MetS_{IDF}$ and 0.71 (0.66, 0.76) for $MetS_{ATPIII}$, was estimated without covariates (Table 2).

On the other hand, in diabetic individuals there was no statistically significant effect of age on the accuracy of HOMA-IR. The AUC show an acceptable performance of HOMA-IR in diabetic men, 0.7 (0.6, 0.8), but not in diabetic women 0.54 (0.44, 0.64) (Table 2).

Cut-off values of HOMA-IR

Table 3 shows gender distribution of HOMA-IR cut-off values, with their corresponding sensitivity and specificity.

Figure 2 depicts the estimated HOMA-IR cut-off values by age in non-diabetic women for $MetS_{ATPIII}$ and $MetS_{IDF}$ respectively. For $MetS_{ATPIII}$ the optimal HOMA-IR cut-off values ranged from 2.07 (sensitivity, 0.72; specificity, 0.71) at 50 years to 2.47 (sensitivity, 0.44; specificity, 0.74) at 70 years when using YI criteria. Very similar values were found for $MetS_{IDF}$.

In non-diabetic men, for $MetS_{ATPIII}$ the optimal HOMA-IR cut-off was 1.85 (sensitivity, 0.78; specificity, 0.57) when YI criteria were used and 2.27 (sensitivity, 0.61) with fixed specificity criteria. Moreover, for $MetS_{IDF}$ the optimal HOMA-IR cut-off was higher, 2.05 (sensitivity, 0.65; specificity, 0.64), when YI criteria were used.

In diabetic individuals the optimal HOMA-IR cut-off value for $MetS_{ATPIII}$ was 1.60 (sensitivity, 0.63; specificity, 0.73) in men and 1.58 (sensitivity, 0.68; specificity, 0.46) in women (YI criteria).

All values are between 70^{nd} and 75^{nd} percentile of HOMA-IR levels in the Spanish adult population.

DISCUSSION

Overall, in non-diabetic individuals the best HOMA-IR cut-off levels ranged from 1.85 in men to 2.07 in women aged 50 years old for the diagnosis of IR take in account cardio metabolic risk. In women without diabetes, the optimal cutoff point should be estimated for each age group due to the non-linear effect of age on the accuracy of HOMA-IR. Even more, in women over 70 years there is no evidence suggesting that HOMA-IR can be used to classify individuals with or without cardio metabolic risk. All values are between the 70^{th}-75^{th} percentiles of HOMA-IR levels in the adult Spanish population [24].

We found lower cut-off values for diabetic than non-diabetic individuals (1.60 vs. 2.05 for $MetS_{IDF}$ in men), probably because in the diabetic population there is an increased

prevalence of hypertension, obesity, and dyslipidemia, thus lower HOMA-IR values identifies individuals with three or more MetS components.

In non-diabetic individuals AUC (95%IC) was 0.69 (0.64, 0.74) for $MetS_{IDF}$ and 0.72 (0.67, 0.77) for $MetS_{ATPIII}$ in men and 0.77 (0.68, 0.82) for $MetS_{IDF}$ and 0.80 (0.71, 0.85) for $MetS_{ATPIII}$ in women These results are similar to the study by Esteghamati that found an AUC of .0.65 (0.63, 0.67) for $MetS_{IDF}$ and 0.68 (0.66, 0.70 for $MetS_{ATPIII}$ [35].

There is a significant effect of age on the diagnostic performance of HOMA-IR levels to identify cardio metabolic risk in non-diabetic women; however, there is no evidence of a significant effect in non-diabetic men. Meanwhile, in diabetic individuals we no found a statistically significant effect of age on the accuracy of HOMA-IR.

The AUC in non-diabetic women presents a plateau, with values greater than 0.7, until patients are in their fifties. Recent studies reported marked gender differences with regard to degrees of IR and body composition. The age effect found in non-diabetic women in our study may reflect the effect of menopausal changes (decreased estrogens levels and increased visceral adipose tissue, VAT) on HOMA-IR performance, with a higher utility to identify cardio metabolic risk below age 50.

IR increases atherogenesis and atherosclerotic plaque instability by inducing proinflammatory activities on vascular and immune cells [36,37]. HOMA-IR is a robust surrogate method to estimate IR in epidemiologic or clinical setting. However, there is great variability in their threshold levels; as can be seen in Table 4, usually the cut-off values of HOMA-IR were defined by population-based percentiles criteria. Furthermore, these cut-off values are different according to ethnicity, clinical methods of estimation, and metabolic conditions of populations studied [14]. The consideration of the attendant risk of cardiovascular and metabolic diseases to establish this cut-off point would increase its clinical utility in identifying those patients in whom the presence of multiple metabolic risk factors imparts an increased metabolic and cardiovascular risk. In Spanish population the threshold value of HOMA-IR drops from 3.46 using 90^{th} percentile criteria to 2.05 take into account MetS components.

Our HOMA-IR cut-off levels are relatively low compared to those reported in a study of healthy Italian patients [38] with a value of 2.77, and in a Spanish non-diabetic population [39], with a value of 3.8. Both studies used the 80^{th} or 90^{th} percentile as cut-off selection criteria. On the other hand, our values are slightly higher than those reported in an Iranian population-based study with 1.77, using YI as cut-off selection criteria [26], but in this case the value was estimated pooled in men and women.

The prevalence of MetS (15% for IDF and 12.7% for $MetS_{ATPIII}$) was quite similar to that found in northwest Spain (18.3 % for $MetS_{IDF}$ and 15.0% for $MetS_{ATPIII}$) [40] and in other European population-based studies [41]. On the other hand, it is significantly lower compared with the NHANES study [42], 23.7%, and SuRFNCD-2007 study [26], 33.6%, probably because of the higher prevalence of obesity and other metabolic alterations in US and eastern Asia compared to the Spanish population [11,12].

The strengths of this study include the use of a large, diverse, and well-characterized population-based sample of adults. We used a novel non-parametric extension of the induced ROC regression methodology to analyze the effect of age on the accuracy of HOMA-IR when predicting the presence of cardio metabolic risk. The induced ROC regression methodology applied in this study is based on first evaluating the effect of covariates on the biomarker in healthy and diseased populations separately, and then computing the covariate effects on the associated ROC curve by deriving the induced form of the ROC curve.

We acknowledge limitations to our approach as well. The cross-sectional nature of our study does not allow us to draw conclusions regarding causality between IR and cardio metabolic risk. Furthermore the small sample size of diabetic patients does not allow us to draw conclusions about the performance of HOMA-IR in identifying cardio metabolic risk in diabetics. More prospective, population-based studies are needed to elucidate these concerns.

CONCLUSIONS

We propose the addition of the components of MetS analysis as a criterion to establish the cut-off points of HOMA-IR to define IR instead of using a percentile of the population distribution. The consideration of the attendant risk of cardiovascular and metabolic diseases to establish this cut-off point would increase its clinical utility in identifying those patients in whom the presence of multiple metabolic risk factors imparts an increased metabolic and cardiovascular risk.

In summary, with the increased prevalence of obesity and diabetes [11,12], the study of IR and body composition has become an important area of research in developed countries and a central public health task.

The effect of age and sex on the ability of HOMA-IR to identify subjects with cardio metabolic risk phenotype should be taken into account in the estimation of their values in different populations. The threshold HOMA-IR levels to define IR must be modified by age in non-diabetic women.

COMPETING INTERESTS

All authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

PG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. AO participated in the design of the study, have made substantial contributions to acquisition of data and helped to draft the manuscript MXRA performed the statistical analysis and helped to draft the manuscript. FGu, FGa, AF and AG participated in the analysis and interpretation of data and helped to draft the manuscript. All authors read and approved the final manuscript.

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FIGURE LEGENDS

Figure 1. Performance of HOMA-IR levels for classification of cardio metabolic risk in non-diabetic population. Influence of age and gender in the area under curve (AUC) distribution, ROC regression models.

Figure 2. Optimal HOMA-IR cut point for classification of cardio metabolic risk in non-diabetic women. The top graphics show the results based on setting the specificity at 0.7, and the bottom graphics the results based on the generalization of the Youden Index. The ATPIII-defined criteria for metabolic syndrome were used on the left, and the IDF-defined criteria for metabolic syndrome on the right.

Table 1. Anthropometric, clinical, and biochemical characteristics of patient sample: distribution by gender in diabetic (n=247) and non-diabetic (n=2212) individuals.

	Women (1308/128)	Men (904/119)	Total
Age (years)			
• Non-diabetic	47.6 ± 15.9	48.2 ± 16.0	47.9 ± 15.9
• Diabetic	64.4 ± 10.7	62.4 ± 10.8	63.4 ± 10.7
Waist Circumference (cm)			
• Non-diabetic***	86.8 ± 13.2	96.3 ± 11.3	90.6 ± 13.3
• Diabetic*	101.5 ± 13.5	105.0 ± 11.4	103.1 ± 12.5
BMI (kg/m^2)			
• Non-diabetic***	26.9 ± 5.4	27.8 ± 4.5	27.3 ± 5.1
• Diabetic***	32.2 ± 5.6	29.4 ± 4.4	31.1 ± 5.2
Systolic Blood Pressure (mmHg)			
• Non-diabetic***	125.4 ± 21.0	135.8 ± 19.0	129.6 ± 20.8
• Diabetic	145.9 ± 21.1	148.6 ± 21.2	147.3 ± 21.1
Diastolic Blood Pressure (mmHg)			
• Non-diabetic***	76.6 ± 11.0	81.1 ± 11.4	78.4 ± 11.4
• Diabetic	82.1 ± 11.7	82.1 ± 10.7	82.1 ± 11.2
Triglycerides (mmol l^{-1})			
• Non-diabetic***	1.0 ± 0.6	1.3 ± 0.9	1.1 ± 0.7
• Diabetic	1.5 ± 0.8	1.9 ± 1.9	1.7 ± 1.4
HDL-Cholesterol (mmol/L)			
• Non-diabetic***	2.0 ± 0.5	1.7 ± 0.4	1.9 ± 0.5
• Diabetic**	1.7 ± 0.4	1.6 ± 0.4	1.8 ± 0.4
Fasting Insulin (U/l)			
• Non-diabetic**	7.7 ± 4.6	8.5 ± 5.2	8.0 ± 4.9
• Diabetic	11.9 ± 6.2	10.9 ± 6.5	11.4 ± 6.3
Fasting Plasma Glucose (mmol l^{-1})			
• Non-diabetic***	4.9 ± 0.6	5.1 ± 0.6	5.0 ± 0.6
• Diabetic*	7.8 ± 2.4	8.1 ± 2.5	8.0 ± 2.5
HOMA-IR (units)			
• Non-diabetic	1.9 ± 1.0	2.1 ± 1.2	2.0 ± 1.1
• Diabetic*	1.9 ± 1.0	1.7 ± 1.1	1.9 ± 1.1
Metabolic syndrome			
ATPIII**	11.1%	14.9%	12.7%
• Non-diabetic**	7.6%	11.1%	9.0%
• Diabetic	46.9%	43.7%	45.3%
IDF***	12.1%	19.2%	15.0%
• Non-diabetic***	8.7 %	14.9 %	11.3%
• Diabetic	46.9 %	51.3 %	49.0 %

Data are presented as mean ± standard deviation, or percentages. BMI, body mass index; HOMA-IR, homeostasis model assessment of IR; ATPIII, Third Adult Treatment Panel; IDF, International Diabetes Federation
Contrast of characteristics by gender was done with the follow statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001

Table 2. Performance of HOMA-IR values in the classification of cardio metabolic risk (both ATPIII MetS and IDF MetS definition), influence of age and gender. Areas under the ROC curves for non-diabetic (A) and diabetic (B) adults (n=2459).

	ROC coefficients*	P value	AUC (95% CI)
Males			
IDF MetS			0.69 (0.65, 0.74)
• Age	0.0102	0.1665	
• Intercept	-1.1411	0.0048	
ATPIII Mets			0.72 (0.67, 0.77)
• Age	0.0117	0.1897	
• Intercept	-1.2976	0.0089	
A			
Females **			
IDF MetS			
• Age 30 yr			0.82 (0.71, 0.90)
• Age 50 yr		<0.001	0.77 (0.68, 0.82)
• Age 70 yr			0.58 (0.48, 0.68)
ATPIII MetS			
• Age 30 yr			0.83 (0.71, 0.91)
• Age 50 yr		0.012	0.80 (0.71, 0.85)
• Age 70 yr			0.61 (0.52, 0.70)
Males			
IDF MetS			0.68 (0.59, 0.78)
• Age	-0.0113	0.8998	
• Intercept	0.1406	0.5160	
ATPIII MetS			0.72 (0.62, 0.81)
• Age	-0.0029	0.8595	
• Intercept	-0.4692	0.6515	
B			
Females			
IDF MetS			0.54 (0.44, 0.64)
• Age	-0.0010	0.9656	
• Intercept	0.0173	0.9914	
ATPIII MetS			0.54 (0.44, 0.64)
• Age	-0.0010	0.9656	
• Intercept	0.0173	0.9914	

AUC (95% CI), area under the ROC curve (95% Confidence Interval). *ROC regression models incorporating age as covariate. **The AUC was estimated for three ages (30, 50, and 70 years) to illustrated the performance of HOMA-IR.

Table 3. Gender distribution of HOMA-IR cut-off levels, with their corresponding sensitivity and specificity, for classify of IDF MetS and ATPIII MetS, in diabetic and non-diabetic individuals.

IDF Criteria						
Population	**Criterion of Specificity = 0.7**			**Youden Index Criterion**		
	Cut point	**Sensitivity**	**Specificity**	**Cut point**	**Sensitivity**	**Specificity**
Diabetic						
Men	1.55	0.60	0.70	1.60	0.59	0.74
Women	2.22	0.37	0.70	1.58	0.68	0.46
Non-diabetic						
Men	2.25	0.57	0.70	2.05	0.65	0.64
Women *						
30 years	2.11	0.77	0.70	2.31	0.71	0.76
50 years	2.05	0.69	0.70	2.05	0.69	0.70
70 years	2.38	0.45	0.70	2.53	0.40	0.75
ATP III Criteria						
Population	**Criterion of Specificity = 0.7**			**Youden Index Criterion**		
	Cut point	**Sensitivity**	**Specificity**	**Cut point**	**Sensitivity**	**Specificity**
Diabetic						
Men	1.57	0.64	0.70	1.60	0.63	0.73
Women	2.22	0.37	0.70	1.58	0.68	0.46
Non-diabetic						
Men	2.27	0.61	0.70	1.85	0.78	0.57
Women *						
30 years	2.12	0.79	0.70	2.36	0.73	0.77
50 years	2.05	0.73	0.70	2.07	0.72	0.71
70 years	2.37	0.48	0.70	2.47	0.44	0.74

*In non-diabetic females HOMA-IR cut-off values are estimated for 30, 50, and 70 years of age, because there is a non linear effect of age on test performance to classify IDF-defined MetS (P value < 0.001) and ATP III-defined MetS (P value = 0.012).

Table 4. Summary of reports (sorted by sample size) on HOMA-IR cut-off in different populations

Study	Characteristics of study population	Threshold value	criteria
Hedblad, 2000	N=4,816 Sweden, Population-based sample	≥ 2.0	75th percentile
Summer, 2008	N=2804,U.S. NHANES population Age≥20 yr., normal BMI and fasting glucose	≥2.73	66th percentile
Geloneze, 2006	N=1317 Brazilian, Age: 40 ± 12 yr, BMI: 34 ± 10 kg/m^2	≥ 2.77	90th percentile
Esteghamati, 2009	N=1,276 Iranian, Age: 38 ± 12 yr, non-diabetic, normotensive		
	IDF-MetS	≥1.80	ROC
	ATPIII-MetS	≥1.95	ROC
		≥1.6	75th percentile
		≥1.8	80th percentile
		≥ 2.3	90th percentile
Marques-Vidal, 2002	N=1153, France Age 35-64 yr. population based sample	≥3.8	75th percentile
Do, 2010	N=738 Thailand, Age: ≥35 yr, normal BMI and fasting glucose	1.55	90th percentile
Miccoli, 2005	N=225 Italian, Age: 40 - 79 yr, healthy subjects	≥ 2.77	80th percentile
Taniguchi, 1992	N=161 Japanese, Age: 41.6 ± 0.4 yr, healthy subjects	≥ 1.7	90th percentile
Ascaso, 2001	N=140 Spanish, Age: 7 - 16 yr	3	ROC
Tome, 2009	N=2860 Spanish, population based Age: 18-104 yr, BMI: 26.2 ± 4.9 kg/m^2	2	ROC

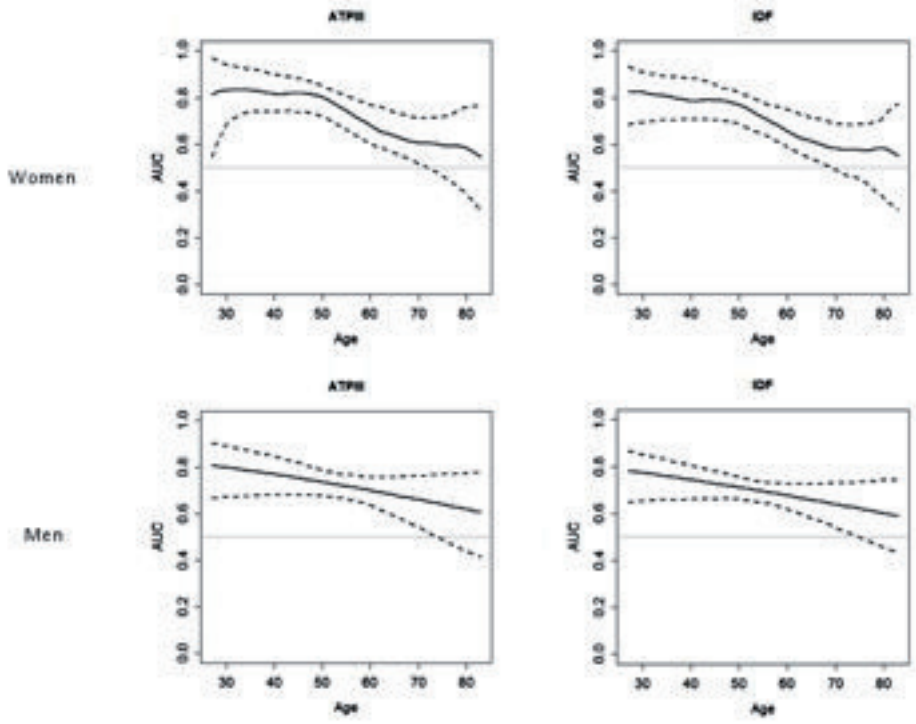

Figure 1

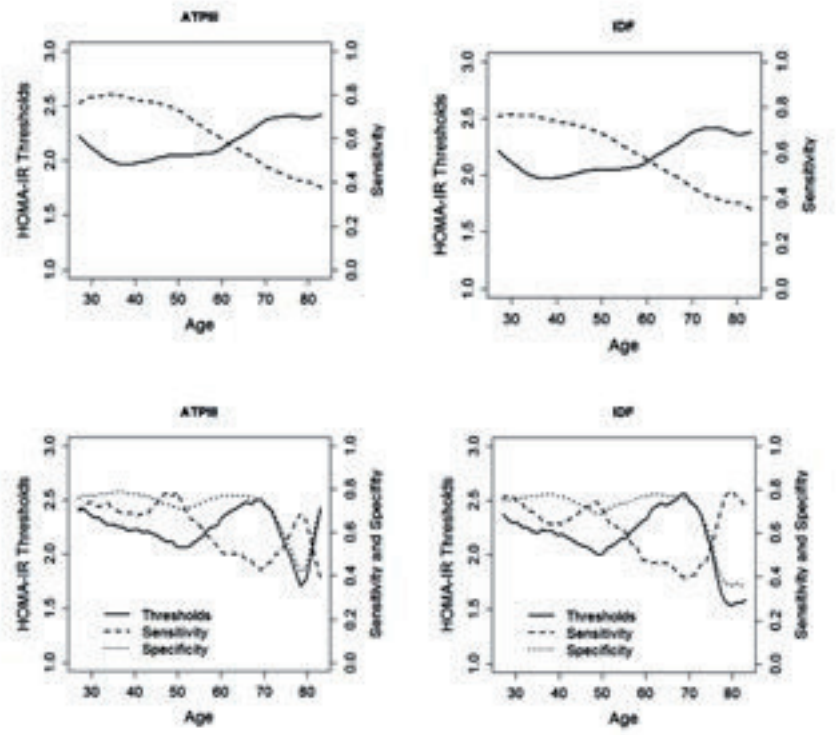

Figure 2

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Strategy to estimate risk progression of chronic kidney disease, cardiovascular risk, and referral to nephrology: the EPIRCE Study

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ABSTRACT

Background: Although the prevalence of chronic kidney disease (CKD) is 10–14%, several prospective studies note a low rate of progression to end-stage renal disease (ESRD) in stages 3 and 4. A correct classification of risk of progression, based on demonstrated predictive factors, would allow better management of CKD. Recent studies have demonstrated the high predictive value of a classification that combines estimated (e) glomerular filtration rate (GFR) and urine albumin–creatinine ratio (ACR). We estimated the clinical risk of progression to ESRD and cardiovascular mortality predicted by the combined variable of eGFR and ACR in the Spanish general population. **Materials and Methods:** This study was a cross-sectional evaluation in the Epirce sample, representative of Spanish population older than 20 years. GFR was estimated using MDRD and CKD-EPI formulas; microalbuminuria was considered to be an ACR 20–200 mg/g (men) or 30–300 mg/g (women) and macroalbuminuria was indicated beyond these limits. Population-weighted prevalence of risk of progression of CKD to ESRD was estimated. **Results:** With MDRD, 1.4% of the adult Spanish population was at moderate risk of progression to ESRD, 0.1% at high risk, and 12.3% at low risk. With CKD-EPI, the moderate risk ratio rose to 1.7% and low risk to 12.6%, but high risk remained stable. **Conclusions:** The addition of ACR to eGFR best classifies the population at risk for renal impairment relative to Kidney/Disease Outcomes Quality Initiative grades 3 and 4. Estimating GFR with CKD-EPI modifies the distribution of low and moderate risk.

Keywords: Albuminuria. Cardiovascular risk classification. Chronic kidney disease. Epidemiology. Prognosis.

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Estrategia para estimar la progresión del riesgo de la enfermedad renal crónica, del riesgo cardiovascular y la remisión a nefrología: el estudio EPIRCE

RESUMEN

Antecedentes: *Si bien la prevalencia de la enfermedad renal crónica (ERC) es del 10-14 %, diversos estudios prospectivos indican que en las fases 3 y 4 existe una tasa baja de progresión hacia enfermedad renal terminal (ERT). Una clasificación correcta del riesgo de progresión basada en factores predictivos demostrados permitiría un mejor manejo de la ERC. Estudios recientes han demostrado el elevado valor predictivo de la clasificación que combina el valor estimado (e) de la tasa de filtrado glomerular (FG) con la ratio albúmina-creatinina (RAC) en orina. Realizamos una estimación del riesgo clínico de una progresión hacia una ERT y de mortalidad cardiovascular existente en la población general española basando la predicción en el uso combinado de las variables tasa (e) de FG y RAC.* ***Materiales y métodos:*** *Evaluación cruzada en la muestra Epirce, que era representativa de la población española mayor de 20 años. Para la estimación del FG se emplearon las fórmulas MDRD y CKD-EPI; se consideraba la existencia de microalbuminuria cuando los valores de RAC oscilaban entre 20-200 mg/g (hombres) o entre 30-300 mg/g (mujeres) y de macroalbuminuria cuando los valores superaban dichos límites. Se realizó una estimación de la prevalencia ponderada poblacionalmente del riesgo de progresión de ERC hacia ERT.* ***Resultados:*** *Con MDRD, el 1,4 % de la población adulta española presentaba un riesgo moderado de evolución hacia ERT; el 0,1 % un riesgo elevado y el 12,3 % un riesgo bajo. Con CKD-EPI, la tasa de riesgo moderado se elevaba hasta 1,7 % y la de riesgo bajo hasta 12,6 %; sin embargo, la tasa de riesgo elevado se mantenía estable.* ***Conclusiones:*** *La adición de la RAC a la tasa (e) de FG permite una mejor clasificación de la población en riesgo de deterioro renal relacionado con el Kidney/Disease Outcomes Quality Initiative, grados 3 y 4. La estimación de la tasa de FG mediante CKD-EPI modifica la distribución existente para el riesgo bajo y moderado.*

Palabras clave: *Albuminuria. Clasificación del riesgo cardiovascular. Enfermedad renal crónica. Epidemiología. Pronóstico.*

INTRODUCTION

Chronic kidney disease (CKD) is a growing health problem in developed countries because of its high prevalence, effect on quality of life, and high vascular-related mortality,[1] although its evaluation is imprecise. Classically, we assess the socioeconomic impact of CKD based on patients receiving renal replacement therapy (RRT),[2] but the real burden of CKD is 50–70 times higher than those because of RRT,[3,4] and patients in CKD stages 3–5 are at greater risk for cardiovascular disease (CVD) mortality than progression to end-stage renal disease (ESRD).[5,6] The most frequently applied estimating formula, the Modification of Diet in Renal Disease (MDRD) equation,[7] has been questioned because it underestimates GFR.[8] The CKD-EPI creatinine equation is more accurate across various study populations and clinical conditions,[9] and recent studies have shown an improved accuracy of CKD-EPI for estimating cardiovascular events and mortality risk.[10-12] Nevertheless, these methods remain inaccurate because the GFR itself is a poor indicator of renal function given that it does not exactly correlate with the rate of uremic toxin.[13]

Guidelines proposed in 2003 by the Kidney Disease Outcomes Quality Initiative[14] and adopted in 2005 by the Kidney Disease Improving Global Outcomes (KDIGO) defined CKD as the presence of a GFR <60mL/min/1.73m^2 or kidney damage persistent for more than three months, regardless of cause.

In 2010, the Chronic Kidney Disease Prognosis Consortium[15] reported the results of the meta-analysis of the association using estimated (e) GFR and ACR with mortality in the general population,[16] and in 2011, the results of the association with progression to ESRD.[17] In addition, this effect is present in people older and younger than 65 years, which again contradicts the belief that the prevalence of CKD increases with age;[18] that belief is likely an artefact of the estimation formula, the retention of a renal functional reserve up to age 80 years,[19] and the fact that age is the seventh leading factor in RRT.[20] Furthermore, the association of eGFR-ACR with progression to ESRD is continuous and independent of other risk factors.[17]

CKD is otherwise a silent process in its early stages, linked to very early development of vascular lesions associated with microinflammation and monocyte activation, with evidence to suggest a turning point for risk at GFR 75.6–89mL/min.[21,22] Strategies to identify patients at risk would allow appropriate management programs of primary or secondary prevention aimed at not only changing the progression of CKD but also at decreasing the risk of CVD mortality. In 2009, Hallan et al.[23,24] proposed a new clinical risk classification system that combined all GFR levels with ACR measurement.

The aim of the current study was to estimate the clinical risk of progression to ESRD and cardiovascular mortality predicted by the combined variable of baseline eGFR and albuminuria in a Spanish general population. We also tested whether CKD-EPI eGFR modified the estimation of risk prediction compared to MDRD eGFR.

SUBJECTS AND METHODS

Study population

Our study population consisted of 2244 individuals who have been enrolled in cross-sectional EPIRCE study and have a urine albumin to creatinine ratio (ACR) estimation. In the Estudio Epidemiológico de la Insuficiencia Renal en España (EPIRCE) study, a random sample, stratified by age, sex, and location was drawn from the 2001 Spanish Census.[25,26] The recruited sample was adjusted to provide valid estimates of age and sex according to the distribution of the Spanish population in 2001. All participants were Caucasians.

Data collection

Data were collected using a standardized questionnaire administered during a structured interview, followed by a detailed physical examination and blood sample collection.[25,26] Serum creatinine concentration was determined in the same reference laboratory for all samples. GFR was calculated as an indicator of renal function with the MDRD-4 formula, $eGFR_{MDRD}$,[7] and the CKD-EPI formula, $eGFR_{CKD\text{-}EPI}$.[9] Participants were classified (eGFR categories: ≥90, 60–89, 45–59, 30–44, 15–29, <15mL/min/1.73m^2) according to the Kidney Disease Outcomes Quality Initiative guidelines.[27] Patients were asked to deliver a spot urine sample, and ACR was used as an expression of albumin excretion. Microalbuminuria was defined as ACR 20 to 200mg/g in men and 30 to 300mg/g in women, and macroalbuminuria was defined as ACR >200mg/g in men and >300mg/g in women.[28]

A new CKD classification system with four categories of eGFR (≥60, 45–59, 30–44, and 15–30 mL/min/1.73m^2) complemented by three categories of albuminuria (normoalbuminuria, microalbuminuria, and macroalbuminuria) was used for the description of low, moderate, and high risk of progression to kidney failure[23] and the relative risk for cardiovascular mortality.[24]

Statistical analyses

Baseline subject characteristics are expressed as the mean ±SD or as percentages. Age- and sex-adjusted eGFR levels are reported as percentages or medians and percentiles.

We cross-tabulated eGFR using clinically relevant categories (≥90, 60–89, 45–59, 30–44, 15–29, <15mL/min/1.73m^2) to evaluate the proportion of participants in each category of MDRD eGFR reclassified by the CKD-EPI equation eGFR. Generalized additive models (GAMs) (29) were used to evaluate the age and sex effect on eGFR categories, both $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$.

The main advantage of GAMs over traditional regression methods is that they do not impose a parametric form on the effects of continuous covariates on the response of interest. Instead, they assume only that these effects are additive and reasonably smooth. In this paper, penalized regression splines combined with thin plate splines as smoothers were used to estimate GAM regression models, and the estimation of the smoothing parameters was chosen automatically by means of a generalized cross validation criterion. A Bayesian approach to uncertainty estimation was used to obtain 95% confidence intervals for the estimated effects.[29] All statistical analyses were performed using R software, version 2.9.1; GAMs were fitted using the mgcv package.[30]

Ethical considerations

The Galician Ethical Committee for Clinical Research approved the study protocol. All participants provided informed consent.

RESULTS

The mean population age was 49.5 years, 52.6% (1445) were women, 25.8% (709) were 65 years old, and 16.6% (457) were 70 years old or older. Their clinical characteristics and lifestyles have been described previously (24), highlighting a regular consumption of alcohol (45.1%), smoking (25.5%), and physical inactivity (28.9%). The population has a high prevalence of dyslipidemia (29.3%), obesity (26.1%), and hypertension (24.1%), and 9.2% had a previous diagnosis of diabetes. Regarding previous cardiovascular events, peripheral vascular disease was the most frequent (10.8%), followed by ischemic heart disease (5.1%) and cerebrovascular disease (1.7%).

The prevalence of CKD stages 3 to 5 (eGFR <60mL/min/1.73m^2) in the general Spanish population was 6.8% with $eGFR_{MDRD}$ and 6.9% with $eGFR_{CKD\text{-}EPI}$; the prevalence of microalbuminuria/macroalbuminuria was 4.0%.

Population-weighted mean estimated GFR was higher when computed using the CKD-EPI equation (86.75mL/min/1.73m^2; 95% confidence interval [CI] 86.06, 87.44) compared to using the MDRD formula (84.64mL/min/1.73m^2; 95% CI 83.96, 85.31; p<0.0001). We also analysed groups by age and sex for eGFR variation between the two methods. The MDRD underestimated GFR values relative to CKD-EPI, but for people over age 60 years, eGFR results were similar and even slightly higher with MDRD (Figure 1).

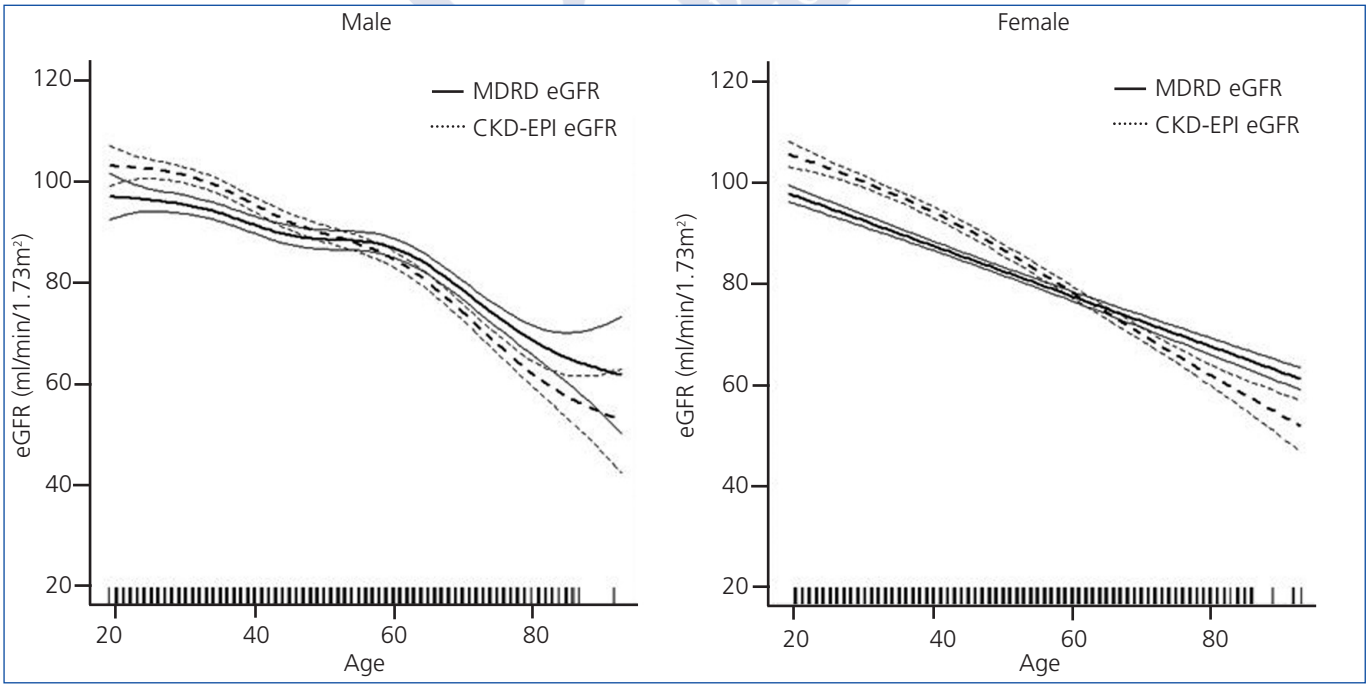

Figure 1. Distribution of estimated glomerular filtration rate (GFR) by age and sex. Differences by estimation equation in the EPIRCE Study.

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease. Estimation and confidence intervals of estimated glomerular filtration rate computed by CKD-EPI equation (solid lines) and by MDRD equation (dotted lines), for males (left) and females (right), respectively.

When we analysed the variation in eGFR categories as computed using CKD-EPI compared with MDRD, we found that 13.3% (365) of the population was reclassified to a higher eGFR category and 3.3% (92) was reclassified to a lower eGFR category (Table 1). Individuals reclassified to a lower category were older than those who were not reclassified (mean age 75.1±5.5 versus 49±17). When we analysed the subgroup of participants ages 65 years or older, we found that those reclassified to a lower category were older (75.5±5.1 vs. 72.6±5.2, p<0.001) and had more anaemia (6.1% vs. 1.6%, p=0.03), diabetes (41% vs. 23%, p=0.006) and a sedentary lifestyle (41% vs. 25%) compared to those who were not reclassified.

Table 2 shows the risk categories of progression to ESRD in the EPIRCE sample. The lower risk percentage was 11.7 with $eGFR_{MDRD}$ and 11.9 with $eGFR_{CKD\text{-}EPI}$; the moderate risk percentages were 1.1 and 1.4, respectively; and the high risk percentage was 0.1 with both eGFR equations. We also assessed the age- and sex-weighted percentages of low (12.3% vs. 12.6%), moderate (1.3% vs. 1.7%), and high risk (0.1%) of progression to ESRD in the general Spanish population based on eGFR with the MDRD and CKD-EPI equations, respectively.

When we analysed the risk of progression to ESRD by CKD stages using $eGFR_{CKD\text{-}EPI}$, we found that only 17.4% (15.0% with $eGFR_{MDRD}$) of participants in CKD stage 3 presented a moderate risk of progression to ESRD, compared with 66.7% (60.0% with $eGFR_{MDRD}$) in CKD stage 4 (Figure 2).

DISCUSSION

Using the stratification of risk of progression to ESRD given by Hallan et al.,[23,24,31] 12.6% of the Spanish population has a low risk of progression to ESRD while 1.7% has a moderate risk (with a hazard ratio [HR] of cardiovascular mortality between 2 and 3), and 0.1% a high risk (with a HR of cardiovascular mortality greater than 3). Although Hallan et al.'s proposal computed eGFR using the MDRD equation, recent studies have shown that CKD-EPI creatinine-based equation more accurately classifies individuals relative to risk for mortality and ESRD compared with MDRD, even after considering albuminuria.[32,33] We computed the risk stratification of ESRD in the EPIRCE population by using both equations and the results show a slight increase in low and moderate risk percentages with $eGFR_{CKD\text{-}EPI}$ (12.6% vs. 12.3% and 1.7% vs. 1.3%) and the same percentage of high risk (0.1%) in the Spanish adult population. In previous studies, estimated GFR and ACR were the major predictors of future kidney failure, and adding age, sex, diabetes, hypertension, and other potential risk factors did not improve prediction.[11,12,17] Risk stratification with a 12-category matrix (eGFR ≥60, 45–59, 30–44, and 15–29) subdivided by ACR into normoalbuminuria, microalbuminuria, and macroalbuminuria was more useful than the current CKD classification system.[23,24,31,34,35] On the other hand, patients with CKD stage 1–3 have a 25 to 100 times higher risk of developing a cardiovascular event or death than of progressing to ESRD,[5,36] presumably because of subclinical atherosclerosis and/or vascular injury from early microinflammation.[22]

Table 1. Reclassification across eGFR categories using the CKD-EPI equation from categories based on the MDRD equation: the EPIRCE study

		CKD-EPI Estimated GFR Categories						
		≥90	60-89	45-59	30-44	15-29	<15	Total
MDRD Estimated GFR Categories	≥90	870[c] (31.7)	50[b] (1.8)					920
	60-89	363[a] (12.9)	1272[c] (46.3)	29[b] (1.1)				1654
	45-59		11[a] (0.4)	116[c] (4.2)	11[b] (0.4)			138
	30-44			1[a] (0.03)	25[c] (0.9)	1[b] (0.03)		27
	15-29					5[c] (0.2)	1[b] (0.03)	6
	<15						1[c] (0.03)	1
	Total	1223	1333	146	36	6	2	2746

CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease. Values in each cell represent number (percent of overall) of subjects reclassified by CKD-EPI: [a]up; [b]down; [b] not reclassified.

Table 2. Distribution of risk of progression to kidney failure in EPIRCE study population.

		eGFR (MDRD)				
		≥60	45-59	30-45	15-29	Total
ACR	Normoalbuminuria	1955	**98**	**18**	**3**	2074
		(87.1)	**(4.4)**	**(0.8)**	**(0.1)**	(92.4)
	Microalbuminuria	**146**	**17**	**4**	**2**	169
		(6.5)	**(0.8)**	**(0.2)**	**(0.1)**	(7.5)
	Macroalbuminuria	**1**	**0**	**0**	**0**	1
		(0.5)				(0.05)
Total		2102	115	22	5	2244
		(93.7)	(5.1)	(1.0)	(0.2)	
		eGFR (CKD-EPI)				
		≥60	45-59	30-44	15-29	Total
ACR	Normoalbuminuria	1943	**101**	**26**	**4**	2074
		(86.6)	**(4.5)**	**(1.2)**	**(0.2)**	(92.4)
	Microalbuminuria	**140**	**22**	**5**	**2**	169
		(6.2)	**(1.0)**	**(0.2)**	**(0.1)**	(7.5)
	Macroalbuminuria	**1**	**0**	**0**	**0**	1
		(0.5)				(0.05)
Total		2084	123	31	6	2244
		(92.9)	(5.5)	(1.4)	(0.3)	

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease.ACR: albumin-to-creatinine ratio. Microalbuminuria was defined as ACR 20 to 200 mg/g in men and 30 to 300 mg/g in women, and macroalbuminuria was defined as ACR 200 mg/g in men and 300 mg/g in women. Values in each cell represent number (percent of overall). Shaded cells represent risk for progression of ESRD: low (blue); moderate (bold); high (red).

When CKD-EPI and MDRD estimation equations were compared in the current study, we found that MDRD underestimated GFR values relative to CKD-EPI, but over 60 years eGFR results were similar and even slightly higher with MDRD. The AUSDIAB study found that in Australians age >25 years, the reference population-weighted eGFR values were similar for the population age ≥65 years, regardless of which equation (MDRD or CKD-EPI) was used, but that the CKD-EPI equation yielded significantly higher reference values in younger age groups.[37] Carter et al, in the East Kent population, observed mean eGFR using CKD-EPI equation to be 11.2% higher than that estimated using the MDRD Study equation for individuals aged 40-49 years; this difference gradually diminished to 0.7% in the 70-79 years old; and in people older than 80 years, the MDRD equation gave a lower CKD prevalence than the CKD-EPI equation.[38] Kilbride et al. in European ancestry people older than 74 years found a mean lower eGFR using CKD-EPI equation than using MDRD equation (50.3 vs. 52.3mL/mn/1.73m^2).[39]

We analysed the variation in eGFR categories when computed using CKD-EPI compared with MDRD. We found that 13.3% (365 participants) were reclassified to a higher eGFR category and 3.3% (92 participants) were reclassified to a lower eGFR category. These results are quite similar to those found by the Chronic Kidney Disease Prognosis Consortium's recent meta-analysis of 25 studies of population cohorts[35] but with a higher percentage of people reclassified to a lower level (3.3% vs. 0.6%). Just as Matsushita et al. reported in that analysis,[35] in our population the individuals reclassified to a lower level were older than those who were not reclassified (mean age 75.1 versus 49 years in EPIRCE population; 77 vs. 49 years in the meta-analysis population). When we analysed the subgroup ages 65 years or older, we found that those reclassified to a lower level were older and had more anaemia and diabetes and sedentary lifestyles than those not reclassified.

We acknowledge limitations to our approach as well. The cross-sectional nature of the study does not allow to us to draw conclusions regarding causality between lower GFR and cardiovascular or progression to RRT risk. But considering the sample representativeness, known in Spanish population behaviour of different estimation equations and the consequences of risk stratification as the proposal can be of interest to clinicians and health policy makers.

Different studies have shown[36,40,41] that active disease management strategies can preserve kidney function and reduce

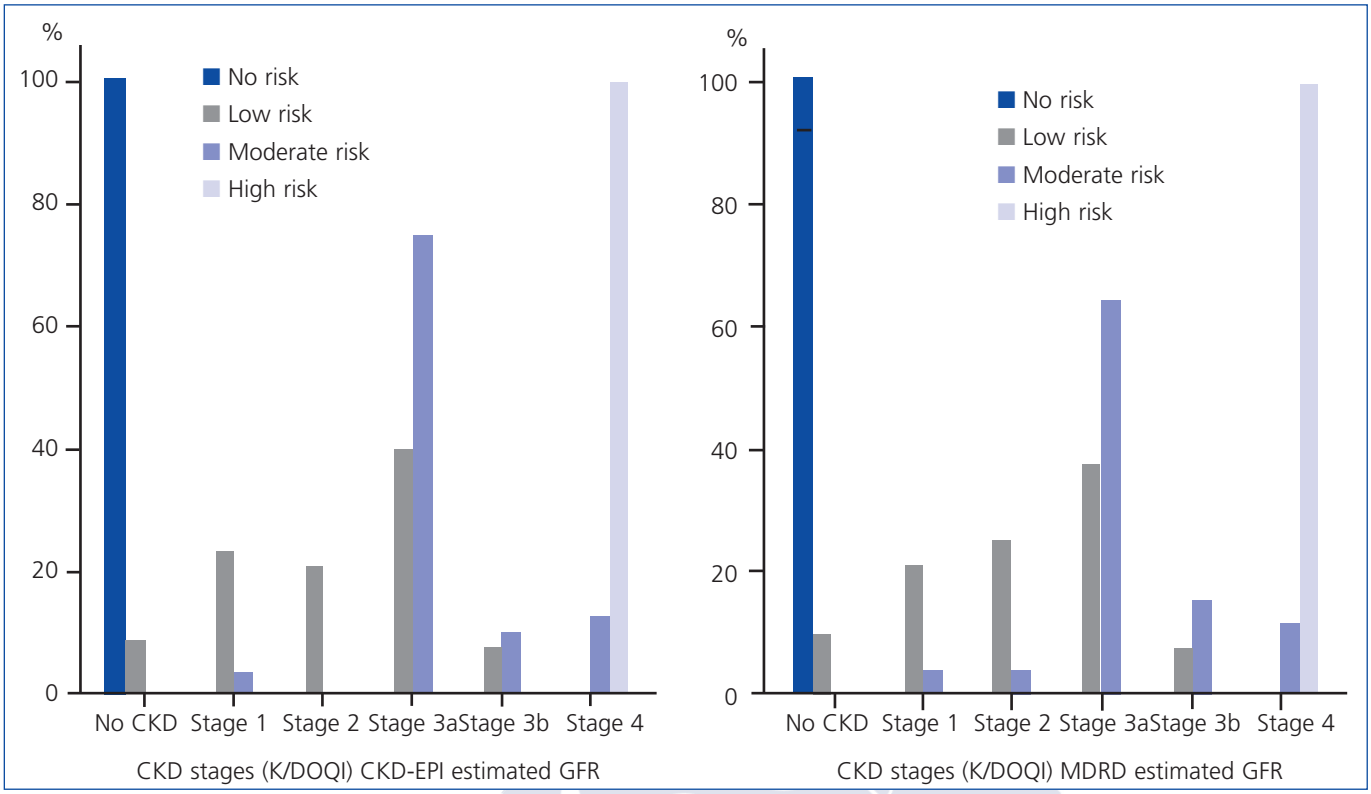

Figure 2. Risk of progression to ESRD categories by CKD stages using eGFR CKD-EPI (left) and eGFR MDRD (right); the EPIRCE Study. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease. Risk stratification of progression to ESRD categories: Hallan et al. proposal.[31] No risk category: eGFR ≥60 and normoalbuminuria. Low risk category: normoalbuminuria with eGFR 30–59 or microalbuminuria with eGFR ≥60. Moderate risk: normoalbuminuria with eGFR <30 or microalbuminuria with eGFR 30–59 or macroalbuminuria with eGFR ≥60. High risk: microalbuminuria with eGFR<30 or macroalbuminuria with eGFR 30–59.

CKD progression in CKD stage 3–5 patients Nevertheless, it remains unclear what the best clinically based criteria are that will result in more people benefiting from this approach. When considering the cost-effective use of health resources for the management of CKD, it is necessary to have instruments for selecting those patients in whom interventions are more efficient. A general practice and public health perspective favours the estimated GFR using the CKD-EPI equation.[42] One strategy to be developed jointly by nephrology and primary care clinicians[41,43,44] will be the establishment of consensus protocols to achieve this incorporation for the stratification of CKD patients. In the central area of Ourense, we have initiated a program for early detection of CKD and associated cardiovascular risk based on these criteria. Systematically, the primary care provider receives, together with $eGFR_{CKD\text{-}EPI}$, an estimated risk of progression to ESRD according to risk stratification using ACR and eGFR. It will be necessary to assess the medium-term effectiveness of this program.

In conclusion, the proportion of the Spanish population with a high risk for progression to ESRD is low, but 1.7% is at moderate risk. The use of an instrument of "Risk Stratification of CKD Progression" employing the formula CKD-EPI+ACR would allow appropriate management not only in the early diagnosis of CKD but also as a tool for cardiovascular risk stratification and as criteria for referral from primary care to nephrology patients at risk of progression.

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Conflicts of interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

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IX.2 Declaración de conflicto de intereses de los coautores.

Los coautores de los trabajos publicados que constituyen el cuerpo de la Tesis Doctoral declaran que no existe ningún conflicto de intereses relacionado con los manuscritos y autorizan la presentación de la presente Tesis Doctoral en la modalidad de compendio de publicaciones.

Así se hace constar en Santiago de Compostela a 30 de enero de 2013.

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