ULPGC
Universidad de
Las Palmas de
Gran Canaria

Doctorado en Investigación en Biomedicina

TESIS DOCTORAL:

Diagnóstico y caracterización de la diabetes en una población de Gran Canaria con hipercolesterolemia familiar heterocigota portadora de la variante genética p.(Tyr400_Phe402del) del gen *LDLR*

Ana María González Lleó

Las Palmas de Gran Canaria

2025

UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA (ULPGC)

ESCUELA DE DOCTORADO DE LA ULPGC

PROGRAMA DE DOCTORADO EN INVESTIGACIÓN EN BIOMEDICINA

Línea de investigación: Promoción de la salud y prevención y tratamiento de enfermedades prevalentes

Título:

Diagnóstico y caracterización de la diabetes en una población de Gran Canaria con hipercolesterolemia familiar heterocigota portadora de la variante genética p.(Tyr400_Phe402del) del gen *LDLR*

Memoria que, para optar al grado de Doctor por la Universidad de Las Palmas de Gran Canaria, presenta la licenciada

Ana María González Lleó

Dirigida por los Dres. Ana Mª Wägner, Mauro Boronat Cortés y Rosa María Sánchez Hernández

Los directores **La doctorando**

Las Palmas de Gran Canaria, 11 de Agosto de 2025

A mi familia

"¿no acaba de decirnos que la sabiduría humana se encierra toda ella en estas dos palabras?: ¡Confiar y esperar!"

Índice

Agradecimientos

Es difícil reflejar solo con palabras mi gratitud hacia todas y cada una de las personas que me han acompañado durante la elaboración de esta tesis doctoral y que, de una forma o de otra, la han hecho posible.

En este largo camino, mi familia siempre ha estado presente. Lo que soy y lo que he logrado en mi vida es sin ninguna duda, gracias a ellos.

A mi padre. Fuiste y serás siempre mi ejemplo de trabajo, constancia y responsabilidad. Aunque no has podido acompañarme en esta etapa, hago mía tu lección de ponerle "*corazón*" a la adversidad. Gracias.

A mi madre, mi pilar y mi faro en la oscuridad. Y con total seguridad, la persona que más ha "soportado" los vaivenes de esta tesis doctoral. Has estado siempre ahí para escuchar y ofrecer una palabra de ánimo cuando el horizonte se volvía gris. No tengo forma de expresar el infinito agradecimiento por todo lo que has hecho por mí. Este trabajo también es tuyo. Mil gracias.

A mi hermano. Por aguantarme los días buenos y los que no lo eran tanto. Por animarme a conseguir mis metas y facilitarme el camino para que no hubiera ningún impedimento que me impidiera conseguirlas. Me siento muy orgullosa de ti y de todo lo que has logrado.

A mis tíos Gustavo y Juan, mis referentes desde que era pequeña y presentes en cada uno de mis logros y fracasos. Gracias.

A mis abuelos. Origen de todo. Un beso al cielo.

A mi familia laboral.

Gracias infinitas a todo el servicio de Endocrinología y Nutrición del Hospital Insular de Gran Canaria. A todos mis compañeros: Javier, Antonio, Armando, Mauro, Mapi, Dunia, Yaiza López, Ana Wägner, Yaiza García, Nuria, María, Carlos, Sara, Rosa, Ana Sánchez, Carolina, Marta, Adriana, Fernando y Carmelo. Mi primera familia profesional. Gracias a todos. Por todos los momentos compartidos, por la paciencia al enseñarme y por permitirme formar parte de este gran equipo durante tantos años.

Y por supuesto, una mención muy especial a mis directores de tesis. Gracias por responder a incontables e-mails, leer infinitas versiones de los artículos y estar siempre dispuestos a proponer mejoras.

A Ana. Ideóloga y promotora primera de este trabajo. Por introducirme en el desconocido camino de la investigación. Eres mi referente como profesional e investigadora. Muchísimas gracias.

Gracias Mauro. Por tus oportunos comentarios, siempre acertados y constructivos. Por esas ideas y líneas de desarrollo que ni en mil vidas se me hubiesen ocurrido a mí.

A Rosa. Siempre ahí para cualquier duda, aunque fuera la más insignificante. Esta tesis es continuación de la tuya; gracias por permitirme formar parte de ella. Por tu generosidad a la hora de compartir tus conocimientos y por acompañarme en este nuevo mundo de la lipidología.

Quiero agradecer especialmente a Virginia, enfermera del servicio de Bioquímica durante el interminable período de las sobrecargas de glucosa. Apareciste en uno de esos

momentos de oscuridad que tiene cualquier tesis doctoral. Muchísimas gracias por implicarte en este proyecto desde el primer minuto sin casi conocerme de nada.

Gracias a todos mis compañeros del grupo de Diabetes y Endocrinología Aplicada del iUIBS, en especial a Yeray, Luisa y Roberto por ayudarme a sobrevivir en el laboratorio cuando la COVID nos dejó bajo mínimos.

Gracias a toda mi familia profesional actual.

A mis compañeros de la Unitat de Recerca en Lípids i Arteriosclerosi (URLA). Por la acogida, el cariño y la ayuda que he recibido desde que llegué. A Josep, Jimmy, Josefa, Ricardo, Montse, Yaiza, Roser, Eli, Pere, Dídac y Gemma. A mis compañeros de la Unitat de Medicina Vascular i del Metabolisme (UVASMET) del Hospital Sant Joan: Lluis, Nùria Plana, Daiana, Natalia, Nùria Amigo, Èrica, Cèlia y Lydia. *Moltes gràcies*.

Especial agradecimiento al profesor Masana. Por ser la llave de una nueva oportunidad y por confiar sin casi conocerme. Por la inmensa sabiduría que compartes con los demás. Gracias eternas Luis.

A Daiana. Por capitanear el barco contra viento y marea y permitirme formar parte de la tripulación. El aprendizaje a tu lado es diario. Muchísimas gracias.

No quiero finalizar sin agradecer de corazón a todos los pacientes que forman parte de mi tesis doctoral. Personas anónimas que de forma altruista (y probablemente sin saberlo) iluminan el camino hacia estos pequeños descubrimientos que, de forma conjunta, hacen grande a la ciencia.

Abreviaturas

ABCG5/G8: transportadores de casete de unión a ATP G5 y G8

AGL: ácidos grasos libres

ANGPTL3: angiopoyetina like-3

APOB: apolipoproteína B

APOE: apolipoproteína E

AUC: área bajo la curva

BIA: impedanciometría bioeléctrica

CAC: calcio de arterias coronarias

CEH: clamp euglucémico hiperinsulinémico

c-HDL: colesterol unido a lipoproteínas de alta densidad (HDL)

c-LDL: colesterol unido a lipoproteínas de baja densidad (LDL)

DEXA: absorciometría dual de rayos X

DLCN: Dutch Lipid Clinic Network

DM: diabetes mellitus

ECV: enfermedad cardiovascular

EMS: enfermedad metabólica sistémica

FRCV: factor de riesgo cardiovascular

GB: glucemia basal

GC: Gran Canaria

GLUT: transportadores de glucosa

HDL: lipoproteína de alta densidad

HF: hipercolesterolemia familiar

HFHe: hipercolesterolemia familiar heterocigota

HMGCR: 3-hidroxi-3-metil-glutaril-CoA reductasa

HOMA-β: Homeostatic Model Assessment of β-cell function (evaluación del modelo homeostático de la función de la célula β)

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance (evaluación del modelo homeostático de la resistencia a la insulina)

HTA: hipertensión arterial

IAM: infarto agudo de miocardio

IMT: grosor íntima-media carotídea

IMC: índice de masa corporal

iPCSK9: inhibidor de la proproteína convertasa subtilisina/kexina tipo 9

IR: insulin resistencia

IRS-1: sustrato 1 del receptor de insulina

MASLD: enfermedad hepática esteatósica asociada a disfunción metabólica

MLV: músculo liso vascular

MODY: Maturity Onset Diabetes of the Young (diabetes del adulto de inicio en la juventud)

mTOR: diana de la rapamicina en mamíferos

NF-kB: factor nuclear κB

NPC1L1: proteína Niemann-Pick C1-like 1

NOS: óxido nítrico sintasa

IVGTT : Test de tolerancia a la glucosa intravenosa

LDL: lipoproteína de baja densidad

LDLR: gen que codifica el receptor de la lipoproteína de baja densidad (LDL)

LDLRAP1: proteína adaptadora tipo 1 del receptor de LDL

LPL: lipoproteín lipasa

LRT: lipoproteínas ricas en triglicéridos

OGIS: índice de sensibilidad a la glucosa e insulina oral

PC: perímetro de cintura

PCSK9: proproteína convertasa subtilisina/kexina tipo 9

QUICKI: Quantitative Insulin Sensitivity Check Index (índice de sensibilidad a la insulina)

RCV: riesgo cardiovascular

RE: retículo endoplasmático

RI: receptor de la insulina

r-LDL: receptor de la lipoproteína de baja densidad (LDL)

VLDL: lipoproteína de muy baja densidad

SNP: polimorfismo de un solo nucleótido

SOG: sobrecarga oral de glucosa

TyG: índice triglicéridos/glucosa

Tablas y figuras

TABLAS

FIGURAS

Introducción

1. Hipercolesterolemia familiar

La hipercolesterolemia familiar heterocigota (HFHe) es una de las enfermedades monogénicas más prevalentes a nivel mundial, con una frecuencia estimada de 1 caso por cada 300 personas. Esta cifra es mayor en regiones de aislamiento geográfico[1] (Fig. 1). La HFHe se caracteriza por niveles elevados de colesterol LDL (c-LDL) desde la infancia y la presencia de estigmas cutáneos como xantomas, xantelasmas y/o arco corneal[2]. No obstante, los eventos cardiovasculares precoces, tales como el infarto agudo de miocardio (IAM), el accidente cerebrovascular y la enfermedad arterial periférica, son los principales determinantes que condicionarán el pronóstico de la enfermedad [2].

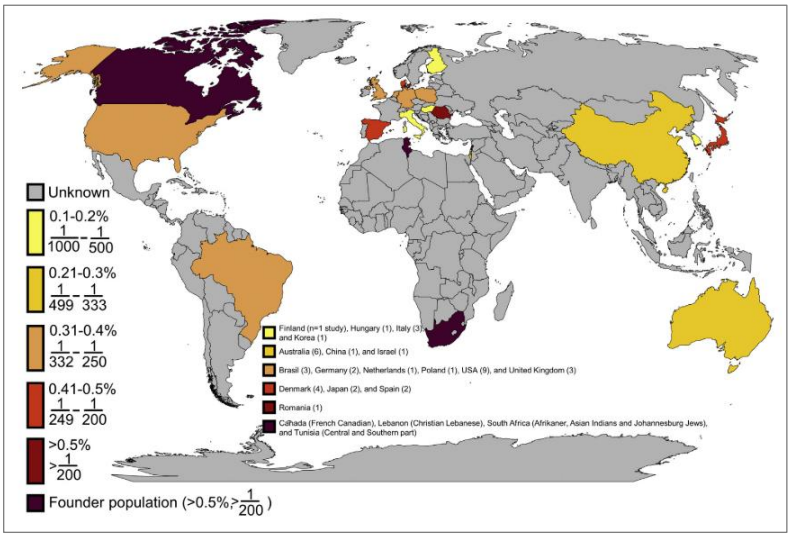


Figura 1. Prevalencia mundial de hipercolesterolemia familiar. Las poblaciones con efecto fundador concentran la mayor prevalencia[1].

La HFHe tiene una herencia autosómica co-dominante y está causada por variantes patogénicas en los alelos de algunos de los genes que regulan el metabolismo

del colesterol, principalmente el gen del receptor de LDL (*LDLR*), y en menor medida, los genes de la apolipoproteína B (*APOB*), de la proproteína convertasa subtilisina/kexina tipo 9 (*PCSK9*), la apolipoproteína E (*APOE*) y la proteína adaptadora tipo 1 del receptor de LDL *(LDLRAP1*), este último de herencia autosómica recesiva[3]. Una característica distintiva de esta enfermedad es su elevada heterogeneidad genética, lo que, junto con otros factores modificadores, origina una amplia variabilidad fenotípica, incluso dentro de una misma población[3,4]. Esta variabilidad puede explicarse por factores como el tipo de variante genética, la edad, el sexo o la presencia de comorbilidades, como la diabetes mellitus (DM)[5].

Aunque el diagnóstico definitivo de esta enfermedad se realiza mediante el análisis genético, es posible estimar la probabilidad de HFHe utilizando sistemas de puntuación como el Dutch Lipid Clinic Network (DLCN), que integra parámetros analíticos, antecedentes personales y familiares, exploración física y pruebas genéticas[6] (Tabla 1).

Criterios	Puntos
Antecedentes familiares	
Familiar de primer grado con enfermedad coronaria o vascular prematura conocida (hombres <55 años; mujeres <60 años), o familiar de primer grado con c-LDL >p95	1
Familiar de primer grado con xantomas tendinosos y/o arco corneal, o niños <18 años con c-LDL >p 95	2
Antecedentes personales	
Paciente con enfermedad arterial coronaria prematura (hombres <55 años; mujeres <60 años)	2
Paciente con enfermedad vascular cerebral o periférica prematura (hombres <55 años; mujeres <60 años)	1
Exploración física	
Xantomas tendinosos	6
Arco corneal antes de los 45 años	4
Niveles de c-LDL (sin tratamiento)	
c-LDL ≥ 325 mg/dL	8
c-LDL 251-325 mg/dL	5
c-LDL 191-250 mg/dL	3
c-LDL 155-190 mg/dL	1
Análisis genético	
Mutación funcional en los genes *LDLR*, *apoB* o *PCSK9*	8

Tabla 1. Criterios de la Dutch Lipid Clinic Network para el diagnóstico de hipercolesterolemia familiar[6].

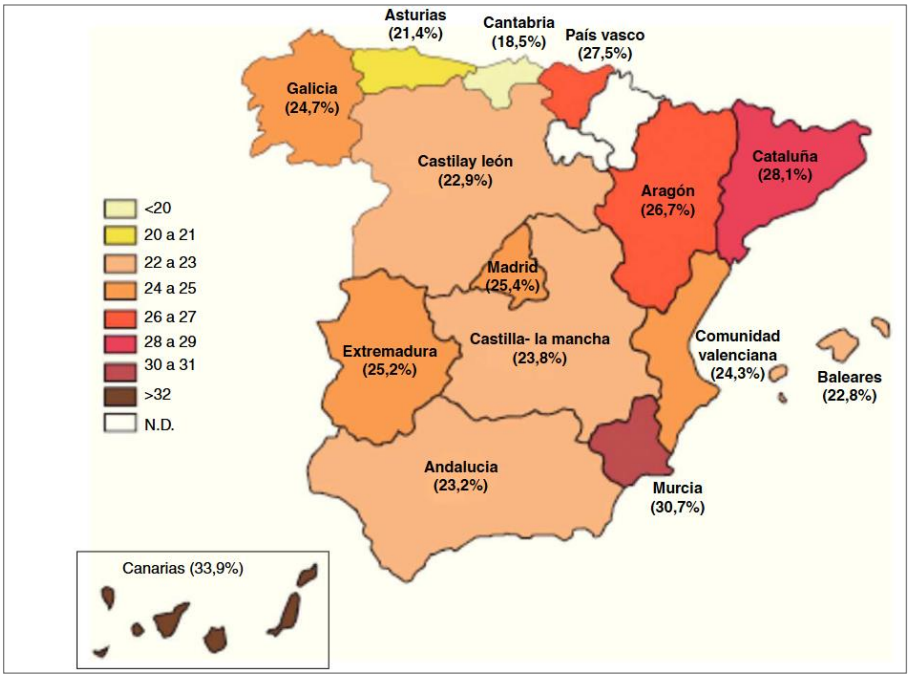
> 8 puntos: diagnóstico definitivo; 6-8 puntos: diagnóstico probable; 3-5 puntos: diagnóstico posible; <3 puntos: diagnóstico improbable.

1.1. Hipercolesterolemia familiar en Canarias

El Archipiélago Canario, compuesto por ocho islas, se sitúa en el océano Atlántico, a menos de 100 km de la costa africana y aproximadamente a de 1.000 km. de la Península Ibérica. Tras la conquista castellana del siglo XV, su ubicación geográfica

contribuyó al aislamiento poblacional prolongado hasta bien entrado el siglo XX. Esta situación redujo la variabilidad genética de sus habitantes, evidenciándose en la elevada frecuencia de determinadas enfermedades con respecto a otras regiones españolas [7-11]. Este fenómeno, asociado a la consanguinidad y elevada homogeneidad genética resultante se conoce como "efecto fundador".

Con más del 30% de su población afecta, Canarias presenta la mayor prevalencia de dislipemia de toda España[12] (Fig. 2), siendo a la vez la región con menor proporción de individuos que alcanzan los objetivos lipídicos recomendados[13].



<u>Figura 2.</u> Prevalencia de dislipidemia ajustada por edad, sexo e índice de masa corporal, por comunidades autónomas españolas [12].

Del total de dislipemias registradas, el 68,7% tenía diagnóstico de hipercolesterolemia pura, un 5,6% de hipertrigliceridemia y el 25,7% de hiperlipemia mixta.

Estudio HISPALIPID. Med Clin (Barc). 2006;127:331-4.

El primer estudio epidemiológico sobre hipercolesterolemia en Canarias fue publicado en 2019 por Sánchez-Hernández et. al[8]. en el que se realizó estudio genético a

una muestra de individuos de la isla de Gran Canaria que presentaban un c-LDL basal ≥220mg/dL y un DLCN ≥8. El 62% de los sujetos obtuvieron un diagnóstico genético positivo siendo el 68% portadores de la misma variante genética p.(Tyr400_Phe402del) en *LDLR*. Este hallazgo contrasta con los datos obtenidos del registro nacional SAFEHEART (Spanish Familial Hypercholesterolaemia Cohort Study), publicado en 2017, en el que la mayoría de las comunidades autónomas muestran prevalencias inferiores al 30% para una misma mutación (Tabla 2) y donde, a nivel nacional, ninguna variante genética individual en *LDLR* supera el 7% del total de mutaciones identificadas[4].

Comunidades autónomas	3 variantes más frecuentes	(%) (n)
Andalucía	c.1845+1G>C; p.Glu615fs*25 c.-135C>G: p.(?) c.1342C>T; p.(Gln448*)	11,5% (49) 8,4% (36) 6,8% (29)
Aragón	c.518del; p.(Cys173Serfs*33) c.91G>T; p.(Glu31*) c.2184del; p.(Arg728Serfs*2)	28,3% (15) 24,5% (13) 7,5% (4)
Asturias	c.1285G>A; p.(Val429Met) c.2548-?_2583+?del; p.(?) c.314-?_940+?del; p.(?)	24,2% (43) 15,7 (28) 11,8% (21)
País Vasco	c.[313+1G>C; 274C>G]; p.[(?); (Gln92Glu)] c.12G>A; p.(Trp4*) c.2399_2403delinsGGGT ; p.(Val800Glyfs*129)	22,4% (19) 8,2% (7) 4,7% (4)
Islas Baleares	c.[313+1G>C; 274C>G]; p.[(?); (Gln92Glu)] c.884del; p.(Val295Alafs*75) c.-135C>G: p.(?)	28,6% (4) 28,6% (4) 14,3% (2)
Islas Canarias	c.1690A>C + c.2397_2405; p.(Asn564His) + p.(Val800_Leu802del) c.1775G>A; p.(Gly592Glu) c.682G>A; p.(Glu288Lys)	42,9% (6) 21,4% (3) 14,3% (2)
Cantabria	c.1358+1G>A; p.(?) c.1359-1G>A; p.Thr454Leufs*51 c.1186+5G>A: p.G396fs∗26	25,0% (2) 25,0% (2) 25,0% (2)
Castilla y León	c.2389+4A>G; p.(?) c.953G>T; p.(Cys318Phe) c.1342C>T; p.(Gln448*)	18,4% (82) 8,7% (39) 7,8% (35)
Castilla La-Mancha	c.1342C>T; p.(Gln448*) c.530C>T; p.(Ser177Leu) c.[313+1G>C; 274C>G]; p.[(?); (Gln92Glu)]	17,8% (39) 14,6% (32) 11,9% (26)

Cataluña	c.1045del; p.(Gln349Serfs*21) c.1342C>T; p.(Gln448*) c.2390-1G>C; p.(?)	12,5% (37) 7,7% (23) 6,4% (19)
Extremadura	c.1342C>T; p.(Gln448*) c.-135C>G: p.(?) c.1690A>C + c.2397_2405; p.(Asn564His) + p.(Val800_Leu802del)	23,3% (40) 14,0% (24) 12,8% (22)
Galicia	c.10580G>A; p.(Arg3527Gln) – *APOB* gene c.1800G>C; p.(Glu600Asp) c.464G>A; p.(Cys155Tyr)	26,9% (50) 16,7% (31) 10,2% (19)
La Rioja	c.301G>A; p.(Glu101Lys) c.[313+1G>C; 274C>G]; p.[(?); (Gln92Glu)] c.1186+5G>A; p.G396fs∗26	30,9% (21) 18,0% (18) 8.8% (6)
Madrid	c.[313+1G>C; 274C>G]; p.[(?); (Gln92Glu)] c.1358+1G>A; p.(?) c.1342C>T; p.(Gln448*)	11,8% (42) 8,1% (29) 3,9% (14)
Murcia	c.460C>T; p.(Gln154*) c.12G>A; p.(Trp4*) c.1690A>C + c.2397_2405; p.(Asn564His) + p.(Val800_Leu802del)	33,3% (9) 22,2% (6) 14,8% (4)
Navarra	c.1342C>T; p.(Gln448*) c.283T>G; p.(Cys95Gly) c.1285G>A; p.(Val429Met)	20,0% (2) 20,0% (2) 20,0% (2)
Valencia	c.97C>T; p.(Gln33*) c.460C>T; p.(Gln154*) c.12G>A; p.(Trp4*)	46,6% (156) 25,4% (85) 7,2% (24)
Otros	c.313+2dupT; p.Leu64_Pro105delinsSer c.590G>A; p.(Cys197Tyr) c.-136C>G; p.(?)	10,4% (5) 10,4% (5) 8,3% (4)

Tabla 2. Variantes genéticas causantes de hipercolesterolemia familiar en España: representación de las 3 principales mutaciones para cada comunidad autónoma[4].

Adaptado de Bourbon M et al. Atherosclerosis. 2017 Jul;262:8-13.

Las características clínicas y bioquímicas de los pacientes con HFHe de la isla de Gran Canaria fueron en general, similares, con la excepción de una mayor prevalencia de diabetes mellitus tipo 2 (DM2) observada entre los portadores de la variante genética p.(Tyr400_Phe402del) del *LDLR*, en comparación con aquellos que presentaban otras mutaciones en el mismo gen (17,8 vs 0%; p=0,021)[8]. En una investigación posterior, se observó que la prevalencia de DM2 era incluso mayor, alcanzando el 25% [(vs 4,8% en portadores de otras variantes en el gen *LDLR*; (p=0,045)][14], sin diferencias en edad, sexo, índice de masa corporal (IMC) o perímetro de cintura (PC). Estos datos duplican la

prevalencia general de DM2 de la población canaria[15] y española[16,17] y cuadruplican la observada entre individuos con HFHe en España[18] (Fig. 3).

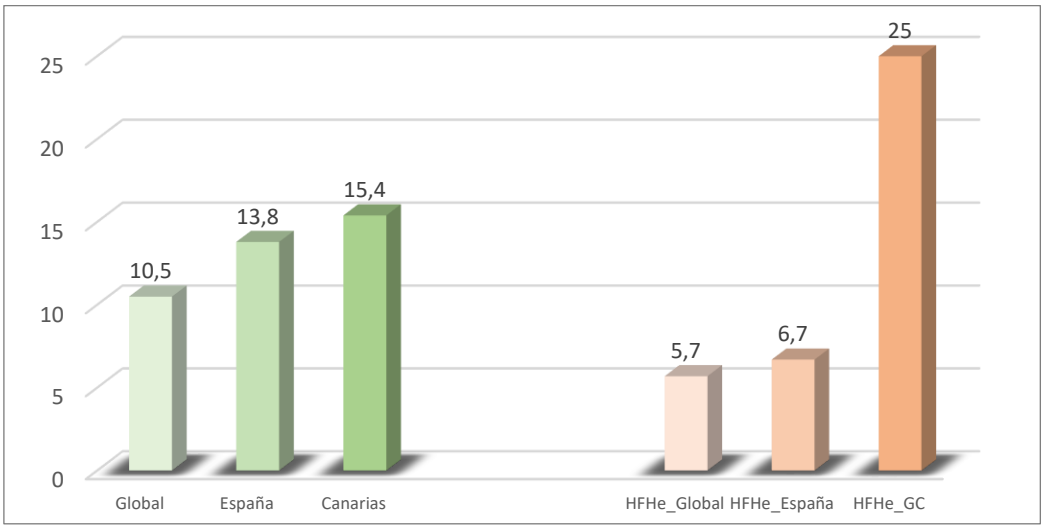


Figura 3. Prevalencia de Diabetes Mellitus, en población general (verde) y población con hipercolesterolemia familiar heterocigota (naranja) [15-18].

GC: Gran Canaria, portadores de la variante patogénica p.(Tyr400_Phe402del) en el gen LDLR

HFHe: hipercolesterolemia familiar heterocigota

En este estudio[14] se determinó que, comparado con HFHe portadores de otras mutaciones en *LDLR*, aquellos con la variante p.(Tyr400_Phe402del) tenían más antecedentes familiares de DM2 (51,5% vs 5%; p<0,001), niveles más elevados de c-LDL (299,7 +-74,8mg/dL vs 273,5 +- 42,2mg/dL ; p=0,048), y de triglicéridos al inicio del seguimiento [131 (91-184)mg/dL vs 100 (72-136)mg/dL; p=0,015] y un mayor uso de fármacos inhibidores de PCSK9 (51,5% vs 24%; p=0,027), probablemente en relación a una prevalencia superior, pero no significativa, de enfermedad cardiovascular (ECV).

1.2. Variante genética p.(Tyr400_Phe402del) del *LDLR*

Más del 90% de las variantes genéticas responsables de la HFHe se localizan en el gen *LDLR* que codifica el receptor de lipoproteínas de baja densidad (r-LDL), una glicoproteína transmembrana de 893 aminoácidos, cuya función principal es la captación e internalización de LDL, fundamentalmente en el hígado[3].

Localizado en el brazo corto del cromosoma 19 (19p13.2), hasta la fecha, se han descrito más de 2.000 variantes distintas en el gen *LDLR*, en las que se incluyen deleciones, inserciones, variantes de empalme (secuencias no codificantes), mutaciones sin sentido, etc[19]. El impacto fenotípico de estas variantes depende de la funcionalidad residual del r-LDL, lo que condiciona la gravedad de la alteración lipídica (Tabla 3)[4,19].

Clase 1	Ausencia de síntesis del r-LDL
Clase 2	Retención completa (A) o liberación deficiente (B) del r-LDL desde el RE (proteínas truncadas)
Clase 3	Defectos en la interacción r-LDL/LDL
Clase 4	Deficiencias en la internalización del complejo r-LDL/LDL (agrupación en fosas revestidas de clatrina defectuosa)
Clase 5	Reciclaje defectuoso del r-LDL (rápida degradación)
Clase 6	Dificultad del r-LDL para alcanzar la membrana basolateral (rápida degradación)

Tabla 3. Clasificación de las variantes genéticas del *LDLR*[22].
RE: retículo endoplasmático; r-LDL: receptor de LDL

La variante genética p.(Tyr400_Phe402del) en *LDLR* se origina por una deleción de 9 nucleótidos entre las posiciones 1199 a la 1207 (c.1199 1207delACCTCTTCT) (Fig. 4 y 5) que conlleva la pérdida de tres aminoácidos consecutivos -tirosina 400, serina 401 y fenilalanina 402- en la proteína codificada. Esta deleción da lugar a formas inmaduras de r-LDL que quedan retenidas en el RE (variante patogénica clase 2A). Como

consecuencia, se reduce su expresión en la superficie celular y con ello, la capacidad de captación de LDL[3,19,20] (Fig. 4).

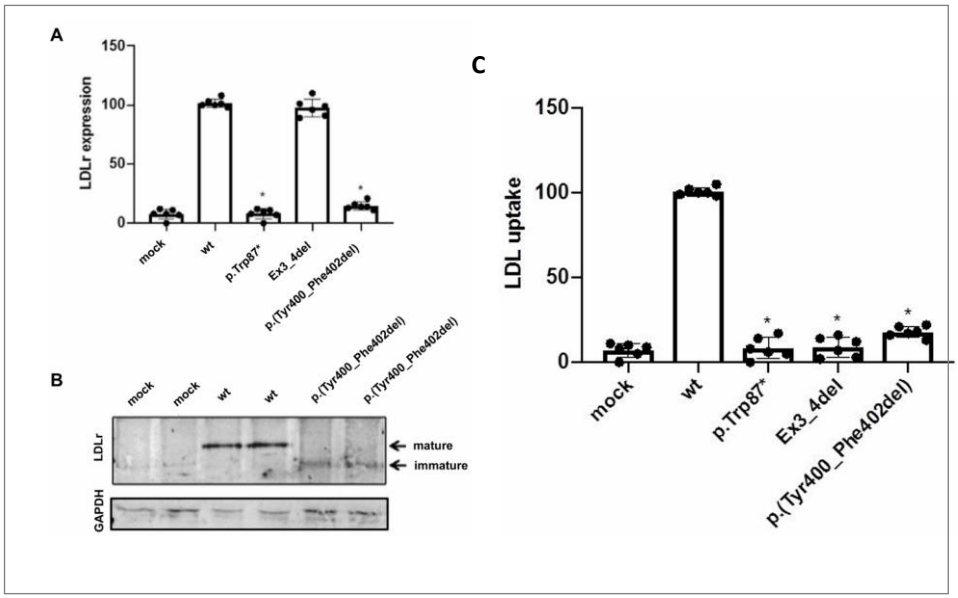


Figura 4. Estudios funcionales de la variante p.(Tyr400_Phe402del) *LDLR* [20].

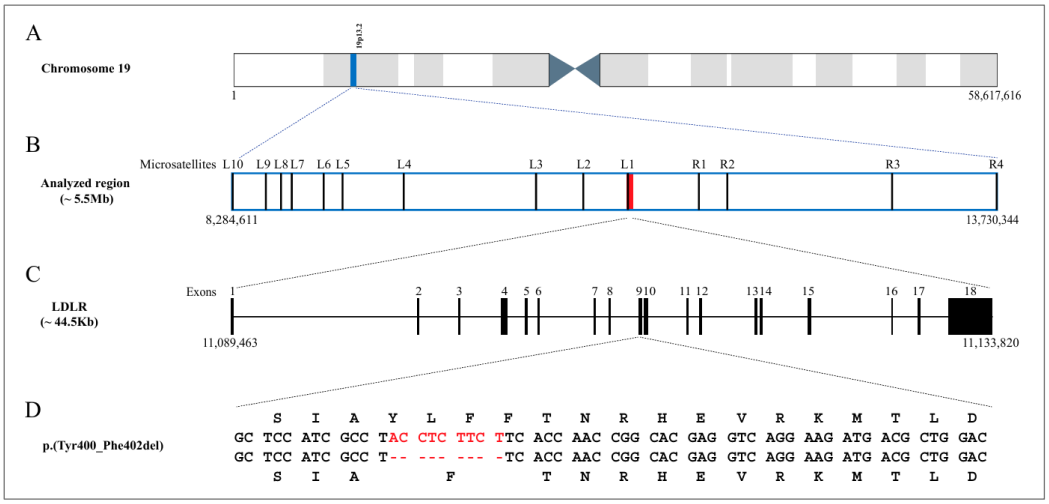
La **expresión** de la variante p.(Tyr400_Phe402del) del *LDLR*, evaluada mediante citometría de flujo (A), evidenció una menor presencia del r-LDL en la superficie celular respecto a las células wt. A las 48 horas tras la transfección, el análisis por Western Blot (B) detectó únicamente la forma inmadura de la proteína. En consecuencia, la **captación** del LDL, evaluada también por citometría de flujo (C), se encontró reducida.

LDLr: receptor de LDL; wt: células wild type; p.Trp87: variante de alelo nulo; Ex3_4del: variante LDLR clase 3; GADPH: gliceraldehído-3-fosfato deshidrogenasa.*

La variante p.(Tyr400_Phe402del) del *LDLR* conlleva la eliminación de un residuo de tirosina del dominio YWTD del polipéptido codificado por *LDLR*, una región altamente conservada y funcionalmente relevante en el reciclaje del r-LDL y su retorno a la membrana plasmática. Asimismo, la proximidad de esta deleción a la región de interacción con PCSK9 (proteína implicada en la degradación del r-LDL), sugiere la posibilidad de alteraciones estructurales que podrían afectar a la afinidad de la PCSK9[8,20].

Basándose en el análisis haplotípico de 14 microsatélites y bajo la hipótesis de un origen común, se ha estimado que esta variante surgió en la población canaria hace

aproximadamente 387 años (15,5 generaciones). Dado que no se ha documentado en otras regiones de España, la explicación más plausible es que se trate de una variante patogénica *de novo* originada entre los habitantes de la isla tras la colonización española[20] (Fig.5).



<u>Figura 5</u>. Ubicación genómica de la variante p.[Tyr400_Phe402del] del *LDLR* (en rojo) en el cromosoma 19 [20]. Cambios de aminoácidos consecuencia de la variante genética prevalente (D).

2. Diabetes Mellitus

La diabetes mellitus es un trastorno que se caracteriza por la aparición de hiperglucemia crónica, secundaria al déficit en la secreción y/o acción de la insulina. Se clasifica principalmente en DM tipo 1 (DM1), debida a la destrucción autoinmune de las células beta pancreáticas, y DM2, que aparece por resistencia progresiva a la insulina y disminución gradual de su secreción. Existen también formas menos frecuentes, como la diabetes gestacional, la secundaria a tratamientos farmacológicos (corticoides, antipsicóticos o estrógenos) y las formas monogénicas de herencia autosómica dominante, como la diabetes tipo MODY ("*Maturity Onset Diabetes of the Young*"). El

enfoque terapéutico varía según el tipo de diabetes, lo que subraya la importancia de una clasificación precisa en el manejo adecuado de la enfermedad[21].

La DM2 es la forma más prevalente de diabetes, representando más del 90% de los casos y en su desarrollo están implicados factores genéticos y ambientales[22]. Se han identificado más de 70 genes asociados y numerosos polimorfismos de nucleótido simple (SNPs) en más de 400 regiones genéticas diferentes[23]. Sin embargo, el efecto de cada SNP aislado es relativamente pequeño. Es el efecto acumulativo de múltiples SNPs, junto con factores como la edad, la dieta, la actividad física y, especialmente, el peso corporal, lo que probablemente determina la aparición de la enfermedad[23].

La DM2 incrementa el riesgo de ECV entre dos y cuatro veces en comparación con la población general, sobre todo en forma de IAM[24]. En Canarias, tanto la prevalencia como la morbimortalidad asociada a las complicaciones de la DM2 es superior a la media nacional (Fig. 6), especialmente en cuanto a aparición de IAM, necesidad de hemodiálisis y amputaciones de extremidades[15,17,25-27]. Aunque las causas de estas diferencias no han sido claramente identificadas, se postula que la elevada frecuencia de síndrome metabólico y obesidad junto con otros determinantes sociales como el bajo nivel educativo, limitados recursos económicos así como factores ambientales y genéticos, podrían desempeñar un papel relevante[28,29]. Además, algunos estudios realizados en población canaria muestran hábitos dietéticos poco saludables[30] y baja adherencia terapéutica, lo que podría contribuir a la peor evolución clínica[31] (Fig. 7 y 8).

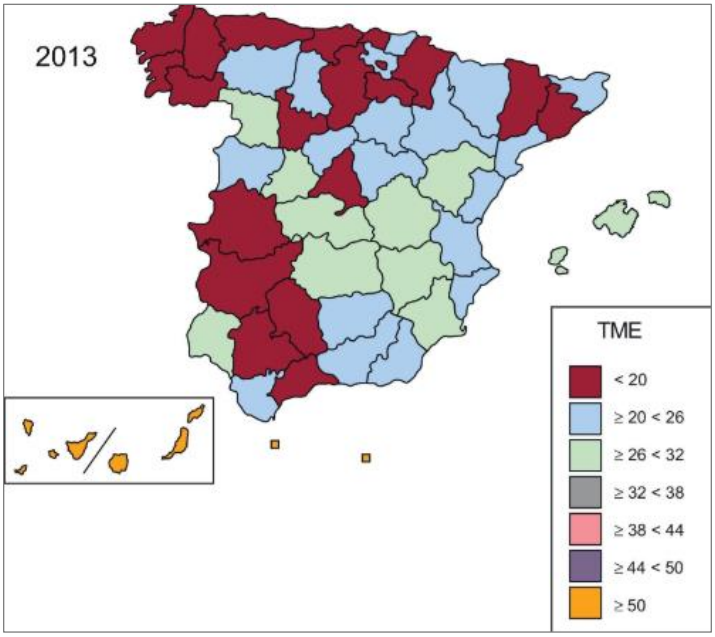
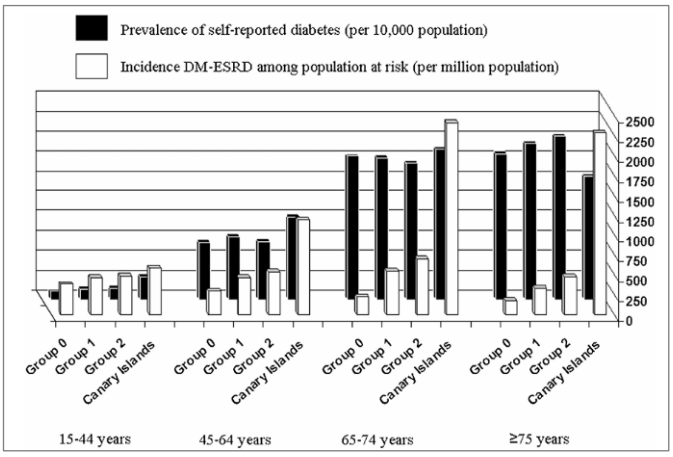


Figura 6. Tasa de mortalidad estandarizada por diabetes mellitus en España y distribución por provincias. Periodo 1998-2013.

TNE: tasa de mortalidad estandarizada[25].



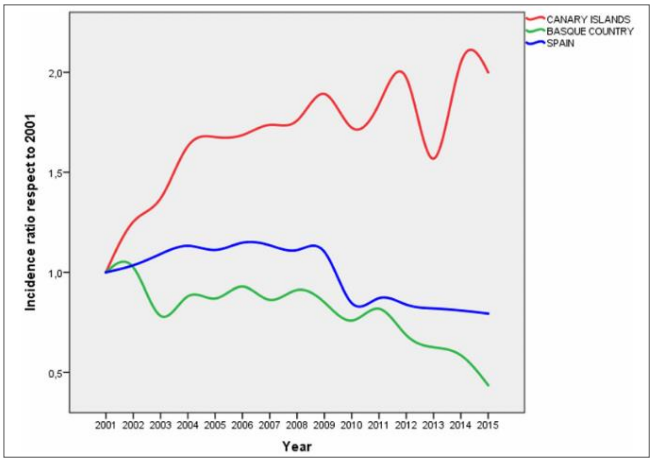


Figura 7. Incidencia de enfermedad renal terminal relacionada con la diabetes mellitus por grupo de edad y grupos de comunidades autónomas españolas (año 2006)[9].

DM: diabetes mellitus

Figura 8. Tasa de incidencia de amputación mayor en pacientes con diabetes mellitus tipo 2 en España, Canarias y País Vasco. Período 2001-2015[10].

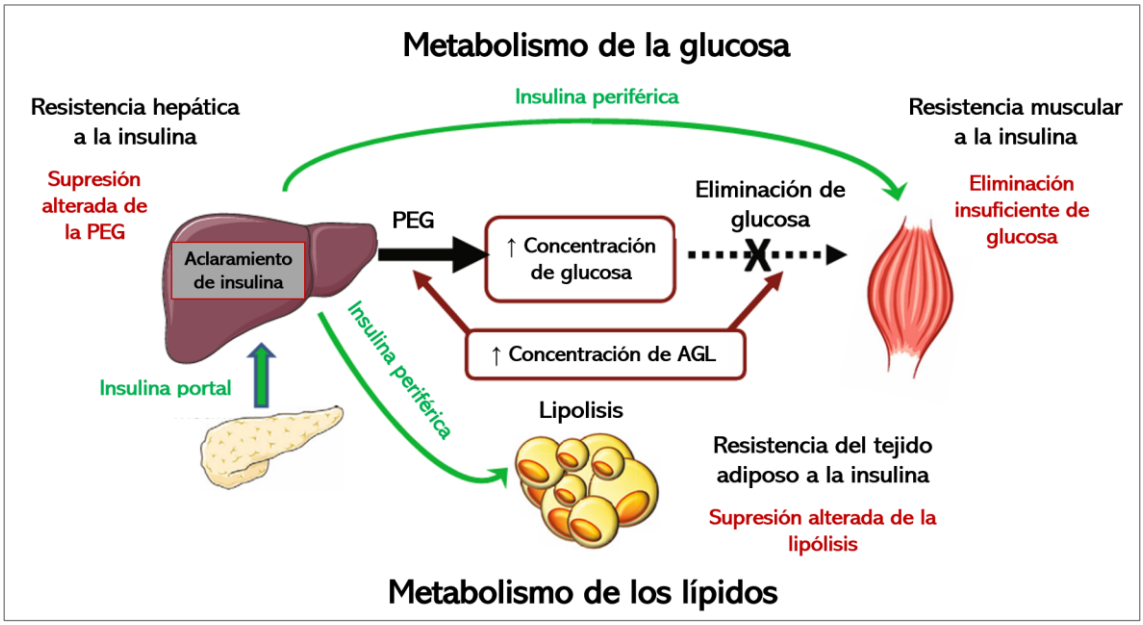
La duración de la enfermedad y el control glucémico son factores clave en el pronóstico, aunque la presencia simultánea de otros factores de riesgo cardiovasculares

(FRCV), como el tabaco, la hipertensión (HTA) o la hipercolesterolemia, acelera el daño endotelial, favorece la arteriosclerosis y contribuye a la aparición precoz de ECV[32,33].

En pacientes con HFHe, la DM2 es un FRCV independiente que duplica el riesgo de desarrollar la ECV[34,35], de forma que el riesgo cardiovascular (RCV) de aquellos individuos en quienes coexisten la HFHe y la DM2 es comparable al de pacientes sin HFHe pero con ECV establecida[36].

2.1. Evaluación de la resistencia a la insulina

La insulina es una hormona peptídica secretada por las células β pancreáticas que participa en la regulación de la homeostasis glucémica, lipídica y proteica. Tras su liberación a la vena porta, aproximadamente entre el 60 y 70% se degrada en el hígado, lo que limita su disponibilidad periférica a cerca del 40% del total. A nivel hepático, inhibe la gluconeogénesis y estimula la síntesis de glucógeno; en el músculo esquelético, favorece la captación de glucosa y la glicólisis, mientras que a nivel del tejido adiposo, reduce la lipólisis y la liberación de ácidos grasos libres, al tiempo que potencia la formación de triglicéridos[37].

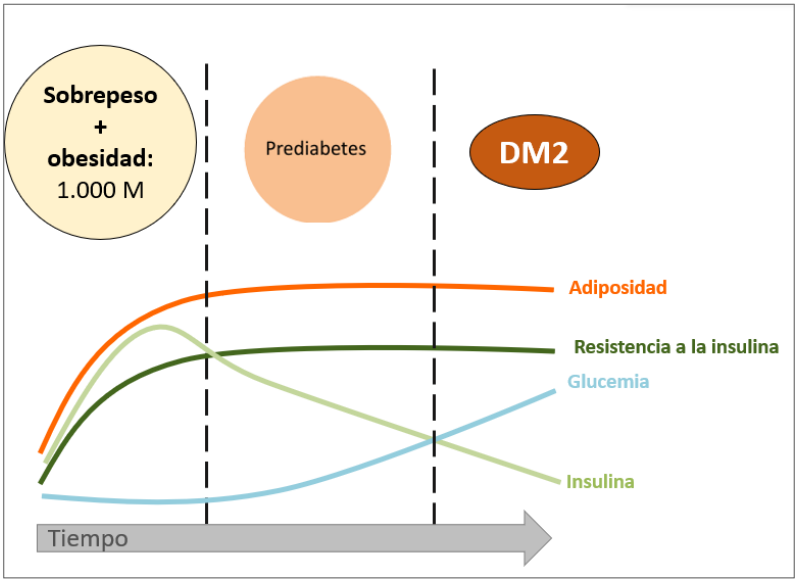


<u>Figura 9</u>. Fisiopatología de la resistencia a la insulina[37]. La resistencia a la insulina altera su acción en múltiples tejidos: en el hígado, se traduce en un aumento de la producción endógena de glucosa; en el músculo, se reduce su captación periférica; y en el tejido adiposo, la inhibición incompleta de la lipólisis conduce a una mayor liberación de ácidos grasos libres a la circulación.

PEG: producción endógena de glucosa; AGL: ácidos grasos libres

Adaptado de: Gastaldelli A. Obesity. 2022;30:1549–63.

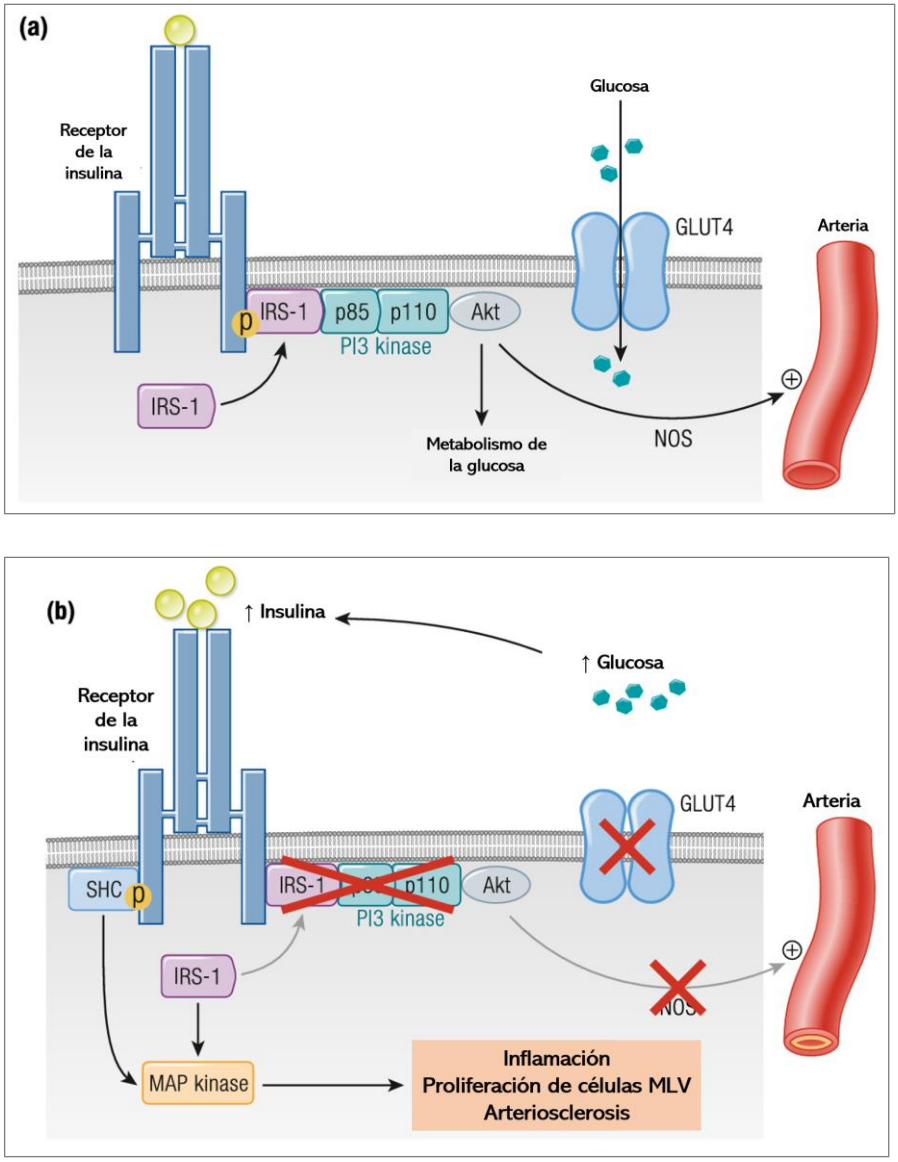
La resistencia a la insulina se define como una disminución de la eficacia biológica de esta hormona en sus tejidos diana (Fig.9). Esto conduce a una menor captación periférica de glucosa, un incremento de la gluconeogénesis hepática y una activación de la lipólisis del tejido adiposo, lo que se traduce en hiperglucemia e hiperlipidemia (Fig. 9 y 10)[38].



<u>Figura 10.</u> Evolución fisiopatológica y clínica de la resistencia a la insulina[38]. El incremento de la resistencia a la insulina asociado al exceso de tejido adiposo induce hiperinsulinemia compensatoria, que contribuye al deterioro progresivo de la célula β pancreática y la reducción progresiva en los niveles de la hormona. En ausencia de intervención, las alteraciones glucémicas más leves (pre-diabetes) progresarán a DM2.

Adaptado de: Page MM et al. Trends Endocrinol Metab. 2018 Jun;29(6):389-399

Además de los efectos sobre el metabolismo de la glucosa (Fig.10), la resistencia a la insulina se ha relacionado con un mayor riesgo de HTA y aterogénesis, por incremento del tono vasoconstrictor mediado por el desequilibrio en la vía del óxido nítrico y la elevación de los niveles de endotelina (Fig.11). Además, la hiperinsulinemia mantenida actúa como factor de crecimiento, promoviendo la proliferación y diferenciación de células musculares lisas vasculares, así como la activación de vías inflamatorias como la mediada por NF-kB[39].



<u>Figura 11</u>. Señalización normal (a) y fisiopatología de la resistencia a la insulina (b)[39]. La señalización de la insulina se ve afectada a nivel de IRS-1, que reduce el transporte, fosforilación y metabolismo de la glucosa, así como una alteración de la activación de la NOS y disfunción endotelial. La hiperinsulinemia compensatoria provoca una estimulación excesiva de la vía MAPK (que mantiene la sensibilidad a la insulina) lo que genera inflamación, proliferación de células musculares lisas vasculares y aterogénesis.

NOS: óxido nítrico sintasa; IRS-1: sustrato 1 del receptor de insulina; MLV: músculo liso vascular

Adaptado de: di Pino A. et al. Endocr Rev. 2019;40(5):1447–67

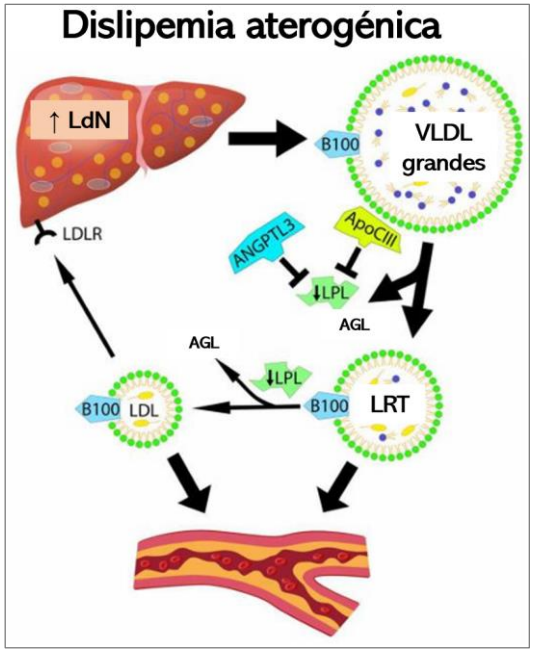
La resistencia a la insulina constituye uno de los ejes fisiopatológicos comunes en el desarrollo de diversas alteraciones cardiometabólicas, fenómeno conocido como *enfermedad metabólica sistémica* (EMS)[40]. Este trastorno se caracteriza por la disrupción

de la homeostasis entre distintos órganos -principalmente tejido hepático, adiposo y muscular- y tiene su origen en la combinación de factores genéticos, étnicos y, de forma destacada, en la obesidad[40].

Se estima que aproximadamente el 58% de la población adulta presenta EMS, que puede manifestarse de forma precoz como pre-DM, sobrepeso, hipertensión arterial, enfermedad hepática esteatósica asociada a disfunción metabólica (MASLD por sus siglas en inglés) o la característica dislipemia aterogénica[40]. Ésta última está estrechamente vinculada a la resistencia a la insulina y se caracteriza por un aumento de las lipoproteínas ricas en triglicéridos (LRT), una mayor proporción de partículas pequeñas y densas de LDL -más susceptibles a la oxidación- y una reducción de las concentraciones de c-HDL (Fig.12)[41]. Sucesivos estudios han demostrado que el potencial aterogénico de las LRT podría ser incluso superior al de las LDL, lo que contribuiría a explicar el riesgo cardiovascular residual observado en algunos pacientes a pesar de un óptimo control del c-LDL[40,41].

En ausencia de intervención, la EMS progresa hacia DM2, fibrosis hepática, disfunción diastólica y enfermedad renal. Además, la coexistencia prolongada de la dislipemia aterogénica junto con los múltiples FRCV de carácter pro-inflamatorio favorece el daño vascular, promoviendo la aparición de arteriosclerosis subclínica -evidenciada por el incremento del grosor íntima-media carotídeo (IMT) y del calcio coronario (CAC)-, lo que se traduce tanto en un aumento tanto del riesgo de ECV como de mortalidad global por cualquier causa [39-41].

.



<u>Figura 12</u>. Dislipemia aterogénica [39]. La resistencia a la insulina induce una alteración significativa del perfil lipídico: el tejido adiposo incrementa la liberación de ácidos grasos libres, mientras que en el hígado se aumenta la lipogénesis de novo y la secreción de lipoproteínas de muy baja densidad (VLDL), de mayor tamaño y mayor contenido de triglicéridos. Además, se observa una reducción en la captación de LDL y una disminución en la actividad de la lipoproteína lipasa (LPL).

LdN: lipogénesis "de novo"; VLDL: lipoproteínas de muy baja densidad; LRT: lipoproteínas ricas en triglicéridos; LDL: lipoproteínas de baja densidad; LDLR: receptor de LDL; LPL: lipoproteín lipasa; AGL: ácidos grasos libres; ANGPTL3: angiopoyetina like-3

Dada la implicación central de la resistencia a la insulina en la fisiopatología de diversas entidades cardiometabólicas así como su estrecha asociación con el desarrollo y progresión de la ECV, su detección y cuantificación adquieren un valor clínico fundamental. Evaluarla de forma adecuada permite no solo identificar a pacientes en riesgo, sino también estimar su evolución pronóstica y orientar intervenciones terapéuticas tempranas[40,41]. La tabla 4 presenta un resumen de las principales herramientas disponibles para su evaluación.

Método	Descripción	Ventajas	Inconvenientes
CLAMP EUGLUCÉMICO-HIPERINSULINÉMICO (CEH)	-Mide la *tasa de utilización de glucosa en tejidos periféricos* (músculo) mediante la perfusión intravenosa de glucosa e insulina.	- Técnica de referencia. -Alta precisión y especificidad.	- Método complejo y costoso (equipamiento especializado, personal entrenado). -Riesgo de hipoglucemia. -Poco práctico para uso clínico.
ÍNDICES DERIVADOS DE LA SOBRECARGA ORAL DE GLUCOSA (SOG) MATSUDA, OGIS, STUMVOLL	-Medición seriada de glucosa e insulina en sangre tras administrar una carga oral de glucosa (2-5 muestras). -Evalúa de forma indirecta la *respuesta glucémica e insulínica postprandial*.	- Poco invasiva y accesible en consulta. - Buena correlación con el CEH. - Detección precoz de alteraciones en el metabolismo de la glucosa.	-Menor precisión. -Variabilidad interindividual (absorción y respuesta). - Múltiples extracciones de sangre. - Modelos matemáticos -No mide directamente la sensibilidad a la insulina en tejidos.
ÍNDICES DERIVADOS DE MUESTRAS EN AYUNAS HOMA-IR, HOMA-β, QUICKI, TyG	-*Estimación indirecta* de la resistencia insulínica mediante valores de *glucosa e insulina plasmática en ayunas.*	-Poco invasivo (1 muestra). -Económico, rápido y accesible en consulta. -Marcador temprano de resistencia hepática a la insulina. -Útil en estudios poblacionales.	-Menos correlación con el CEH. -Variabilidad según estado metabólico.

Tabla 4. Métodos para la evaluación de la resistencia a la insulina.

CEH: clamp euglucémico-hiperinsulinémico; TyG: triglicéridos/glucosa

2.1.1. Clamp euglucémico hiperinsulinémico (CEH)

El clamp euglucémico hiperinsulinémico es el gold estándar para evaluar la resistencia a la insulina. Esta técnica cuantifica la cantidad de glucosa metabolizada por unidad de concentración plasmática de insulina, siendo la prueba más precisa para valorar la sensibilidad a la insulina a nivel muscular en humanos.

El procedimiento consiste en una infusión de insulina a una velocidad de 40mU/m^2/min (o superiores en pacientes con resistencia a la insulina conocida), con el objetivo de reducir la gluconeogénesis (principalmente, hepática) y estimular la captación periférica de glucosa. De forma simultánea, se administra una perfusión ajustable de

glucosa para mantener una concentración plasmática estable cercana a 100 mg/dL. (Fig.13). Cuando se alcanza un estado estacionario, la tasa de infusión de glucosa equivale a la de su eliminación (captación periférica por el músculo)[37].

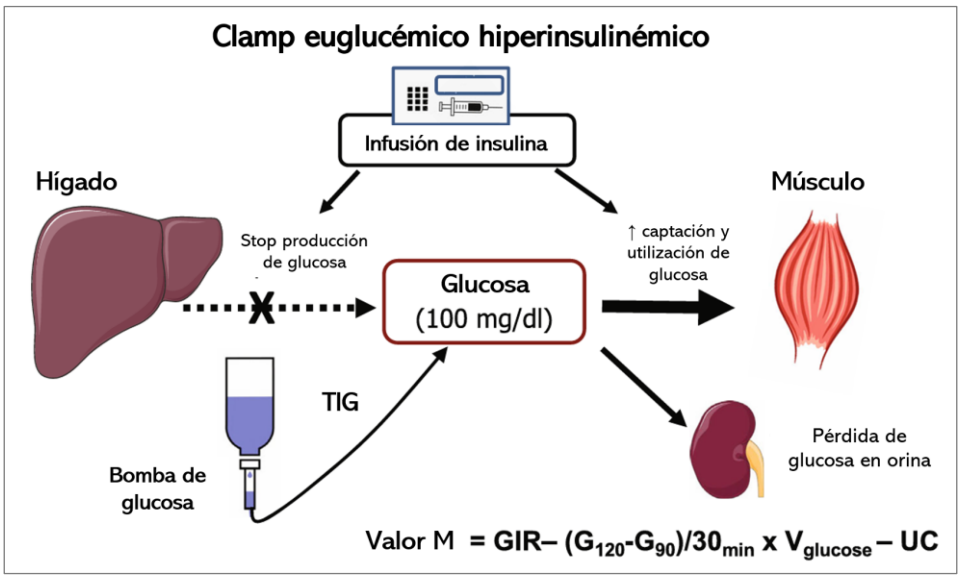


Figura 13. Clamp euglucémico hiperinsulinémico [37]. La perfusión de insulina suprime la producción endógena de glucosa (hepática) y favorece la captación periférica (muscular). La sensibilidad a la insulina se mide como "valor M" descrito en la fórmula.

TIG: tasa de infusión de glucosa (mg/kg/min); G: concentración de glucosa a los 90 y 120min (mg/dL); V:volumen de distribución de la glucosa (generalmente, 2,5dL/kg); UC: factor de corrección por pérdidas urinarias de glucosa.

Pese a su alta precisión y valor diagnóstico, se trata de una prueba técnicamente compleja que precisa de determinaciones sanguíneas frecuentes, requiere de personal entrenado y una infraestructura hospitalaria especializada con equipamiento específico (bombas de perfusión de glucosa, insulina y suero, glucómetro, monitorización, etc). Entre sus limitaciones se incluye el riesgo de hipoglucemia, la necesidad de suprimir completamente la producción endógena de glucosa lo cual exige mayores dosis de insulina en sujetos con resistencia significativa la posibilidad de interferencias en la interpretación por variaciones en las tasas de perfusión de glucosa para mantener

euglucemia o en los métodos analíticos empleados entre distintos centros para medir glucosa e insulina[37].

2.1.2. Test de tolerancia a la glucosa intravenosa (IVGTT)

El IVGTT permite evaluar la sensibilidad a la insulina mediante la administración en bolo de glucosa (0,3g/kg) y la posterior monitorización seriada de las concentraciones plasmáticas de glucosa e insulina, en intervalos frecuentes, hasta que la glucemia retorne a los niveles basales. Dado que el descenso de la glucosa puede ser más lento en sujetos con resistencia a la insulina, a los 20 minutos se administra tolbutamida (que actúa como secretagogo) o insulina, con el fin de acelerar la reducción glucémica.

Aunque representa una alternativa más sencilla al CEH, esta prueba presenta una duración prolongada (aproximadamente tres horas), requiere un elevado número de extracciones (en los tiempos 0, 3, 4, 5, 6, 8, 10, 14, 19, 22, 27, 30, 35, 40, 50, 70, 100, 140 y 180 minutos) y precisa de un análisis matemático final para la interpretación de los resultados. A pesar de estas limitaciones, ha demostrado una buena correlación con los valores obtenidos mediante CEH[37].

2.1.3. Pruebas alternativas para evaluar la resistencia a la insulina

Tanto el CEH como la IVGTT son métodos técnicamente complejos y de larga duración, que requieren infusión intravenosa y múltiples extracciones seriadas de sangre. Estas características los hacen inapropiados para su uso en población general, y poco viables fuera del ámbito de investigación, lo que limita su aplicabilidad en la práctica clínica habitual.

Como alternativas, se han desarrollado técnicas indirectas más económicas y accesibles para estimar la resistencia y la sensibilidad a la insulina. Estos métodos se

basan en pruebas dinámicas, como la sobrecarga oral de glucosa, o en determinaciones basales de glucosa e insulina. Aunque menos precisos, han mostrado buena correlación con las pruebas de referencia y resultan especialmente útiles tanto en la práctica clínica como en estudios epidemiológicos.

Un aspecto importante a considerar a la hora de interpretar estos índices es la variabilidad entre laboratorios, especialmente en las determinaciones de insulina, cuyas discrepancias pueden alcanzar hasta un 25%.

Índices derivados de la sobrecarga oral de glucosa (SOG)

Los índices dinámicos se basan en modelos matemáticos que describen la respuesta de la insulina y la glucosa en distintos momentos antes y después de la administración de una sobrecarga oral de glucosa de 75 gramos (SOG)[42]. La cantidad de determinaciones sanguíneas necesarias varía entre dos (a los 0 y 120 minutos) y cinco (0, 30, 60, 90 y 120 minutos), en función del índice empleado[37,42].

La mayoría de los estudios indican que estos índices presentan una mayor correlación con los métodos de referencia para la evaluación de la resistencia a la insulina, en comparación con los obtenidos exclusivamente a partir de medidas aisladas en ayunas. Esto se debe a que la SOG permite identificar alteraciones tempranas en la homeostasis glucémica que pueden no detectarse mediante datos basales[42]. Sin embargo, su utilidad puede verse limitada por la baja reproducibilidad, consecuencia de la elevada variabilidad intraindividual en la respuesta a la carga de glucosa.

En este contexto, la respuesta glucémica inicial se asocia principalmente con la insulino-resistencia (IR) hepática, mientras que la fase tardía refleja principalmente la IR periférica, especialmente en el músculo esquelético[37,42]. Entre los índices derivados de la SOG (Tabla 5), los que han mostrado mayor correlación con la CEH son el índice de

Matsuda, el índice de sensibilidad a la glucosa e insulina oral (OGIS) y el índice de Stumvoll, todos ellos validados en distintas poblaciones[37].

Index	Metabolic state	Condition (units)	Formula	Cutoff for IR	Duration	Number of samples	Validation (*R* value)
EHC	Fasting	Sensitivity (μmol kg_{FFM}^{-1} min^{-1})	$M = GIR - [G_{120\ mg/dL} - G_{90\ mg/dL}]/30_{min} \times V_{glucose\ dL/kg} - UC$	< 28	2 h	15–20	
EHC	Fasting	Sensitivity (μmol kg_{FFM}^{-1} min^{-1} pM^{-1})	M/I	< 0.08	2 h	15–20	
IVGTT	Fasting	Sensitivity (min^{-1}·pM)	SI (from minimal model)	< 0.000107 for log(SI)	3 h	20	$R = 0.89$, $p < 0.001$ vs. EHC
OGIS	OGTT or MMT	Sensitivity mL/kg/min (or $mL/m^2/min$)	f (G_0, G_{90}, G_{120}, I_0, I_{90}, D)[a]	<9.8 (or <390)	2–3 h (OGTT) or 4-6 h (MMT)	3	$R = 0.77$, $p < 0.0001$ vs. EHC
ISI Matsuda	OGTT or MMT	Sensitivity	$10^4/\sqrt{[(G_{0\ mg/dL} \times I_{0\ mU/mL}) \times (G_{mean} \times I_{mean})]}$	<4.3	2-3 h (OGTT) or 4-6 h (MMT)	3–5	$R = 0.73$, $p < 0.0001$ vs. EHC
ISI Stumvoll	OGTT	Sensitivity (μmol · kg^{-1} · min^{-1}· pM^{-1})	$ISI^{nodem} = 0.157 - 0.00004576 \times I_{120\ pmol/L} - 0.000299 \times I_{0\ pmol/L} - 0.00519 \times G_{120\ mmol/L}$	< 0.08	2 h	3	$R = 0.707$, $p < 0.00005$ vs. EHC
ISI^{dem} Stumvoll	OGTT	Sensitivity (μmol · kg^{-1} · min^{-1}· pM^{-1})	$ISI^{dem} = 0.226 - 0.0032 \times BMI - 0.0000645 \times I_{120\ pmol/L} - 0.000375 \times G_{90\ mmol/L}$	<0.08	2h	2	$R = 0.79$, p < 0.00005 vs. EHC
eMCR Stumvoll	OGTT	Sensitivity (mL · kg^{-1} · min^{-1})	$eMCR^{nodem} = 13 - 0.0042 \times I_{120\ pmol/L} - 0.384 \times G_{90\ mmol/L} - 0.0209 \times I_{0\ pmol/L}$	<9.8	2h	3	$R = 0.686$, $P < 0.00005$ vs. EHC
$eMCR^{dem}$ Stumvoll	OGTT	Sensitivity (mL · kg^{-1} · min^{-1})	$eMCR^{dem} = 18.8 - 0.271 \times BMI - 0.0052 \times I_{120\ pmol/L} - 0.27 \times G_{90\ mmol/L}$	<9.8	2h	2	$R = 0.80$, $P < 0.00005$ vs. EHC
Gutt	OGTT	Sensitivity (mL/kg/min)	$[75{,}000 + (G_0\text{-}G_{120})_{mg/dL} \times 0.19 \times BW_{kg/m^2}] / (120 \times LOG[(I_0 + I_{120})_{mU/L}/2] \times [(G_0 + G_{120})/2])$	<9.8	2 h	2	$R = 0.63$, $p < 0.001$ vs. EHC
SIOGTT	OGTT	Sensitivity	$1/[LOG(G_0 + G_{30} + G_{90} + G_{120})_{mg/dL} + LOG(I_0 + I_{30} + I_{90} + I_{120})_{mU/mL}]$	NA	2 h	4	$R = 0.65$, $p < 0.0001$ vs. EHC
BIGTT-SI	OGTT	Sensitivity (min^{-1}·pM)	$SI = EXP(4.9 - (0.00402 \times I_{0\ pmol/L}) - (0.000556 \times I_{30\ pmol/L}) - (0.00127 \times I_{120\ pmol/L}) - (0.152 \times G_{0\ mmol/L}) - (0.00871 \times G_{30\ mmol/L}) - (0.0373 \times G_{120\ mmol/L}) - (0.145 \times Gender) - (0.0376 \times BMI)$	< 0.000107 For Log(SI)	2 h	3	$R = 0.88$, $p < 0.0001$ vs. IVGTT
Cederholm	OGTT	Sensitivity	$[75{,}000 + (G_0\text{-}G_{120})_{mg/dL} \times 1.15 \times 180 \times 0.19 \times BW_{kg/m^2}]/(120 \times LOG\ I_{mean\ mU/L} \times G_{mean\ mg/dL})$	NA	2 h	5	$R = 0.75$, $p < 0.001$ vs. EHC

Tabla 5. Índices de resistencia y sensibilidad a la insulina basados en test dinámicos[37].

BW: peso corporal; EHC: clamp euglucémico hiperinsulinémico; FFM: masa libre de grasa; GIR: tasa de infusión de glucosa; G: glucosa; I: insulina; IR: resistencia a la insulina; ISI: índice de sensibilidad a la insulina; IVGTT: test de tolerancia a la glucosa intravenosa; OGIS: índice de sensibilidad a la glucosa e insulina oral; OGTT: sobrecarga oral de glucosa; eMCR: estimación de la tasa de depuración metabólica (con -dem- o sin -nodem- parámetros demográficos); MMT: test de comida mixta.

Índices derivados de muestras en ayunas

Los índices calculados a partir de muestras aisladas obtenidas en ayunas (Tabla 6) reflejan el comportamiento de la insulina basal, en combinación o no con los niveles de

glucosa. Debido a su sencillez metodológica -solo requieren una extracción sanguínea en ayunas-son los índices más utilizados para estimar la IR[42].

La IR hepática, principal determinante de la hiperglucemia en ayunas, suele manifestarse antes que la IR periférica. Por ello, estos índices pueden considerarse marcadores tempranos de alteraciones en la homeostasis glucémica[42].

El índice más utilizado es el HOMA-IR (*Homeostatic Model Assessment of Insulin Resistance*), propuesto inicialmente en 1985 y actualizado en 1998. Aunque su punto de corte puede variar en función de factores como la raza, el IMC o los niveles de c-HDL, de forma general se considera que un valor superior a 2 se asocia con resistencia a la insulina en población caucásica[37].

El índice HOMA-β (*Homeostatic Model Assessment of β-cell function*) es un parámetro derivado del mismo modelo matemático que el HOMA-IR y permite estimar la función de las células β pancreáticas. Refleja la capacidad secretora basal de insulina y expresa la función beta como un porcentaje respecto a la población general. Además, el descenso de este marcador en personas sin DM2 se relaciona con mayor probabilidad de ECV, sugiriendo que la reducción progresiva en la secreción de insulina puede contribuir en el pronóstico cardiovascular. Su interpretación debe realizarse de forma conjunta con el HOMA-IR, ya que la secreción de insulina está modulada por el grado de resistencia a la misma. Por tanto, el HOMA-β constituye una herramienta útil para valorar la reserva funcional pancreática, especialmente en etapas tempranas de disfunción metabólica[37,39,42,43].

El índice QUICKI (*Quantitative Insulin Sensitivity Check Index*) se obtiene mediante una transformación logarítmica del HOMA-IR, lo que mejora su precisión y aumenta su correlación con el CEH.

Otros índices propuestos para estimar con mayor precisión la resistencia o sensibilidad a la insulina hepática y del tejido adiposo emplean triglicéridos séricos en lugar de glucosa plasmática —como el índice triglicéridos-glucosa—, o incorporan parámetros lipídicos adicionales, como el c-HDL o los ácidos grasos no esterificados[37].

Index	Metabolic state	Condition (units)	Formula	Cutoff for IR	Validation (*R* value)
HOMA-IR	Fasting	Resistance	$(I_{0\ mU/mL} \times G_{0\ mg/dL})/405$	>4.65 or >3.6 if BMI > 27.5 >2 if NAFLD	$R = 0.60–0.88$, $p < 0.0001$ vs. EHC
QUICKI	Fasting	Sensitivity	$1/(LOG_{10}\ I_{0\ mU/mL} + LOG_{10}\ G_{0\ mg/dL})$	<0.33	$R = 0.43–0.78$, $p < 0.0001$ vs. EHC
Revised QUICKI	Fasting	Sensitivity	$1/(LOG_{10}\ I_{0\ mU/mL} + LOG_{10}\ G_{0\ mg/dL} + LOG_{10}\ FFA_{0\ mmol/L})$	<0.37	$R = 0.51$, $p < 0.001$ vs. EHC
Insulin	Fasting	Resistance	$I_{0\ mU/L}$	>12.2	$R = 0.59$, $p < 0.001$ vs. EHC
IGR	Fasting	Resistance	$I_{0\ mU/L}/G_{0\ mmol/L}$	>2.4	$R = -0.56$, $p < 0.001$ vs. EHC
ISI Bennett	Fasting	Sensitivity	$1/(\ln G_{0\ mg/dL} \times \ln I_{0\ mU/L})$	<0.089	$R = 0.48$, $p < 0.0001$ vs. EHC
VAI	Fasting	Resistance	*Men*: $(Waist_{cm}/39.68 + [1.88 \times BMI]) \times (TG_{mmol/L}/1.03) \times (1.31/HDL\text{-}C_{mmol/L})$; *Women*: $(Waist_{cm}\ 36.58 + [1.89 \times BMI]) \times (TG_{mmol/L}\ 0.81) \times (1.52/HDL\text{-}C_{mmol/L})$	>0.34	$R = -0.39$, $p < 0.0001$ vs. EHC
TG/HDL-C	Fasting	Resistance	$TG_{mg/dL}/HDL\text{-}C_{mg/dL}$	>0.57	$R = -0.41$, $p < 0.0001$ vs. EHC
TyG	Fasting	Resistance	$Ln[TG_{mg/dL} \times glucose_{mg/dL}/2]$	>9.36	$R = -0.38$, $p < 0.0001$ vs. EHC
LAP	Fasting	Resistance	*Men*: $(Waist_{cm} - 65) \times (TG_{mmol/L})$ *Women*: $(Waist_{cm} - 58) \times (TG_{mmol/L})$	>3.84	$R = -0.47$, $p < 0.0001$ vs. EHC
McAuley index	Fasting	Sensitivity	$\exp [2.63–0.28x\ln (I_{0\ mU/L}) - 0.31x \ln (TG_{mmol/L})]$	<6.07	$R = -0.39$, $p < 0.0001$ vs. EHC

Tabla 6. Índices de resistencia y sensibilidad a la insulina basados en datos obtenidos en ayunas[37].

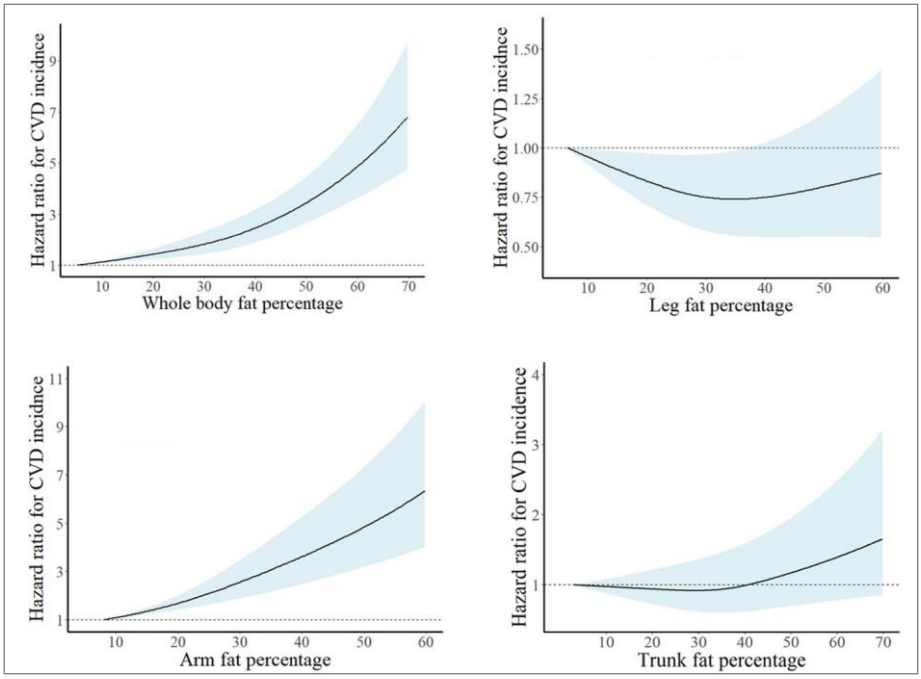
EHC: clamp euglucémico hiperinsulinémico; G: glucosa; c-HDL: colesterol unido a lipoproteínas de alta densidad; HOMA: modelo de evaluación de la homeostasis; I: insulina; IGR: cociente insulina/glucosa; IR: resistencia a la insulina; ISI: índice de sensibilidad a la insulina; LAP: producto de la acumulación de lípidos; QUICKI: índice cuantitativo de verificación de la sensibilidad a la insulina; Tg: triglicéridos; Tg/c-HDL: cociente entre triglicéridos y colesterol unido a lipoproteínas de alta densidad; TyG, triglicéridos/glucosa; VAI, índice de adiposidad visceral.

2.2. Evaluación de la composición corporal y distribución del tejido adiposo

La obesidad se define como una acumulación excesiva de grasa corporal que conlleva un riesgo significativo para la salud, y actualmente presenta una prevalencia global del 16 % en la población adulta[44]. Aunque su diagnóstico suele basarse en un IMC superior a 30 kg/m², una definición más precisa la caracteriza por un porcentaje de masa grasa superior al 30 % en varones y al 42 % en mujeres[44,45].

El incremento ponderal se asocia con múltiples complicaciones metabólicas, siendo el principal factor predictivo del desarrollo de DM2[46]. Sin embargo, evidencias recientes sugieren que no solo la cantidad total de masa grasa, sino también su morfología, funcionalidad y distribución, desempeñan un papel clave en la alteración del metabolismo glucémico y en el pronóstico cardiovascular, incluso de forma independiente al IMC. De hecho, una composición corporal desfavorable puede incrementar el RCV incluso en personas con normopeso, lo podría explicar las diferencias de RCV observadas entre individuos con un mismo IMC[47].

El exceso de grasa visceral se asocia con una mayor producción de sustancias bioactivas, como citoquinas y ácidos grasos libres, que favorecen un estado de inflamación crónica de bajo grado, disfunción endotelial, hipertrigliceridemia, elevación del c-LDL y resistencia a la insulina[48-51]. En este sentido, la distribución del tejido adiposo adquiere especial relevancia. En personas con DM2, tanto la adiposidad general como el porcentaje de grasa localizada en determinadas regiones como brazos y tronco superior, se han relacionado con un mayor riesgo y mortalidad cardiovascular, incluso tras ajustar por indicadores tradicionales de obesidad[47] (Fig.14).



<u>Figura 14.</u> Relación dosis-respuesta entre el porcentaje de grasa corporal y el riesgo de enfermedad cardiovascular entre pacientes con diabetes mellitus tipo 2 [47].

CVD: enfermedad cardiovascular

Adaptado de: Qiu Z. et al. The J. of Clin. End. & Met. 2025, 110, e372–e381

En este contexto, ha cobrado creciente interés la evaluación de la composición corporal, especialmente en pacientes con sobrepeso y/u obesidad, como herramienta para predecir alteraciones glucémicas y mejorar la estratificación del RCV[45,47,51].

Aunque la absorciometría dual de rayos X (DEXA) se considera el método de referencia para estimar la cantidad y distribución de la masa grasa, su uso en la práctica clínica es limitado debido a su coste, complejidad técnica y necesidad de personal especializado. Por ello, se han estandarizado métodos alternativos más accesibles, como los indicadores antropométricos indirectos -perímetro de cintura, perímetro de cadera o índice cintura-cadera[47]- o el análisis mediante impedanciometría bioeléctrica.

2.2.1. Impedanciometría bioeléctrica

La impedanciometría bioeléctrica (BIA, por sus siglas en inglés) es una técnica no invasiva accesible y ampliamente utilizada para la estimación de la composición corporal. Su principio se basa en la oposición que presenta el organismo al paso de una corriente eléctrica alterna constante de baja intensidad y alta frecuencia[52]. La conductividad eléctrica de los tejidos depende de su contenido en agua y electrolitos: los tejidos magros como el músculo, conducen mejor la corriente que los tejidos grasos, que presentan menor contenido hídrico. La BIA mide dos parámetros principales: la resistencia (R), que refleja la oposición al paso de corriente a través de los líquidos corporales, y la reactancia (Xc), que representa la capacidad de las membranas celulares para almacenar carga eléctrica. A partir de estos valores se calcula la impedancia total (Z) y se deriva el ángulo de fase, considerado un marcador del estado funcional celular. Dado que la corriente fluye preferentemente a través del agua corporal, esta técnica permite estimar con precisión el volumen de agua total y, mediante ecuaciones específicas, obtener otros parámetros como la masa grasa, la masa libre de grasa o el estado de hidratación del individuo[52-54].

Gracias a su rapidez, bajo coste y facilidad de uso, la BIA se ha incorporado de forma rutinaria en el ámbito clínico, especialmente para la valoración nutricional, el seguimiento enfermedades crónicas y la evaluación del riesgo cardiometabólico en personas con sobrepeso u obesidad. Además, al ser inocua para el paciente, puede repetirse de forma seriada para monitorizar cambios en la masa celular corporal o en los compartimentos hídricos, incluyendo el agua intracelular y extracelular, lo que resulta especialmente útil en situaciones clínicas que requieren vigilancia estrecha del estado nutricional o del equilibrio hidroelectrolítico [52-54].

No obstante, la interpretación de los resultados obtenidos mediante BIA debe realizarse con cautela, ya que la precisión de las estimaciones puede verse afectada por diversos factores, como el estado de hidratación, la temperatura corporal, la posición del paciente, el tipo de dispositivo y electrodos empleados, así como características individuales como la edad, el sexo, la raza o determinadas condiciones clínicas. Además, es imprescindible emplear ecuaciones predictivas validadas para la población evaluada, dado que su aplicabilidad no es universal[54]. Finalmente, aunque la BIA ha demostrado una buena correlación con la DEXA en la estimación de masa grasa y masa magra, puede infra o sobrestimar la grasa corporal en individuos con valores extremos de IMC o en contextos patológicos específicos[53].

3. Hipercolesterolemia familiar y metabolismo de la glucosa

La mayoría de los estudios epidemiológicos han evidenciado que los individuos con HFHe presentan una prevalencia de DM2 relativamente baja (aproximadamente del 5,7%)[55], inferior a la observada en población general[17]. Esta proporción es aún menor (<2%) en aquellos con diagnóstico genético confirmado y fenotipos de hipercolesterolemia grave[56]. Tradicionalmente estos hallazgos se han atribuido a una mayor adherencia a estilos de vida saludables entre los sujetos con HFHe[35]. Sin embargo, son escasos los estudios que han evaluado de forma directa el metabolismo de la glucosa en esta población. La mayoría no han encontrado alteraciones relevantes en la función de la insulina o en la captación periférica o hepática de glucosa, incluso en pacientes tratados con estatinas. No obstante, el reducido tamaño muestral de muchas investigaciones, el predominio del diagnóstico clínico frente al genético, y las características de los participantes (principalmente sujetos jóvenes y con normopeso), puede haber limitado la

detección de alteraciones glucémicas[57-63] y dificultan la extrapolación de los resultados al conjunto de la población con HFHe (Tabla 7).

Autor, año	**N** *HF vs controles*	**Edad HF**	**IMC (kg/m²)**	**Diagnóstico de HF**	**Método**	**Resultados** *(HF vs controles)*
Paolisso [57], 1992	39 vs 36	58,9	23	Clínica y analítica	75g. SOG	> [insulina basal] y > [insulina a las 2h] > [GB a las 2h]
Karhapaa [58], 1993	8 vs 13	31	23	Clínica y analítica Función r-LDL en linfocitos	Clamp euglucémico + 75g. SOG	Dif. no sig: GB, insulina, péptido C, captación glucosa, oxidación glucosa, oxidación lípidos…
Galvan[59], 1993	13 vs 15	46	23,9	Clínica y analítica	Clamp euglucémico	Dif.no sig: GB, insulina, AGL, niveles de c-LDL
Paolisso [60], 1993	8 vs 8	30,6	22,4	Clínica y analítica	Clamp euglucémico	Dif.no sig: captación glucosa, neoglucogénesis hepática
Galvan[61], 1996	20 vs 10	46	24,9	Clínica y analítica	75g. SOG + Clamp euglucémico	Dif.no sig: tolerancia glucosa, respuesta a insulina, neoglucogénesis hepática, lipolisis, captación y oxidación de glucosa
Koks[62], 2017	22 vs 14	54,7	25,6	DLCN	SOG + activación leucocitos	> AUC post SOG
Xu[63], 2017	82 vs 641	41	26,5*	Genético (APOB)	SOG	Dif.no sig: prevalencia de DM2, [glucemia], [insulina]

Tabla 7. Estudios que evalúan el metabolismo de la glucosa en individuos con hipercolesterolemia familiar.

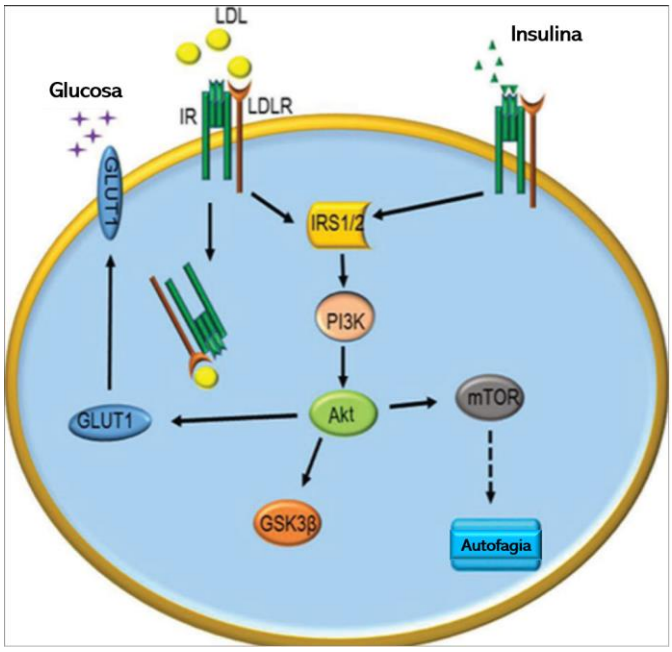
IMC: índice de masa corporal; SOG: sobrecarga oral de glucosa; GB: glucemia basal; r-LDL: receptor de LDL; AGL: ácidos grasos libres; c-LDL: colesterol LDL; AUC: área bajo la curva; DM2: diabetes mellitus tipo 2.

**De la muestra completa de HF n=625*

El complejo metabolismo que interrelaciona el metabolismo glucémico y lipídico aún no se comprende completamente, aunque se propone la existencia de una relación bidireccional. Diversos estudios han evidenciado que la insulina incrementa la expresión del r-LDL de manera dependiente de las concentraciones intracelulares de ésteres de colesterol[64], lo que sugiere que el aclaramiento podría estar influido, al menos en parte, por los niveles de insulina circulantes. No obstante, estudios experimentales in vitro indican que el principal regulador de la actividad del r-LDL es la concentración

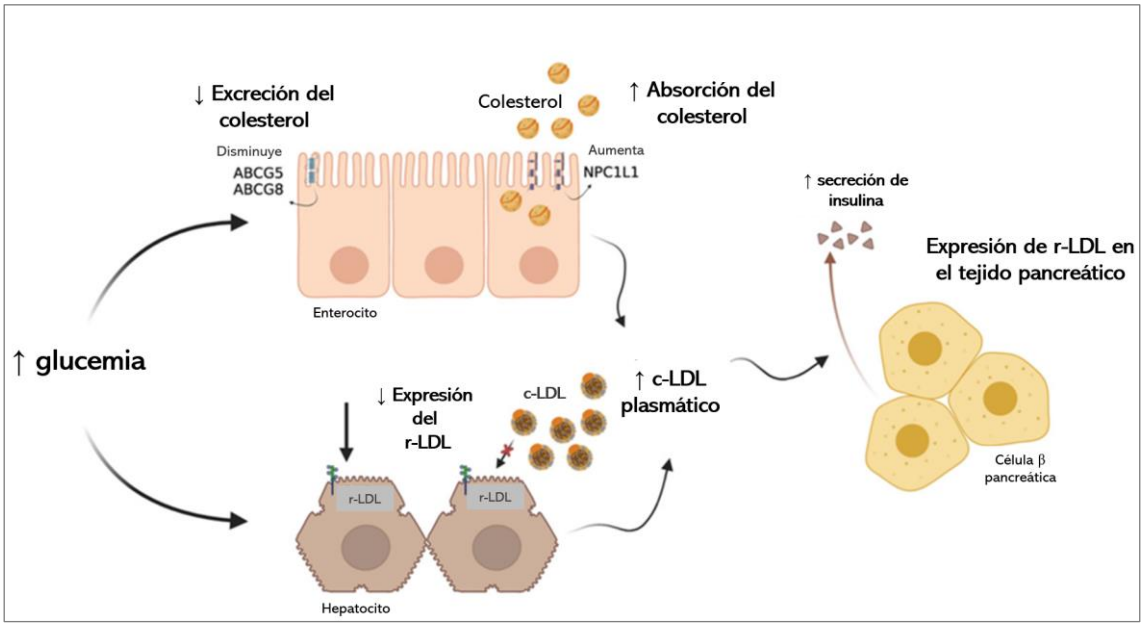
intracelular de esteres de colesterol, por lo que la transcripción del gen *LDLR* mediada por insulina estaría condicionada, por los niveles intracelulares de c-LDL[64].

Además, investigaciones mediante microscopía confocal han demostrado que los receptores de insulina (RI) y los r-LDL pueden formar complejos tanto en la superficie celular como en el medio intracelular. En este estado de interacción, el r-LDL permanece funcionalmente inactivo, lo que impide su participación efectiva en el aclaramiento del LDL. La unión de la insulina a su receptor induce la disociación de este complejo, permitiendo la activación del r-LDL y, con ello, la captación y eliminación de LDL plasmático. Por el contrario, en ausencia de insulina, el propio LDL puede simular parcialmente la acción de esta hormona a través del r-LDL, modulando procesos como la autofagia y favoreciendo la captación de glucosa en células endoteliales, mediante la traslocación de transportadores de glucosa desde el citoplasma hacia la membrana celular (Fig. 15). A nivel hepático, la señalización de insulina activa la vía de mTOR, lo que incrementa la expresión de r-LDL y disminuye los niveles de PCSK9, potenciando así su capacidad de captación de LDL[64-66].



<u>Figura 15.</u> Representación esquemática del complejo r-LDL- receptor de la insulina[66]. La unión de la insulina con su receptor desbloquea el complejo con el r-LDL y permite aumentar la captación de LDL. A su vez, la unión del LDL con el r-LDL favorece la captación de glucosa extracelular mediante la traslocación de los receptores GLUT a la superficie celular.

En consecuencia, se ha postulado que el déficit de insulina – ya sea por resistencia periférica (DM2) o ausencia absoluta (DM1)- junto con la hiperglucemia mantenida, podrían comprometer tanto la expresión como la funcionalidad del r-LDL[64,65] (Fig.16). Este deterioro limitaría la capacidad de captación intracelular del LDL, favoreciendo su acumulación en la luz arterial y contribuyendo de forma directa al desarrollo de arteriosclerosis en estos pacientes.



<u>Figura 16</u>. Efecto del aumento de glucosa en el metabolismo del c-LDL y la secreción de insulina[65].

r-LDL: receptor de LDL; c-LDL: colesterol LDL; NPC1L1: proteína Niemann-Pick C1-Like 1; ABCG5/8: transportadores de casete de unión a ATP G5 y G8.

Adaptado de: Bonilha I. et al. Metabolites 2021, 11, 807.

Estudios en modelos in vitro[67] han demostrado que la exposición a concentraciones suprafisiológicas de ácidos grasos puede resultar tóxica para las células β pancreáticas, reduciendo la expresión del gen de la insulina y provocando necrosis celular, fenómeno conocido como lipotoxicidad[68] (Fig.17). Esta hipótesis podría contribuir a explicar los hallazgos de estudios de secuenciación génica y randomización mendeliana, que han mostrado que los individuos portadores de variantes genéticas con ganancia de función que reducen los niveles de c-LDL desde etapas tempranas de la vida-como aquellas que afectan a *NPC1L1*, *HMGCR*, *PCSK9* o *ABCG5*/G8- presentan un menor RCV, pero una mayor probabilidad de desarrollar DM2[69].

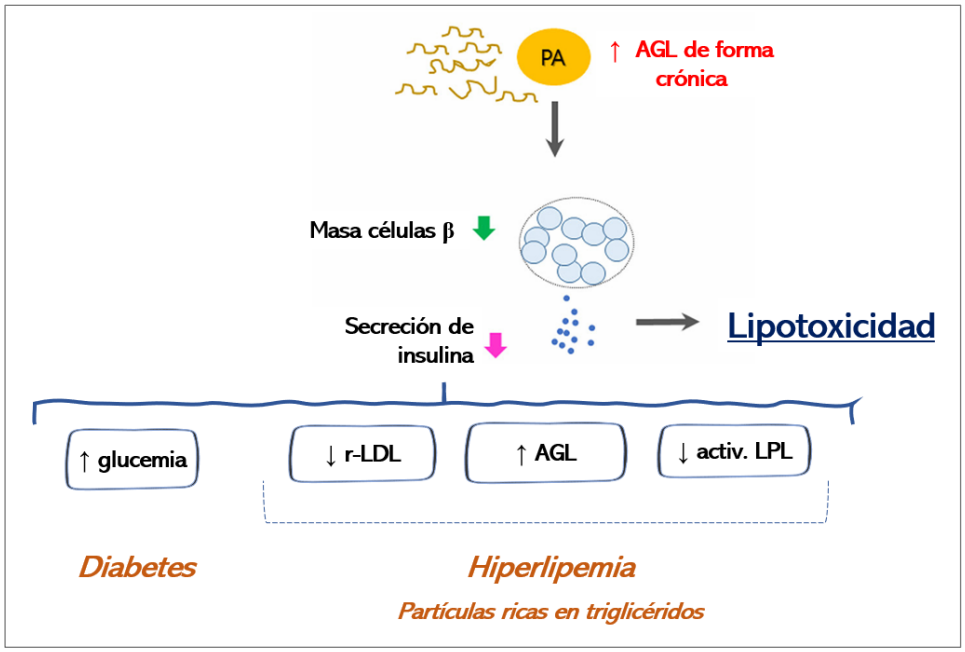
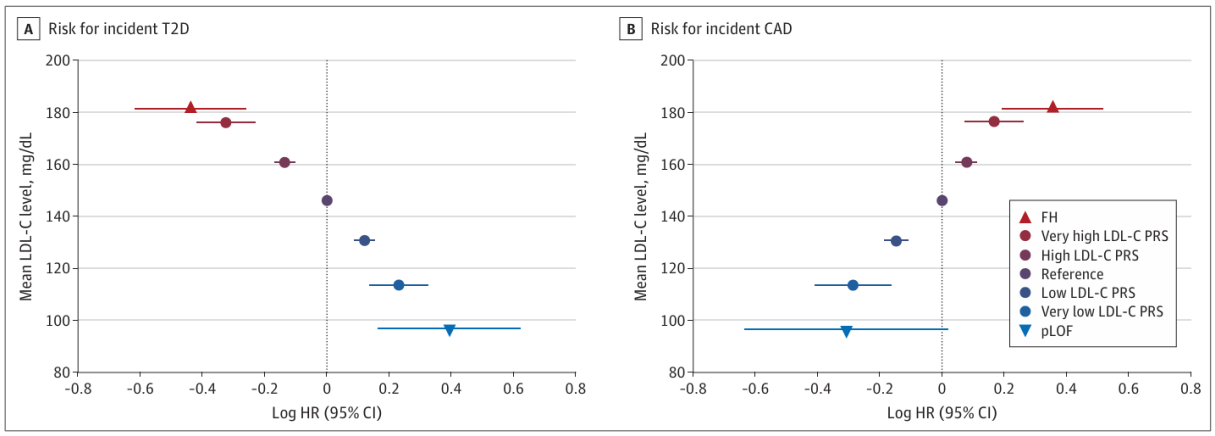


Figura 17. Hipótesis de la lipotoxicidad pancreática[68]. La exposición prolongada a ácidos grasos libres, como el ácido palmítico, induce apoptosis de las células β-pancreáticas a través de mecanismos inflamatorios y de estrés oxidativo, lo que reduce la masa funcional de células β. La consecuencia clínica de este descenso en la secreción de insulina es la aparición de diabetes e hiperlipidemia secundaria a la disminución en la expresión de los r-LDL. Además, la actividad de la lipoproteín lipasa se ve comprometida, lo que favorece la acumulación de ácidos grasos libres y de lipoproteínas ricas en triglicéridos, de mayor potencial aterogénico y menor afinidad por el r-LDL.

PA: ácido palmítico; AGL: ácidos grasos libres; r-LDL: receptor LDL; LPL: lipoprotein lipasa

Adaptado de: Oh Y. et al. Front End. (Lausanne). 2018 Jul 16;9:384.

En cambio, los pacientes con HFHe, que presentan niveles elevados de c-LDL desde el nacimiento y suelen iniciar tratamiento hipolipemiante de forma precoz, parecen tener un menor riesgo de desarrollar DM2[70] (Fig. 18).



<u>Figura 18.</u> Asociaciones directas e inversas de los niveles del c-LDL con el riesgo de diabetes mellitus tipo 2 y de enfermedad coronaria[70].

HR: hazard ratios; c-LDL: colesterol LDL;T2D: diabetes mellitus tipo 2; FH: hipercolesterolemia familiar; CAD: enfermedad coronaria; PRS: score de riesgo poligénico; pLOF: variantes de pérdida de función (APOB y PCSK9).

No obstante, los resultados observados en la práctica clínica han sido inconsistentes. Exceptuando el reconocido efecto diabetógeno de las estatinas[71], otros agentes hipolipemiantes que incrementan los niveles intracelulares de c-LDL no han demostrado una asociación clara con un mayor riesgo de hiperglucemia[72,73]. Así mismo, pacientes con hipolipidemias genéticas graves como la abetalipoproteinemia o la hipobetalipoproteinemia, no presentan una mayor prevalencia de DM2[74].

Estudios recientes han identificado grupos específicos de genes que están implicados tanto en la síntesis, exportación y captación hepática de lípidos como en la secreción y acción de la insulina, así como en el desarrollo de enfermedad hepática metabolica[75]. Estos hallazgos sugieren que el riesgo de alteraciones glucémicas no depende exclusivamente de los niveles de c-LDL, sino probablemente del extenso entramado genético que regula de forma conjunta el metabolismo lipídico y la homeostasis de la glucosa[76].

Referencias

1. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: Meta-analyses of 11 million subjects. J Am Coll Cardiol. 2020;75(20):2553–66. doi:10.1016/j.jacc.2020.03.057.
2. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. J Am Heart Assoc. 2019;8(24):e013225. doi:10.1161/JAHA.119.013225.
3. Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. Nat Rev Cardiol. 2019;16(1):9–20. doi:10.1038/s41569-018-0052-6.
4. Bourbon M, Alves AC, Alonso R, Mata N, Aguiar P, Padró T, Mata P. Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: The SAFEHEART registry. Atherosclerosis. 2017;262:8–13. doi:10.1016/j.atherosclerosis.2017.04.002.
5. Akioyamen LE, Genest J, Chu A, et al. Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: A systematic review and meta-analysis. J Clin Lipidol. 2019;13(1):15–30. doi:10.1016/j.jacl.2018.10.012.
6. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88. doi:10.1093/eurheartj/ehz455
7. García-Villarreal L, Daniels S, Shaw SH, Cotton D, Galvin M, Geskes J, et al. High prevalence of the very rare Wilson disease gene mutation Leu708Pro in the island of Gran Canaria (Canary Islands, Spain): A genetic and clinical study. Hepatology. 2000;32(6):1329–36.
8. Sánchez-Hernández RM, Tugores A, Nóvoa FJ, et al. The island of Gran Canaria: A genetic isolate for familial hypercholesterolemia. J Clin Lipidol. 2019;13(4):618–26. doi:10.1016/j.jacl.2019.04.099.
9. Lorenzo V, Boronat M, Saavedra P, Rufino M, Maceira B, Novoa FJ, et al. Disproportionately high incidence of diabetes-related end-stage renal disease in the Canary Islands: An analysis based on estimated population at risk. Nephrol Dial Transplant. 2010;25(7):2283–8. doi:10.1093/ndt/gfp761.
10. Rodríguez Pérez MDC, Chines C, Pedrero García AJ, Sousa D, Cuevas Fernández FJ, Marcelino-Rodríguez I, et al. Major amputations in type 2 diabetes between 2001 and 2015 in Spain: regional differences. BMC Public Health. 2020;20(1):54. doi:10.1186/s12889-019-8137-7.
11. Nóvoa-Medina Y, Marcelino-Rodriguez I, Suárez NM, Barreiro-Bautista M, Rivas-García E, Sánchez-Alonso S, et al. Does HLA explain the high incidence of childhood-onset type 1 diabetes in the Canary Islands? The role of Asp57 DQB1 molecules. BMC Pediatr. 2024;24(1):569.
12. Vegazo O, Banegas JR, Civeira F, Serrano Aisa PL, Jiménez FJ, Luengo E. Prevalencia de dislipemia en las consultas ambulatorias del Sistema Nacional de Salud: Estudio HISPALIPID. Med Clin (Barc). 2006;127(9):331–4.
13. Millán Núñez-Cortés J, Alegría E, Álvarez-Sala Walther L, Ascaso Gimilio J, Lahoz Rallo C, Mantilla Morató T, et al. Documento Abordaje de la dislipidemia. Sociedad Española de Arteriosclerosis (parte III). Clin Investig Arterioscler. 2012;24(2):102–7.

14. Sánchez-Hernández RM, González-Lleó AM, Tugores A, et al. Familial hypercholesterolemia in Gran Canaria: Founder mutation effect and high frequency of diabetes. Clin Investig Arterioscler. 2021;33(5):247–53. doi:10.1016/j.arteri.2021.02.010.
15. Atlas for monitoring diabetes care in the Canary Islands, 2022. Available from: https://cienciadedatosysalud.org/atlas/cuidados-diabetes-canarias.
16. Soriguer F, Goday A, Bosch-Comas A, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: The Di@bet.es Study. Diabetologia. 2012;55(1):88–93. doi:10.1007/s00125-011-2336-9.
17. International Diabetes Federation. Our network: Our members - Spain [Internet]. International Diabetes Federation; [cited 2025 Jul 13]. Available from: https://idf.org/europe/our-network/our-members/spain/.
18. Pérez-Calahorra S, Civeira F, Guallar-Castillón P, et al. Behavioral cardiovascular risk factors and prevalence of diabetes in subjects with familial hypercholesterolemia. Eur J Prev Cardiol. 2020;27(15):1649–60. doi:10.1177/2047487319896138.
19. Warden BA, Fazio S, Shapiro MD. Familial Hypercholesterolemia: Genes and Beyond. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000– [updated 2024 Sep 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK343488/.
20. Suárez NM, Jebari-Benslaiman S, Jiménez-Monzón R, Benito-Vicente A, Brito-Casillas Y, Garcés L, et al. Age, origin and functional study of the prevalent LDLR mutation causing familial hypercholesterolaemia in Gran Canaria. Int J Mol Sci. 2023;24(14):8725.
21. ElSayed NA, McCoy RG, Aleppo G, Balapattabi K, Beverly EA, Briggs Early K, et al. Diagnosis and classification of diabetes: Standards of care in diabetes—2025. Diabetes Care. 2025;48(Suppl_1):S27–49. Available from: https://diabetesjournals.org/care/article/48/Supplement_1/S27/157566/2-Diagnosis-and-Classification-of-Diabetes.
22. Sirdah MM, Reading NS. Genetic predisposition in type 2 diabetes: A promising approach toward a personalized management of diabetes. Clin Genet. 2020;98(6):525–47.
23. Imamura M, Shigemizu D, Tsunoda T, Iwata M, Maegawa H, Watada H, et al. Assessing the clinical utility of a genetic risk score constructed using 49 susceptibility alleles for type 2 diabetes in a Japanese population. J Clin Endocrinol Metab. 2013;98(11):E1667–73.
24. Dal Canto E, Ceriello A, Rydén L, Ferrini MB, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. Eur J Prev Cardiol. 2019;26(2 Suppl):25–32. doi:10.1177/2047487319878371.
25. Orozco-Beltrán D, Sánchez E, Garrido A, Quesada JA, Carratalá-Munuera MC, Gil-Guillén VF. Trends in mortality from diabetes mellitus in Spain: 1998-2013. Rev Esp Cardiol (Engl Ed). 2017;70(6):433–43. doi:10.1016/j.rec.2016.09.022.
26. Fernández-Bergés D, Cabrera de León A, et al. Metabolic syndrome in Spain: Prevalence and coronary risk associated with harmonized definition and WHO proposal. DARIOS study. Rev Esp Cardiol (Engl Ed). 2012 Mar;65(3):241–8. doi:10.1016/j.recesp.2011.10.015. Epub 2012 Feb 3.
27. Ministerio de Sanidad. Mortalidad por cáncer, por enfermedad isquémica del corazón, por enfermedades cerebrovasculares y por diabetes mellitus en España [Internet]. Disponible en: www.msc.es.

28. Marcelino-Rodríguez I, Elosua R, Pérez M del CR, Fernández-Bergés D, Guembe MJ, Alonso TV, et al. On the problem of type 2 diabetes-related mortality in the Canary Islands, Spain. The DARIOS Study. Diabetes Research and Clinical Practice. 2016 Jan 1;111:74–82.
29. Boronat M, Chirino R, Varillas VF, Saavedra P, Marrero D, Fabregas M, et al. Prevalence of the metabolic syndrome in the island of Gran Canaria: comparison of three major diagnostic proposals. Diabet Med. 2005 Dec;22(12):1751–6.
30. Godenau D, Martin-Rodriguez G, Gonzalez-Gomez JI, Caceres-Hernandez JJ. Food consumption in the Canary Islands: nutritional implications of food imports and local production. BMC Public Health. 2022 Dec 1;22(1):1–11.
31. Cabrera de León A, Castillo Rodríguez JC, Domínguez Coello S, Rodríguez Pérez MC, Brito Díaz B, Borges Álamo C, et al. Estilo de vida y adherencia al tratamiento de la población canaria con diabetes mellitus tipo 2. Rev Esp Salud Publica [Internet]. 2009 Aug [cited 2025 Jun 7];83(4):567–75. Available from: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1135-57272009000400008&lng=es
32. Zoungas S, Woodward M, Li Q, Cooper ME, Hamet P, Harrap S, et al; ADVANCE Collaborative Group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia. 2014;57(12):2465–74. doi:10.1007/s00125-014-3369-7.
33. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: Clinical insights and vascular mechanisms. Can J Cardiol. 2018 May;34(5):575–84. doi:10.1016/j.cjca.2017.12.005. Epub 2017 Dec 11. PMID: 29459239; PMCID: PMC5953551.
34. Jansen AC, van Aalst-Cohen ES, Tanck MW, Trip MD, Lansberg PJ, Liem AH, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: Data in 2400 patients. J Intern Med. 2004;256(6):482–90. doi:10.1111/j.1365-2796.2004.01405.x.
35. Climent E, Pérez-Calahorra S, Benaiges D, Pintó X, Suárez-Tembra M, Plana N, et al. Clinical and genetic differences between heterozygous familial hypercholesterolemia patients with and without type 2 diabetes. Rev Esp Cardiol (Engl Ed). 2020 Sep;73(9):718–24. doi:10.1016/j.rec.2019.09.001. Epub 2019 Oct 28. PMID: 31672559.
36. Paquette M, Cariou B, Bernard S, et al. Increased FH-Risk-Score and diabetes are cardiovascular risk equivalents in heterozygous familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2024 Feb;44(2):505–12. doi:10.1161/ATVBAHA.123.319957.
37. Gastaldelli A. Measuring and estimating insulin resistance in clinical and research settings. Obesity. 2022;30:1549–63. John Wiley and Sons Inc.
38. Page MM, Johnson JD. Mild suppression of hyperinsulinemia to treat obesity and insulin resistance. Trends Endocrinol Metab. 2018;29(6):389–99. Elsevier Inc.
39. di Pino A, Defronzo RA. Insulin resistance and atherosclerosis: Implications for insulin-sensitizing agents. Endocr Rev. 2019;40(5):1447–67. Oxford University Press.
40. Romeo S, Vidal-Puig A, Husain M, Ahima R, Arca M, Bhatt DL, et al. Clinical staging to guide management of metabolic disorders and their sequelae: a European Atherosclerosis Society consensus statement. Eur Heart J [Internet]. 2025 May 7 [cited 2025 Jul 23]; Available from: doi/10.1093/eurheartj/ehaf314/8125503
41. Jialal I, Singh G. Management of diabetic dyslipidemia: An update. World J Diabetes. 2019 May 15;10(5):280–90.

42. Borai A, Livingstone C, Kaddam I, Ferns G. Selection of the appropriate method for the assessment of insulin resistance [Internet]. 2011. Disponible en: http://www.biomedcentral.com/1471-2288/11/158.
43. Ichikawa Y, Watanabe Y, Irie K, Yokomichi H, Horikoshi T, Yoshizaki T, et al. Decreased Homeostasis Model Assessment of β-Cell Function in Patients Without Diabetes Can Predict Future Events in Patients With Cardiovascular Disease. Circulation Journal. 2025 Mar 1;89(3):347–53.
44. World Health Organization (WHO). Obesity and overweight. 2023 [cited 2024 Mar 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
45. Potter AW, Chin GC, Looney DP, Friedl KE. Defining Overweight and Obesity by Percent Body Fat Instead of Body Mass Index. J Clin Endocrinol Metab. 2025 Apr 1;110(4):e1103–7.
46. Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. Int J Mol Sci. 2024;25(XX).
47. Qiu Z, Lee DH, Lu Q, Li R, Zhu K, Li L, et al. Associations of Regional Body Fat With Risk of Cardiovascular Disease and Mortality Among Individuals With Type 2 Diabetes. J Clin Endocrinol Metab. 2025 Feb 1;110(2):e372–81.
48. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021 Mar 1;320(3):C375–91.
49. Nalini M, Sharafkhah M, Poustchi H, Sepanlou SG, Pourshams A, Radmard AR, et al. Comparing anthropometric indicators of visceral and general adiposity as determinants of overall and cardiovascular mortality. Arch Iran Med. 2019 Jun 1;22(6):301–9.
50. Webb RJ, Mazidi M, Lip GYH, Kengne AP, Banach M, Davies IG. The role of adiposity, diet and inflammation on the discordance between LDL-C and apolipoprotein B. Nutr Metab Cardiovasc Dis. 2022;32(3):605–15. doi:10.1016/j.numecd.2021.12.004.
51. Sharafi M, Razavi FS, Baeradeh N, Bagheri P, Rousta A, Afrashteh S, et al. Latent profiles of body composition indices and their associations with cardiovascular diseases, hypertension, and diabetes: results from the Fasa Adult Cohort study (FACS). J Health Popul Nutr [Internet]. 2025 Jul 3;44(1):228. Available from: https://jhpn.biomedcentral.com/articles/10.1186/s41043-025-00980-6.
52. Kyle UG, Bosaeus I, de Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis - Part I: Review of principles and methods. Clin Nutr. 2004;23(5):1226–43.
53. Moonen HPFX, van Zanten ARH. Bioelectric impedance analysis for body composition measurement and other potential clinical applications in critical illness. Curr Opin Crit Care. 2021 Aug 1;27(4):344–53.
54. Bellido Guerrero D, Cornejo Pareja M, García Almeida M. Técnicas morfológicas en evaluación morfofuncional. Manual de la Sociedad Española de Endocrinología Nutrición (SEEN) [Documento técnico].
55. Elshorbagy A, Lyons ARM, Vallejo-Vaz AJ, et al. Association of BMI, lipid-lowering medication, and age with prevalence of type 2 diabetes in adults with heterozygous familial hypercholesterolemia: A worldwide cross-sectional study. Lancet Diabetes Endocrinol. 2024;8587(24):1–13. doi:10.1016/S2213-8587(24)00221-3.
56. Besseling J, Kastelein JJ, Defesche JC, Hutten BA, Hovingh GK. Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. JAMA. 2015;313(10):1029–36. doi:10.1001/jama.2015.78.

57. Paolisso G, Ferrannini E, Sgambato S, Varricchio M, Onofrio FD'. Hyperinsulinemia in Patients with Hypercholesterolemia. J Clin Endocrinol Metab. 1992 Dec;75(6):1409–12. doi:10.1210/jcem.75.6.1464641.
58. Karhapaa P, Voutilainen E, Kovanen PT, Laakso M. Insulin resistance in familial and nonfamilial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 1993;13(1):41–7. doi:10.1161/01.ATV.13.1.41.
59. Galvan AQ, Santoro D, Natali A, et al. Insulin sensitivity in familial hypercholesterolemia. Metabolism. 1993;42(12):1583–7. doi:10.1016/0026-0495(93)90138-E.
60. Paolisso G, Ferrannini E, D'Amorea A, Volpea C, Varricchio M, D'Onofrio F. Effects of physiological plasma insulin levels on glucose turnover parameters in familial hypercholesterolemia. Atherosclerosis. 1993;101(1):111–5. doi:10.1016/0021-9150(93)90106-5.
61. Galvan AQ, Natali A, Baldi S, et al. Effect of a reduced-fat diet with or without pravastatin on glucose tolerance and insulin sensitivity in patients with primary hypercholesterolemia. J Cardiovasc Pharmacol. 1996;28(4):595–602. doi:10.1097/00005344-199610000-00019.
62. Koks N, de Vries MA, Birnie E, Alipour A, Castro Cabezas M. Glucose-dependent leucocyte activation in familial hypercholesterolemia. Eur J Clin Invest. 2017;47(11):839–46. doi:10.1111/eci.12818.
63. Xu H, Ryan KA, Jaworek TJ, et al. Familial hypercholesterolemia and type 2 diabetes in the Old Order Amish. Diabetes. 2017;66(7):2054–8. doi:10.2337/db17-0173.
64. Chandra NC. A comprehensive account of insulin and LDL receptor activity over the years: A highlight on their signaling and functional role. J Biochem Mol Toxicol. 2021;35(9):e22840. doi:10.1002/jbt.22840.
65. Bonilha I, Hajduch E, Luchiari B, Nadruz W, Le Goff W, Sposito AC. The reciprocal relationship between LDL metabolism and type 2 diabetes mellitus. Metabolites. 2021;11(12):807. doi:10.3390/metabo11120807.
66. Zhu L, Wu G, Yang X, Jia X, Li J, Bai X, et al. Low density lipoprotein mimics insulin action on autophagy and glucose uptake in endothelial cells. Sci Rep. 2019 Dec 1;9(1):[artículo sin paginar].
67. Briaud I, Harmon JS, Kelpe CL, Segu VBG, Poitout V. Lipotoxicity of the pancreatic beta-cell is associated with glucose-dependent esterification of fatty acids into neutral lipids. Diabetes. 2001;50(2):315–21. doi:10.2337/diabetes.50.2.315.
68. Oh YS, Bae GD, Baek DJ, Park EY, Jun HS. Fatty acid-induced lipotoxicity in pancreatic beta-cells during development of type 2 diabetes. Front Endocrinol (Lausanne). 2018;9:384.
69. Lotta LA, Sharp SJ, Burgess S, Perry JRB, Stewart ID, Willems SM, et al. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 diabetes: A metaanalysis. JAMA. 2016;316(12):1383–91. doi:10.1001/jama.2016.12446.
70. Ravi A, Koyama S, Cho SMJ, Haidermota S, Hornsby W, Ellinor PT, Natarajan P. Genetic predisposition to low-density lipoprotein cholesterol and incident type 2 diabetes. JAMA Cardiol. 2025;10(4):379–83. doi:10.1001/jamacardio.2024.5072.
71. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: An analysis from the JUPITER trial. Lancet. 2012;380(9841):565–71.
72. Leiter LA, Banach M, Catapano AL, Duell PB, Gotto AM, Laufs U, et al. Bempedoic acid in patients with type 2 diabetes mellitus, prediabetes, and normoglycaemia: A

post hoc analysis of efficacy and glycaemic control using pooled data from phase 3 clinical trials. Diabetes Obes Metab. 2022;24(1):131–40. doi:10.1111/dom.14582.
73. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: A prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5(12):941–50. doi:10.1016/S2213-8587(17)30325-3.
74. Gill PK, Hegele RA. Low cholesterol states: clinical implications and management. Expert Rev Endocrinol Metab. 2023;18:241–53.
75. Klimentidis YC, Arora A, Newell M, Zhou J, Ordovas JM, Renquist BJ, et al. Phenotypic and genetic characterization of lower LDL cholesterol and increased type 2 diabetes risk in the UK biobank. Diabetes. 2020 Oct 1;69(10):2194–205.
76. Liu DJ, Peloso GM, Yu H, Butterworth AS, Wang X, Mahajan A, et al. Exome-wide association study of plasma lipids in >300,000 individuals. Nat Genet. 2017 Dec 1;49(12):1758–66.
77. Ministerio de Sanidad. Estadísticas de mortalidad [Internet]. Madrid: Ministerio de Sanidad; [citado 13 jul 2025]. Disponible en: https://www.sanidad.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/mortalidad/mortalidad.htm.
78. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.

Hipótesis

La variante patogénica *p.(Tyr400_Phe402del) del LDLR*, responsable de la mayoría de los casos de HFHe en Gran Canaria, predispone al desarrollo de DM2, sugiriendo una posible co-segregación entre ambas enfermedades. La presencia de esta variante podría modificar vías metabólicas comunes que provocan de manera simultánea hipercolesterolemia e hiperglucemia. En caso de que no exista esta co-segregación, podría tratarse de una nueva variante de DM2 de herencia autosómica dominante, aún no descrita.

Objetivos

El objetivo principal de esta tesis doctoral es evaluar si existe co-segregación entre la DM2 y otras alteraciones del metabolismo de la glucosa con la variante patogénica *p.(Tyr400_Phe402del)* de *LDLR* en individuos con HFHe de Gran Canaria.

Objetivos secundarios

Este trabajo de investigación se propone como objetivos secundarios:

1. Revisar la literatura existente sobre la relación entre el metabolismo glucémico y lipídico en pacientes con HFHe.
2. Evaluar la respuesta al tratamiento con iPCSK9 en los pacientes atendidos en la Unidad de Lípidos del Complejo Universitario Materno Insular de Gran Canaria, analizando los cambios en el perfil lipídico, posibles alteraciones en el metabolismo glucémico y las diferencias según el tipo de variante genética causante de HFHe.
3. Ampliar el diagnóstico genético de portadores de la variante genética *p.(Tyr400_Phe402del)* de *LDLR* dentro de las familias estudiadas.
4. Realizar una búsqueda activa de nuevos casos de DM2, tanto en portadores como en no portadores de la variante genética prevalente, que hasta el momento no hubieran sido diagnosticados.
5. Caracterizar fenotípicamente el metabolismo de la glucosa en individuos sin DM2, estimar la prevalencia de sus alteraciones y comparar los resultados de los HFHe portadores de la variante genética p.(Tyr400_Phe402del) en *LDLR* con los de sus familiares no portadores y con pacientes con HFHe debida a otras variantes genéticas.

Presentación de artículos de tesis

1. "**Diabetes and Familial Hypercholesterolemia: Interplay between Lipid and Glucose Metabolism"**

   Autores: Ana M. González-Lleó, Rosa María Sánchez-Hernández, Mauro Boronat y Ana M. Wägner.

   Revista: *Nutrients 2022, Apr 3;14(7):1503.* **DOI**:10.3390/nu14071503.

   Factor de impacto (Journal Impact Factor, JIF; Journal Citacion Reports, JCR): 6.706.

   Orden de la revista en su área (2021): 21/109, **Q1,** Nutrition & Dietetics. **D2**.

   Citas: 19 (Aug2025)

2. "**Impact of PCSK9 inhibitors in glycaemic control and new-onset diabetes**"

   Autores: Ana M. González-Lleó, Rosa M. Sánchez-Hernández, Núria Plana, Daiana Ibarretxe, Pere Rehues, Josep Ribalta, Dídac Llop, Ana M. Wägner, Lluís Masana y Mauro Boronat.

   Revista: *Cardiovascular diabetology (2024) Jan 3;23(1):4.* **DOI**: 10.1186/s12933-023-02077-y.

   Factor de impacto (JIF; JCR): 8.5

   Orden de la revista en su área (2023): 16/222: **Q1** Cardiac & Cardiovascular Systems. 11/186: **Q1** Endocrinology & Metabolism. **D1.**

   Citas: 9 (Aug2025)

3. **"Glucose metabolism in heterozygous familial hypercholesterolemia with a founder effect and a high diabetes prevalence: a cross sectional study"**

Autores: Ana M. González-Lleó, Yeray Brito-Casillas, Virginia Martín-Santana, Yaiza Gil-Quintana, Antonio Tugores, Roberto Scicali, Marta Riaño, Luisa Hernández-Baraza, Roberto Jiménez-Monzón, Josefa Girona, Francesco Di Giacomo-Barbagallo, Luis Masana, Mauro Boronat, Ana M Wägner, Rosa M Sánchez-Hernández.

Revista: *Cardiovascular diabetology (2025) Aug 6;24(1):322.* **DOI***: 10.1186/s12933-025-02857-8.*

Factor de impacto (JIF; JCR): 10.6

Orden de la revista en su área (2024): 14/230: **Q1** Cardiac & Cardiovascular Systems. 11/191: Q1 Endocrinology & Metabolism. **D1.**

Citas: 0 (Aug2025)

OTROS ARTÍCULOS

"Familial hypercholesterolemia in Gran Canaria: Founder mutation effect and high frequency of diabetes"

Autores: Rosa M Sánchez-Hernández, Ana M González-Lleó, Antonio Tugores, Yeray Brito-Casillas, Fernando Civeira, Mauro Boronat, Ana Wägner.

Revista: *Clínica e Investigación en Arteriosclerosis (2021). Sep-Oct;33(5):247-253.* **DOI**: 10.1016/j.arteri.2021.02.010.

Factor de impacto (JIF; JCR): NA

Orden de la revista en su área (2020): 69/84. **Q4.** Peripheral Vascular Disease. **D9.**

Citas: 4 (Aug2025)

"Age, Origin and Functional Study of the Prevalent *LDLR* Mutation Causing Familial Hypercholesterolaemia in Gran Canaria"

Autores: Nicolás M Suárez, Shifa Jebari-Benslaiman, Roberto Jiménez-Monzón, Asier Benito-Vicente, Yeray Brito-Casillas, Laida Garcés, Ana M González-Lleó, Antonio Tugores, Mauro Boronat, César Martin, Ana M Wägner, Rosa M Sánchez-Hernández.

Revista: *International Journal of Molecular Sciences (2023). Jul 11;24(14):11319.* **DOI**: 10.3390/ijms241411319.

Factor de impacto (JIF; JCR): 5.6

Orden de la revista en su área (2022): 66/285. **Q1** Biochemistry & Molecular biology. 52/178. Q2 Chemistry, multidisciplinary. **D3.**

Citas: 2 (Aug2025)

"ApoC-III proteoforms are associated with better lipid, inflammatory, and glucose profiles independent of total apoC-III"

Autores: Pere Rehues, Josefa Girona, Montse Guardiola, Enrique Ozcariz, Núria Amigó, Roser Rosales, Yaiza Esteban, Helena Banús, Gemma Gavaldà-Alsina, Ana González-Lleó, Gemma Rojo-Martínez, Josep Ribalta.

Revista: *Cardiovascular diabetology 2024 Dec 4;23(1):433.* **DOI***: 10.1186/s12933-024-02531-5.*

Factor de impacto (JIF; JCR): 8.5

Orden de la revista en su área (2023): 16/222: **Q1** Cardiac & Cardiovascular Systems. 11/186: Q1 Endocrinology & Metabolism. **D1**.

Citas: 1 (Aug2025)

“Inclisiran, Reasons for a Novel Agent in a Crowded Therapeutic Field”

Autores: Francesco Di Giacomo-Barbagallo, Natalia Andreychuk, Roberto Scicali, Ana Gonzalez-Lleó, Salvatore Piro, Lluis Masana, Daiana Ibarretxe.

Revista: *Current Atherosclerosis Reports 2025 Jan 9;27(1):25.* **DOI***: 10.1007/s11883-024-01271-x.*

Factor de impacto (JIF; JCR): 5.2

Orden de la revista en su área (2024): 12/98: **Q1** Peripheral Vascular Disease. **D2.**

Citas: 4 (Aug2025)

“Evaluation of glycemic status and subclinical atherosclerosis in familial hypercholesterolemia subjects with or without LDL receptor mutation”

Autores: Francesco Di Giacomo Barbagallo, Giosiana Bosco, Maurizio Di Marco, Sabrina Scilletta, Nicoletta Miano, Marco Musmeci, Marina Martedì, Ana M González-Lleó, Daiana Ibarretxe, Ernestina Marianna De Francesco, Roberta Malaguarnera, Antonino Di Pino, Luís Masana, Francesco Purrello, Salvatore Piro, Roberto Scicali.

Revista: *Cardiovascular diabetology 2025 Mar 20;24(1):126.* **DOI***: 10.1186/s12933-025-02683-y.*

Factor de impacto (JIF; JCR): 10.6

Orden de la revista en su área (2024): 14/230: **Q1** Cardiac & Cardiovascular Systems. 11/191: Q1 Endocrinology & Metabolism. **D1.**

Citas: 7 (Aug2025)

Justificación de la unidad temática de la tesis

Las enfermedades cardiovasculares (ECV) constituyen la principal causa de discapacidad y de mortalidad en España, siendo responsables del 26,6 % de las defunciones totales [77], lo que implica un impacto económico considerable sobre el sistema sanitario. En este contexto, el control de los factores de riesgo cardiovascular (FRCV) modificables, como los hábitos de vida —alimentación saludable, práctica regular de ejercicio físico y abstinencia de tóxicos—, así como el manejo adecuado de enfermedades como la diabetes mellitus tipo 2 (DM2) o la dislipemia, resultan fundamentales en las estrategias de prevención[78]. A pesar de los avances en la comprensión acerca de los factores que influyen en la evolución y el pronóstico de las ECV, el conocimiento sobre la interacción entre el metabolismo de la glucosa y los lípidos es aún limitado [3,64,65].

La reducida variabilidad genética de la población canaria, consecuencia del prolongado aislamiento geográfico mantenido hasta mediados del siglo XX, podría explicar la elevada prevalencia de determinadas enfermedades hereditarias en el archipiélago[7,8]. Este mismo contexto genético, junto con factores ambientales y sociodemográficos, podría contribuir a que Canarias presente la mayor prevalencia de DM2 entre las comunidades autónomas españolas, así como una evolución especialmente desfavorable en cuanto a la aparición y progresión de sus complicaciones [9,10,25,28]. En este sentido, un estudio publicado en 2019[8] evidenció una prevalencia inesperadamente alta de DM2 entre individuos con HFHe portadores de la variante genética más frecuente en la isla de Gran Canaria.

La notable homogeneidad genética y ambiental de esta población la convierte en un modelo idóneo para el estudio clínico, genético y molecular de ambas enfermedades. Desde una perspectiva de medicina de precisión, la caracterización genética de la DM2 y

su posible co-segregación con la HFHe representan una oportunidad única para avanzar en estrategias de diagnóstico y tratamiento individualizado. Los hallazgos derivados de este análisis permitirán establecer un diagnóstico más certero de dos entidades clínicas con alta carga de enfermedad y morbimortalidad, ofrecer asesoramiento genético a los portadores de variantes patogénicas y, fundamentalmente, instaurar intervenciones terapéuticas tempranas orientadas a reducir tanto las complicaciones metabólicas como el riesgo cardiovascular (RCV) en esta población.

Resultados

nutrients

MDPI

Review

Diabetes and Familial Hypercholesterolemia: Interplay between Lipid and Glucose Metabolism

Ana M. González-Lleó [1,2], Rosa María Sánchez-Hernández [1,2,*], Mauro Boronat [1,2] and Ana M. Wägner [1,2,*]

[1] Endocrinology and Nutrition Department, Complejo Hospitalario Universitario Insular Materno-Infantil, 35016 Las Palmas de Gran Canaria, Spain; agonlle@gobiernodecanarias.org (A.M.G.-L.); mborcor@gobiernodecanarias.org (M.B.)

[2] Instituto Universitario de Investigaciones Biomédicas y Sanitarias, Universidad de Las Palmas de Gran Canaria, 35016 Las Palmas de Gran Canaria, Spain

* Correspondence: rsanherj@gobiernodecanarias.org (R.M.S.-H.); awagfah@gobiernodecanarias.org (A.M.W.)

Abstract: Familial hypercholesterolemia (FH) is a genetic disease characterized by high low-density lipoprotein (LDL) cholesterol (LDL-c) concentrations that increase cardiovascular risk and cause premature death. The most frequent cause of the disease is a mutation in the LDL receptor (*LDLR*) gene. Diabetes is also associated with an increased risk of cardiovascular disease and mortality. People with FH seem to be protected from developing diabetes, whereas cholesterol-lowering treatments such as statins are associated with an increased risk of the disease. One of the hypotheses to explain this is based on the toxicity of LDL particles on insulin-secreting pancreatic β-cells, and their uptake by the latter, mediated by the LDLR. A healthy lifestyle and a relatively low body mass index in people with FH have also been proposed as explanations. Its association with superimposed diabetes modifies the phenotype of FH, both regarding the lipid profile and cardiovascular risk. However, findings regarding the association and interplay between these two diseases are conflicting. The present review summarizes the existing evidence and discusses knowledge gaps on the matter.

Keywords: familial hypercholesterolemia; diabetes; LDL receptor; genetic risk; insulin resistance; review

Citation: González-Lleó, A.M.; Sánchez-Hernández, R.M.; Boronat, M.; Wägner, A.M. Diabetes and Familial Hypercholesterolemia: Interplay between Lipid and Glucose Metabolism. *Nutrients* **2022**, *14*, 1503. https://doi.org/10.3390/nu14071503

Academic Editor: Takao Kimura

Received: 4 March 2022
Accepted: 30 March 2022
Published: 3 April 2022

1. Introduction

1.1. Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetic disease characterized by high low-density lipoprotein (LDL) cholesterol (LDL-c) concentrations that increase cardiovascular risk and cause premature death [1]. The most frequent mutations are found in the LDL receptor gene (-*LDLR*- responsible for LDL uptake), though other genes involved in LDL metabolism can also cause the disease, such as apolipoprotein B 100 (*APOB*), apolipoprotein E (*APOE*) or proprotein convertase subtilisin/Kexin-type 9 (*PCSK9*) [2,3]. Heterozygous FH (HeFH) (one affected allele) is the usual presentation form, with a prevalence of 1/250 [4], higher in isolated regions [5–7]. LDL-c concentrations in people with HeFH are often twice those of the general population [8]. Homozygous FH (HoFH) is infrequent (1/160,000–1/300,000) but more severe, with LDL-c concentrations exceeding 500 mg/dL from birth. Without treatment, subjects with HoFH develop atherosclerosis before the age of 20 and die before 30 [9]. The diagnosis of FH is usually made based on LDL-c concentrations, family history, and the presence of corneal arcus, xanthomas, or xanthelasmas [8]. Although affected individuals have a higher cardiovascular risk than the general population [10], subjects with the same mutation show enormous phenotype variability. These differences might be explained by other factors such as the type of mutation [11], age [12], gender [10,13], or the existence of other concomitant diseases [14].

1.2. Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic disorders defined by increased blood glucose concentrations. The most frequent types of DM are type 1 diabetes (-T1DM- mediated by autoimmune destruction of pancreatic ß cells and absolute insulin deficiency), type 2 diabetes (-T2DM- caused by progressive loss of insulin secretion in the context of insulin resistance) and gestational DM (first diagnosed during pregnancy), but there are also other, less frequent forms of the disease, such as monogenic DM or drug-induced DM [15]. A correct classification of DM is important since both treatment and follow-up depend on it. The prevalence of DM has doubled since the 1990s [16]; nowadays, there are about 537 million subjects with DM around the world (mostly T2DM), and this is expected to continue increasing in the near future [17]. Its complex physiopathology involves modifiable factors such as weight, diet, or physical activity [18], and non-modifiable factors such as genetics, age, or gender [19]. Patients have an increased all-cause mortality [20], but about 50% die because of cardiovascular complications [21], especially women [22], and people with long-standing disease [23,24]. This cardiovascular risk is enhanced in the presence of other risk factors such as smoking, hypertension, or dyslipidemia that contribute to endothelial damage and the progression of atherosclerosis [25].

The prevalence of DM is generally lower in people with FH than in the general population [26], suggesting a relationship between glucose and lipid metabolism. The aim of this paper is to summarize the existing evidence and contribute to the understanding of the complex underlying mechanisms that relate DM and HF.

2. Familial Hypercholesterolemia and Diabetes: Molecular Causes

2.1. Genetics of FH

FH is the most common monogenic disorder. It has high penetrance (90%) and autosomal dominant inheritance [1] and is caused by mutations in genes related to LDL metabolism.

HeFH is mainly caused by loss-of-function mutations in *LDLR* (85–90%) or *APOB* (5%), or gain-of-function mutations in *PCSK9* (1–3%) [27]. Mutations have also been identified in *APOE* [3] and in the adaptor protein type 1 gene (*LDLRAP1*), the latter with autosomal recessive inheritance [28]. However, 10–40% of patients with a clinical phenotype of FH have negative genetic tests, probably representing severe polygenic forms of hypercholesterolemia [29].

HoFH is a more severe form that involves two mutations in the aforementioned genes. According to the combination of mutations, HoFH is classified into the following: true homozygotes (two equal mutations in both alleles of the same gene, mostly in *LDLR)*; compound heterozygotes (a different mutation in each allele of the same gene); double heterozygotes (two different mutations in different genes); autosomal recessive hypercholesterolemia (mutations in *LDLRAP1*) [9]. The phenotype of HFHo will depend on the degree of residual LDLR activity, which is defined by the genetic defect. Indeed, in some cases, the LDLR protein is almost absent (less than 2%), leading to the most extreme phenotypes [30].

LDLR is the most frequently affected gene in HF and more than 3000 mutations have been described so far, most of them disease-causing or pathogenic [2]. Traditionally, mutations were classified into classes I to V, with class I mutations being the most severe, where no protein synthesis is present (large rearrangements, insertions, nonsense frameshifts, or splicing mutations). Classes II-IV include alterations in LDLR transport, LDLR binding, internalization, or recycling of LDLR, corresponding to in-frame, missense mutations, or small deletions [27]. Currently, there is a tendency to simplify this classification into class 1 and non-class 1 mutations [31], which would correspond to null or defective alleles, respectively, and this correlates with the severity of the individual phenotype. Null *LDLR* allele carriers present with very high LDL-c concentrations, premature coronary heart disease and poor response to treatment [32]. However, LDL-c concentrations have been shown to improve cardiovascular risk prediction more than the genetic defect per se. A cohort study in 12,245 FH *LDLR* mutation carriers showed that the classification of pathogenic *LDLR*

variants according to LDL-c concentration percentile was indeed more accurate than class 1 vs. non-class 1. The relative risk of major cardiovascular events ranged from 2.2 in subjects with an LDL-c concentration below the 75th percentile to 13 when the LDL-c concentration was above the 98th percentile of the cohort [33].

APOB was the second gene identified to be associated with FH, also called familial defective APOB [34]. It is less frequent than FH caused by *LDLR* mutations, and there are currently about 35 pathogenic mutations described, generally located in the LDLR-binding domain of apolipoprotein B (apoB) [27]. The most common is the R3500Q mutation, which accounts for 5–10% of FH cases in northern Europe [35]. Patients with this form of FH present with less severe phenotypes than *LDLR* mutation carriers and have lower LDL-c concentrations and less cardiovascular events [36].

FH type 3 is caused by gain of function mutations in *PCSK9* [37], and there are about 30 pathogenic variants reported [27]. The phenotype is variable, with variants such as p.(Asp374Tyr), which causes an extreme FH phenotype with very high LDL-c concentrations and premature coronary heart disease [38], and other mutations affecting distinct domains of the protein, leading to milder phenotypes and better response to treatment [39].

In patients with an FH phenotype but no mutation identified, a polygenic mechanism should be considered, caused by the aggregation of common LDL-c-raising genetic variants or single nucleotide polymorphisms (SNPs), which can be studied using validated polygenic risk scores [40,41].

There are other genes that are no longer considered to cause FH, such as *STAP1*, which seemed to be associated with the disease, but subsequent in vitro and family segregation studies have shown that it does not cause FH [42,43].

2.2. Genetics of Type 2 Diabetes

Regarding the genetics of DM, there are both monogenic forms, including neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY), and the following polygenic forms: T1DM or T2DM [44]. Neonatal diabetes is caused mainly by paternally inherited duplications in chromosome 6q24 that cause overexpression of paternally imprinted genes, mutations in K_{ATP} channels, potassium inwardly rectifying channels, subfamily J, member 11 (*KCNJ11*) or ATP Binding Cassette Subfamily C Member 8 (*ABCC8*) genes, among others [45]. Mutations in the hepatocyte nuclear factor 1-α (*HNF1A*), 4-α (*HNF4A*), 1-ß (*HNF1B/TCF2*) and glucokinase (*GCK*) genes are responsible for most of the cases of MODY [46].

The development of T2DM depends on both environmental [47] and genetic causes. The genetics of T2DM are very complex, and genome-wide association studies and whole-genome sequencing have shown more than seventy genes related to the pathogenesis of the disease [48,49]. A large number of SNPs have been described in more than 400 distinct genomic regions [50]. The heritability of T2DM ranges from 20 to 80% [51], the highest concordance corresponding to monozygotic twins [52]. Despite the huge number of risk SNPs identified, each one accounts only for a small effect on the risk of T2DM, around 10–20% increase per risk allele [44]. Because of this, various genetic risk scores have been developed to evaluate the cumulative effect of multiple SNPs and to identify individuals with a high genetic risk of T2DM [53,54].

The genes with the most reported risk variants are *KCNJ11*, peroxisome proliferator-activated receptor gamma (*PPARG*), *HNF1B/TCF2* and wolfram syndrome 1 (wolframin) (*WFS1*), confirmed by genome-wide association studies [55]. Other genes related to T2DM are insulin receptor substrate 1 gene (*IRS1*) and *IRS-2*, *ABCC8*, Phosphatase and Tensin Homolog (*PTEN*), Zinc Transporter-8 Gene (*SLC30A8*), GATA Binding Protein 6 (*GATA6*), ISL LIM Homeobox 1 (*ISL-1*), Transcription Factor 7-like 2 (*TCF7L2*), Insulin-like Growth Factor 2 mRNA-Binding Protein 2 (*IGF2BP2*), among many others [48,50,56].

The effects of variants in these genes can lead to impaired insulin response, decreasing insulin sensitivity, loss of the ß cell morphology, generate oxidative stress in the pancreas, destruction of pancreatic β-cells altering insulin biosynthesis, causing insulin receptor dys-

function, etc. [48,56]. Due to the polygenic feature, many genes and their SNPs contribute to an enhanced risk of T2DM, which together with environmental triggers, like obesity, leads to the development of the disease [51].

2.3. Genetic Studies Assessing the Link between Hyperlipidemia and Type 2 Diabetes

Mendelian randomization studies suggest that there is an overlap between the risks of DM and hyperlipidemia. Indeed, after combining and analysing existing information provided by three large consortia, Fall et al. report a significant association between gene variants determining higher LDL-c and a lower risk of T2DM, whereas the association with variants determining HDL-c and triglycerides was less clear [57,58]. When constructing the risk scores, the authors excluded SNPs associated with adiposity, which they considered a possible confounder. White et al. used a modified approach in a dataset combining several genome-wide association studies, including 188,577 individuals with measured blood lipids and 34,840 with T2DM. A 130 SNP score was developed for LDL-c (explaining 7.9% of its variance), and 140 SNP scores, for HDL-c and triglycerides. For each SD (38 mg/dL) estimated increase in LDL-c, the risk of T2DM was reduced by 21% (R 0.79 (0.71–0.88)). For triglycerides, every 89 mg/dL estimated increase was also associated with a reduction in T2DM (OR 0.83 (0.72–0.95)), as was the case for every 16 mg/dL estimated increase in HDL-c (OR 0.83 (0.76–0.90)) [59]. Although the protective effect of triglycerides seems somewhat unexpected, other studies in different ethnic groups agree with this finding [60,61].

3. Familial Hypercholesterolemia and Glucose Metabolism: Risk of Diabetes

3.1. Epidemiological Studies

In 2019, the worldwide prevalence of DM was 9.3%, higher in men (9.6 vs. 9%) and in high-income countries (10.4 vs. 4%) [17]. Most epidemiological studies in FH subjects have shown a lower DM prevalence than in the general population (see Table 1). In a Dutch cohort with more than 14,000 FH subjects, only 2.8% had DM [62], whereas a British cohort showed an even lower prevalence (0.8%) [63], and intermediate results were described in 263 French-Canadian patients with FH [64]. Recently, a Spanish study with more than 1700 subjects with FH found a T2DM prevalence close to 6%, around one third of the national average [65]. However, another recently published Spanish study, performed on the island of Gran Canaria, showed an unexpectedly high prevalence of DM in HeFH *LDLR* mutation carriers (25%) [66]. Other studies show a high prevalence of DM too, above 20%, but in patients with only clinical diagnosis of FH without genetic confirmation [67,68].

Table 1. Prevalence of diabetes in representative populations with FH.

Author, Year	Country	*N*	Sample Characteristics	Diagnostic Criteria of FH	Diabetes (%)
Ferrières, 1995 [64]	Canada	263	French Canadian HeFH patients	Genetic test (*LDLR* mutation)	Men with CHD 1.9% Women and men without CHD 0%
Vuorio, 1997 [69]	Finland	179	55 HeFH with CHD and 124 HeFH without CHD	Genetic test (*LDLR* mutation)	9 and 0%, respectively
Neil, 1998 [63]	UK	1185	HeFH	Simon Broome Criteria	1.2% men 0.5% women
Fuentes, 2015 [70]	Spain	3823	2558 HeFH vs. 1265 unaffected relatives	Genetic test (*LDLR* mutation)	2.3%
Saavedra, 2015 [71]	Canada	188	HeFH	Genetic test (PCSK9-InsLEU or LDLR mutations)	4 and 2%, respectively
Besseling, 2015 [26]	Netherlands	63,320	25,137 HeFH vs. 38,183 unaffected relatives	Genetic test (*APOB*, *PCSK9* or *LDLR* mutations)	1.75%
Skoumas, 2017 [72]	Greece	280	90 HeFH vs. 112 familial combined hyperlipidemia vs. 78 controls	Clinical criteria or genetic test	2%
Climent, 2017 [65]	Spain	1732	HeFH	Definite or probable DLCN criteria	5.9%
Sun, 2018 [68]	China	289	HeFH	Definite or probable DLCN criteria	20.1%
Sánchez-Hernández, 2021 [66]	Spain	68	p.[Tyr400 Phe402del] *LDLR* carriers	Genetic test (*LDLR* mutation)	25%
Mehta, 2021 [73]	Mexico	336	332 HeFH and 4HoFH	Definite, probable, or possible DLCN criteria	11.3%

DM: diabetes mellitus, BMI: body max index, CHD: coronary heart disease, HeFH: Heterozygous familial hypercholesterolemia, HoFH: Homozygous familial hypercholesterolemia, DLCN: Dutch Lipid Clinical Network.

Regarding the relationship between FH mutations and DM, the results are not consistent. Patients with mutations in *APOB,* with a less severe phenotype, had a higher prevalence of T2DM (1.91%) than *LDLR* mutation carriers, and amongst these, the most severe phenotype (receptor-negative) had the lowest prevalence of DM (1.12%) [26]. In accordance with these findings, *PCSK9* InsLEU mutation carriers had a higher prevalence of DM and a lower incidence of coronary heart disease. However, other studies have not found an association between mutation type and DM [74,75].

3.2. Lipid-Lowering Treatment and Risk of Diabetes

In recent years, many drugs have been developed to treat hypercholesterolemia, and several studies have shown that they could alter glucose tolerance, highlighting the link between cholesterol and glucose metabolism (see Table 2).

Table 2. Studies assessing the association between lipid-lowering drugs and disorders of glucose metabolism.

Author, Year	*N*	Characteristics/Therapy	Mean Follow-Up	Mean Results	Statistical Measures (OR, HR or RR) (95% CI)
Sattar, 2010 [76]	91,140	Meta-analysis. All statins	4 years	NODM 9%	OR 1.09 (1.02–1.17)
Waters, 2013 [77]	15,056	Atorvastatin 80 mg vs. atorvastatin 10 mg or simvastatin 20–40 mg	4.9 years	0–1 NODM risk factors: NODM 3.22% vs. 3.35% 2–4 NODM risk factors: NODM 14.3% vs. 11.9%	HR 0.97 (0.77–1.22) HR 1.24 (1.08–1.42)
Cederberg, 2014 [78]	8749	Non-diabetic patients. All statins vs. control	5.9 years	NODM 11.2% vs. 5.8% High and low dose simvastatin High dose atorvastatin	HR 1.46 (1.22–1.74) HR 1.44 (1.23–1.68) and 1.28 (1.01–1.62) HR 1.37 (1.14–1.65)
Khan, 2019 [79]	163,688	Non-diabetic patients. Intensive therapy (PCSK9i or statins) vs. less intensive therapy (placebo/usual care)	4.2 years	NODM 6.1% vs. 5.8%	RR 1.07 (1.03–1.11)
Ko, 2019 [80]	2,162,119	Duration of statin use (<1 year vs. 1–2 years vs. >2 years) Cumulative dosing of statin (low-tertile vs. middle-tertile vs. high-tertile)	3.9 years	NODM 8.2% vs. 14.6% vs. 19.8% NODM 6.7% vs. 11.5% vs. 18.6%	HR 1.25 (1.21–1.28) vs. 2.22 (2.16–2.29) vs. 2.62 (2.56–2.67) HR 1.06 (1.02–1.10) vs. 1.74 (1.70–1.79) vs. 2.52 (2.47–2.57)
Choi, 2018 [81]	2483	5–10 mg rosuvastatin vs. 10–20 mg and atorvastatin vs. 2–4 mg pitavastatin	3 years	NODM 10.4% vs. 8.4% vs. 3%	HR Rosuvastatin vs. Pitavastatin: 3.9 (1.8–8.7) HR Atorvastatin vs. Pitavastatin: 2.6 (1.2–5.9)
Freeman, 2001 [82]	5974	All statins	3.5–6.1 years	NODM 2.3%	Pravastatin therapy HR 0.70 (0.50–0.99)
Hiramitsu, 2010 [83]	120	Ezetimibe	12 weeks	HbA1c: −3.4%; $p = 0.05$	
Dagli, 2007 [84]	100	High-dose pravastatin (40 mg) vs. combination low-dose pravastatin (10 mg) plus ezetimibe (10 mg)	6 months	HOMA IR: 3.16 vs. 2.05; $p = 0.01$	
Her, 2010 [85]	76	Atorvastatin 20 mg vs. rosuvastatin 10 mg vs. atorvastatin 5 mg plus ezetimibe 5 mg	8 weeks	HbA1c: +3% vs. +1.2% vs. −0.4%; $p = 0.03$	
Takeshita, 2013 [86]	32	Ezetimibe vs. placebo in NAFLD patients	6 months	HbA1c: 6.5% vs. 6%; $p = 0.041$	
Sabatine, 2017 [87]	27,564	EVOLOCUMAB vs. placebo	2.2 years	NODM 8% vs. 7.6%	HR 1.05 (0.94–1.17)
de Carvalho, 2017 [88]	68,123	Meta-analysis: PCSK9i vs. placebo	78 weeks	Mean difference in FBG 1.88 (0.91–2.68) mg/dL; $p < 0.001$ HbA1c 0.032% (0.011–0.050); $p < 0.001$ NODM	RR 1.04 (0.96–1.13); $p = 0.427$
Chen, 2019 [89]	65,957	Meta-analysis: PCSK9i vs. placebo		Global NODM ALIROCUMAB Homogeneous statin use ALIROCUMAB and EVOLOCUMAB vs. ezetimibe	RR 0.97 (0.91–1.02) RR 0.91 (0.85–0.98) RR 2.14 (1.12–4.07) RR 0.60 (0.37–0.99)
Leiter, 2022 [90]	3621	Bempedoic acid vs. placebo	1 year	NODM 0.3% vs. 0.8%; $p > 0.05$ T2DM: HbA1c −0.12% vs. 0.07%; $p < 0.0001$ pre-T2DM: HbA1c −0.06% vs. −0.02; $p < 0.0004$	
Masson, 2020 [91]	3629	Meta-analysis: bempedoic acid vs. placebo	4–52 weeks	NODM	OR 0.66 (0.48–0.90)
Handelsma, 2010 [92]	216	Colesevelam vs. placebo in pre-T2DM patients	16 weeks	FBG: −4.0 mg/dL vs. −2.0 mg/dL; $p = 0.02$ HbA1c: −0.12% vs. −0.03%; $p = 0.02$	

OR: odd ratio; HR: hazard ratio; RR: risk ratio; CI: confidence interval; NODM: new-onset diabetes mellitus; HbA1c: glycosylated hemoglobin; HOMA-IR: insulin-resistance index; NAFLD: non-alcoholic fatty liver disease; PCSK9i: PCSK9 inhibitors; FBG: fasting blood glucose; T2DM: type 2 diabetes.

3.2.1. Statins

Statins are the treatment of choice for hypercholesterolemia, both in primary and secondary prevention [93,94]. They inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), increase LDLR expression, and reduce plasma LDL-c concentration by over 50% [95]. New-onset DM (NODM) has a prevalence of 9–12% and is one of most recognized side effects of statins [76,96]. Risk increases with age in women [97], and in people with more than two risk factors for DM (impaired fasting plasma glucose, hypertriglyceridemia, hypertension, obesity, or the metabolic syndrome) [77,78]. The risk of DM seems to be independent of LDL-c concentrations [76,79] and varies according to statin type and dose, as well as exposure time [80,98]. Nevertheless, this association with NODM should not discourage health professionals from prescribing these drugs, given their proven cardiovascular benefit, especially in high-risk individuals [99,100]. Simvastatin, atorvastatin, and rosuvastatin have shown more glucose impairment, while pitavastatin has a lower risk of NODM compared with atorvastatin and rosuvastatin [81,96,101]. Pravastatin has also shown favourable results, probably related to its lower liposolubility and limited potency [82]. However, FH subjects seem to be protected against these diabetogenic effects [70].

3.2.2. Ezetimibe

Ezetimibe inhibits intestinal absorption of cholesterol by blocking the Niemann-Pick C1 like1 (NPC1L1) transporter [102], and is frequently used as a concomitant treatment to statins. Its relationship with glucose metabolism is controversial. Several studies have shown that fasting plasma glucose, glycosylated haemoglobin (HbA1c) and insulin sensitivity improve with ezetimibe treatment, both in DM and non-DM individuals [103,104]. This drug also improves inflammation markers and obesity and reduces waist circumference [83]. Based on these positive results, a possible compensatory effect on the diabetogenic effects of statins has been studied. Dragi et al. found that the combination of low-dose-pravastatin plus ezetimibe improved insulin resistance and inflammation compared with high-dose-pravastatin alone [84]. In 2018, a meta-analysis concluded that patients who used low-dose-statins plus ezetimibe for more than 3 months had lower fasting plasma glucose compared with those treated with high-dose statins [105]. Nevertheless, no differences in the HOMA-IR index were found when two statins in monotherapy were compared with a combination of low-dose-statin plus ezetimibe [85]. No significant differences were found either, in a recent study that compared statins alone versus their combination with ezetimibe in glucose intolerant patients followed for 7 years [106]. Other studies have found neutral [107] or deleterious effects on glycemic metabolism with ezetimibe, with an increase in HbA1c and hepatic long-chain fatty acids in patients with non-alcoholic fatty liver disease [86].

The discrepancies in the results could be explained by the small number of participants in some studies, insufficient follow-up, or the presence of other lipid-lowering drugs that could act as confounders.

3.2.3. PCSK9 Inhibitors (PCSK9-i)

Inhibition of the PCSK9 enzyme prevents LDLR degradation after cellular internalization, reducing LDL-c by about 60%. Approved in 2015, monoclonal antibodies against PCSK9 (alirocumab and evolocumab) have shown a favourable safety profile with few side effects [108], but the consequences on glucose metabolism are still not clear. Despite the fact that most clinical studies have not found an association between PCSK9-i and NODM or worsening of pre-existing DM [87,109].

A large study including more than 96,000 individuals followed for 1.5 years found a small but significant increase in plasma glucose and HbA1c but not a higher incidence of NODM in those treated with PCSK9-i [88]. In 2020, a meta-analysis found that alirocumab was associated with a reduction in the risk of DM and, when compared with ezetimibe

in monotherapy, evolocumab was also associated with this risk reduction. However, when used in combination with statins, an increased risk of NODM was found in the PCSK9-i group, even though the use of statins was equivalent between the experimental and active comparator arms [89]. It seems that the combination with other lipid-lowering drugs (especially statins) could change the studies' results due to the discrepancies in background treatment between groups. Furthermore, mendelian randomization studies must be interpreted carefully. As is the case for other lipid-lowering drugs, follow-up is often limited and could be insufficient to see an effect on glucose metabolism [110].

3.2.4. Bempedoic Acid

Bempedoic acid is a newly developed drug that inhibits adenosine triphosphate citrate lyase, increasing LDLR expression and reducing LDL-c [90]. In the phase 3 "CLEAR" studies, bempedoic acid was associated with a reduced incidence of DM and an improvement in fasting blood glucose and HbA1c in week 12 in pre-DM or DM subjects, without increasing NODM risk for 1 year [90,91]. A recent meta-analysis found a reduction of 34% in NODM risk [91].

3.2.5. Other Cholesterol-Lowering Drugs

Nicotinic acid (B3 vitamin) reduces triglyceride and LDL-c concentrations and raises high-density lipoprotein cholesterol (HDL-c) by up to 35% [111]. It is associated with an increased risk of NODM and higher fasting plasma glucose and HbA1c, especially in predisposed individuals, with a dose-dependent effect [112]. Niacin has other side effects, such as flushing, and does not reduce cardiovascular events in secondary prevention [113], so its use is currently limited.

Bile acid sequestrants (resins) reduce bile acid reabsorption and increase hepatic LDLR, lowering LDL-c by 15–25%. They improve the glucose profile but do not cause hypoglycemia in T2DM subjects. Similar results have been found with different resins and in both pre-DM and healthy individuals [92,112,114]. Although they have a moderate lipid-lowering effect, they could be useful in subjects with DM because of their dual effects on lipid and glucose metabolism.

3.3. Genetics and Metabolism

The cause of the lower prevalence of DM in FH subjects found in most studies is not clearly known yet. In vitro, long exposure to fatty acids has been associated to β-cells dysfunction and reduced insulin secretion, especially when coexisting with hyperglycemia [115,116]. Moreover, in vitro studies have shown that intracellular cholesterol accumulation also induces apoptosis of pancreatic β-cells [117]. LDL particle uptake causes β-cell death in a dose-dependent manner, and this toxicity can be counteracted by HDL, very LDL (VLDL) particles, or antioxidants [118]. Supporting these findings, polymorphisms in ATP-binding cassette transporter 1 gene (*ABCA1*), involved in cholesterol efflux and HDL synthesis, have been associated to obesity, the metabolic syndrome, and DM [119,120]. On the β-cell, HDL particles have an anti-inflammatory effect and participate in cholesterol efflux [121]. Higher HDL-c levels are associated with less hyperglycemia and HDL particle size is inversely correlated to T2DM risk in the general population [122].

A large meta-analysis of genetic association studies assessing the effects of cholesterol-lowering variants in or near *NPC1L1*, *HMGCR*, *PCSK9*, *ABCG5*/G8 and *LDLR* showed an overall increased risk of DM with an odds ratio of 1.19–2.42 for every 1 mmol/L (38.6 mg/dL) reduction in LDLc [110]. However, there was rather high heterogeneity in the meta-analysis, suggesting gene-specific associations with DM. Indeed, the highest risk of T2DM was associated with variants in or near *NPC1L1*, whereas the *HMGCR* locus was associated with body mass index and waist-to-hip ratio, and *PCSK9,* with higher fasting and two-hour glucose concentrations [110].

The lipotoxicity hypothesis could, at least partially, explain how statins increase NODM and how FH reduces the risk of DM. The rise in LDLR increases LDL particle

uptake by pancreatic β-cells, thereby promoting dysfunction and apoptosis, especially in those with baseline glucose disturbances. On the other hand, genetic mutations that prevent cholesterol input, like FH, could be protective and explain the inverse relationship between mutation severity and DM prevalence [123]. However, clinical studies do not clearly reflect this theory. No differences in insulin, C peptide, or fasting plasma glucose concentrations have been found comparing FH with non-FH subjects, regardless of their insulin sensitivity [124–126]. Indeed, in some studies, FH has even been associated with an increased risk of impaired glucose metabolism [7,127].

In vivo studies show controversial results. When comparing prediabetic wildtype vs. LDLR knock-out (KO) mice, no differences were observed in glucose levels, although less insulin secretion and more β-cell apoptosis were seen in LDLR KO mice [128].

In a study in PCSK9 KO and PCSK9/LDLR double knock-out mice, the former showed reduced insulin secretion and glucose intolerance, as well as cholesteryl ester accumulation in β-cells compared with WT mice. In the double knock-out mice, these alterations were restored, supporting the hypothesis that LDLR, the target of PCSK9, is responsible for the phenotype [129]. However, a later study with PCSK9 KO and PCSK9 ß-cell specific KO mice does not show any alteration on glucose homeostasis nor in β-cell function [130].

Thus, other molecular or environmental factors are probably involved in DM risk. For example, plasma lipoprotein(a) (Lp(a)) has been shown to be higher in HeFH compared with the general population [131], and an inverse association has been described between Lp(a) concentrations and the risk of T2DM [132]. However, this effect has to be confirmed, and a mechanism explaining it is still to be found.

Regarding environmental factors, a study comparing a cohort of 2185 HeFH subjects from the Spanish Dyslipidaemia Registry with a representative sample of the background population showed more favorable cardiovascular risk profiles in the former. Indeed, HeFH subjects without cardiovascular disease showed a lower body mass index and a lower prevalence of smoking than the background populations, suggesting that the lower prevalence of T2DM could, at least partially, be explained by a healthier lifestyle in patients with FH [133].

4. Coexistence of Diabetes and Familial Hypercholesterolemia: Clinical Consequences

4.1. Effects on the Lipoproteins

Cardiovascular disease is the leading cause of death in people with DM. Traditionally, DM has been considered to increase the risk of ischemic heart disease, stroke, and peripheral arterial disease by 2–4 times [134]. Although recent studies show that contemporary treatment for cardiovascular risk has reduced the excess mortality associated with the disease, DM remains a very strong independent risk factor for cardiovascular morbidity and mortality [135]. Therefore, since FH is associated with an elevated risk of premature atherosclerosis, it is conceptually reasonable to assume that the coexistence of both DM and FH has a strong impact on cardiovascular disease risk.

While decreased clearance of LDL particles and accumulation of LDL-c is the main determinant for increased cardiovascular disease in FH, multiple interconnected mechanisms have been involved in vascular damage caused by DM, including hyperglycemia-induced overproduction of reactive oxygen species, accumulation of advanced glycation products, activation of protein kinase C and chronic inflammation [136]. In addition, DM is also responsible for a characteristic cluster of lipid disorders with high atherogenic potential, known as diabetic dyslipidemia. Although diabetic dyslipidemia and FH share hyperbetalipoproteinemia as the fundamental mechanism for atherogenesis, the mechanisms behind them and their biochemical expression are different.

The hallmarks of diabetic dyslipidemia are hypertriglyceridemia and decreased HDL-c, whereas LDL-c concentrations are normal or only slightly increased. Although the mechanisms of diabetic dyslipidemia are not completely understood, it is accepted that insulin resistance is its main underlying element [137]. Under physiological conditions, insulin inhibits lipolysis in adipose tissue and activates lipoprotein lipase, an enzyme

involved in the plasma clearance of triglycerides from VLDL and chylomicrons. In a state of insulin resistance, lipolysis is not inhibited, and increased circulating free fatty acids are readily taken up by the liver and used as substrates for synthesis and subsequent release of VLDL. Hypertriglyceridemia stimulates the enzymatic activity of cholesteryl ester transfer protein and, during their passage through the circulation, VLDL particles transfer their triglycerides to HDL and LDL in exchange for cholesteryl esters [137]. Triglyceride-enriched HDL undergoes lysis by hepatic lipase, a mechanism by which they are converted into small, dense particles with reduced antioxidant, anti-inflammatory, and anti-atherogenic capacity compared to normal HDL. The smaller HDLs, in turn, are cleared more rapidly from the circulation, resulting in a decrease in HDL-c and apolipoprotein A-1 (apoA-1) concentrations [137]. In a similar manner, LDL particles also become smaller and denser due to a higher ratio of protein to lipid (LDL phenotype B). These LDL particles are resistant to receptor binding, pass more readily through the arterial wall, bind to proteoglycans and are more susceptible to oxidation [138]. On the whole, although LDL-c is not characteristically increased, diabetic dyslipidemia is characterised by an increase in the total number of apoB-containing particles (VLDL, IDL, and LDL).

Several studies have assessed the presence of phenotypic features of diabetic dyslipidemia in non-diabetic subjects with FH. LDL particles from both HoFH and HeFH patients appear to be larger, more buoyant, and more resistant to oxidation than those from healthy controls [139]. Thus, the qualitative properties of LDL do not seem to play a significant role in the development of atherosclerosis in people with FH. Furthermore, patients with FH usually have normal triglyceride concentrations. However, experimental studies have suggested that defective LDLR promotes liver uptake of chylomicrons and remnants and increases VLDL secretion [140,141]. In fact, disturbed triglyceride-rich lipoprotein metabolism and, particularly, postprandial dyslipoproteinemia have been proposed as a putative modulator of cardiovascular risk in HeFH [142]. The possible role of lipoprotein lipase in postprandial hyperlipemia among subjects with HeFH has not been specifically studied. However, individuals with HeFH who carry an *LPL* gene variant that reduces lipoprotein lipase activity, show higher triglyceride levels and lower HDL-c levels than non-carriers of this mutation [143]. This suggests that a decreased lipoprotein lipase activity, as occurs in insulin resistance, could condition the phenotype of HeFH. Finally, results have been discordant regarding serum concentrations of HDL-c in subjects with FH [141]. This is probably related to the fact that, in subjects with FH, there is an increase in both synthesis and catabolism of HDL particles, but there may be an imbalance between both processes that varies depending on population-specific genetic or environmental factors. Increased apoA-1 catabolism due to increased cholesteryl ester transfer protein activity favours the generation of small HDL particles rich in triglycerides and apolipoprotein E [144,145]. Moreover, HDL particles in subjects with FH may show different functional abnormalities not detectable by measuring HDL-c alone. This may include a defective ability to reverse cholesterol transport from macrophages and impaired anti-inflammatory and antioxidant capacity [144,145].

As mentioned above and depicted in Figure 1, it is reasonable to think that subjects with FH who develop DM may have alterations in lipid metabolism resulting from the additive effect of both diseases. A few studies have compared the clinical characteristics and lipid profiles of HeFH subjects with and without T2DM [68,74,146]. Patients with DM were older, had a higher prevalence of hypertension, and had a higher body mass index than patients without DM. As expected, they also had a lipid profile more characteristic of diabetic dyslipidemia, including higher triglyceride and lower HDL-c and apoA-1 concentrations [68,74,146], as well as higher concentrations of markers of subclinical systemic inflammation, such as C-reactive protein and neutrophil count [68], typical of individuals with insulin resistance.

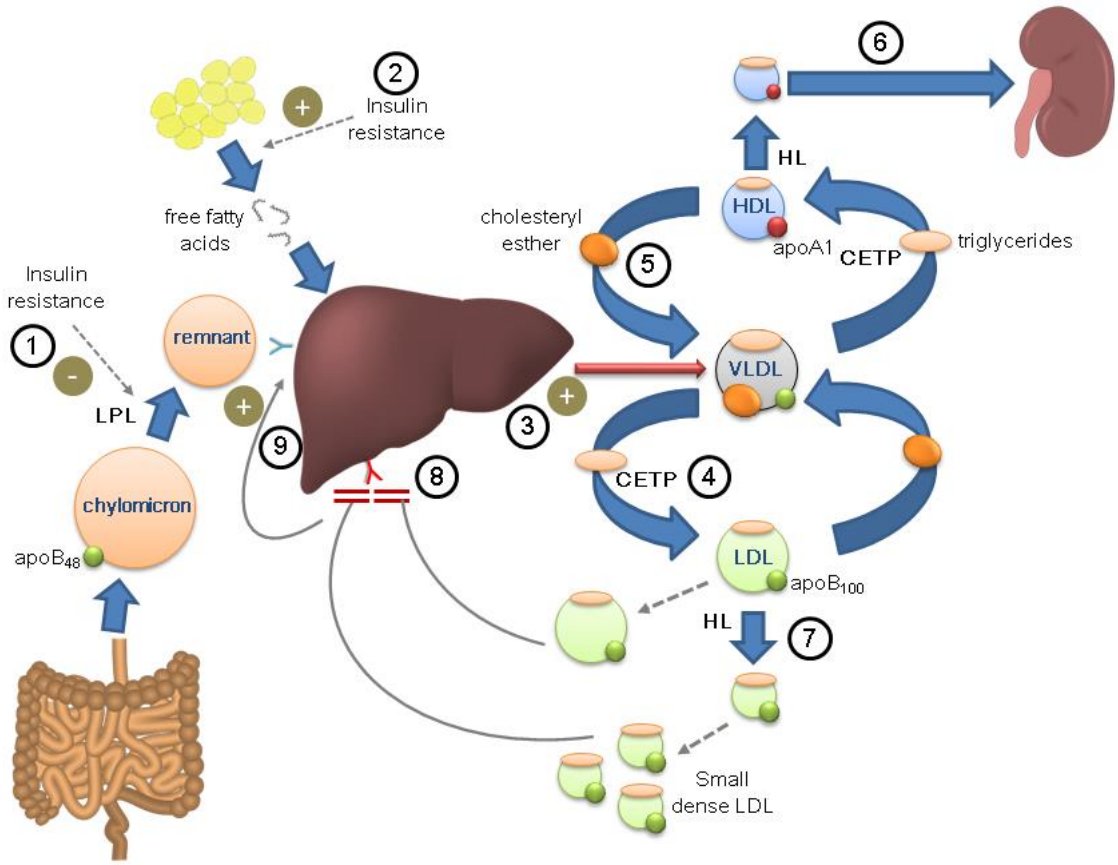


Figure 1. Potential combination of the physiopathological mechanisms of diabetes and familial hypercholesterolemia in the same individual. Diabetic dyslipidemia. Insulin resistance reduces lipoprotein lipase activity (LPL) ①, decreasing plasma triglyceride clearance, and promotes the release of free fatty acids ②, which are taken up by the liver and used for the synthesis and release of VLDL ③. VLDL exchange triglycerides and cholesterol esters with LDL ④ and HDL ⑤ through the action of cholesteryl ester transfer protein (CETP). Triglyceride-rich HDL particles, through the action of hepatic lipase (HL), are converted into smaller particles, with less anti-atherogenic properties, which are cleared more rapidly in the kidney ⑥. LDL particles also become smaller and denser (LDL phenotype B), more pro-atherogenic ⑦. Familial hypercholesterolemia. The genetic defect in LDL receptor prevents its uptake and metabolism in the liver, favoring the accumulation of LDL particles ⑧. This generates an increase in the uptake of chylomicrons and remnants in the liver ⑨, in turn boosting the synthesis of VLDL.

4.2. Effects on Chronic Arterial Wall Inflammation and Endothelial Dysfunction

In recent decades, abundant scientific evidence has highlighted the preponderant role of immunological and inflammatory mechanisms in the development and progression of atherosclerosis. As mentioned above, inflammatory mechanisms may be particularly important in the development of cardiovascular disease in individuals with T2DM. Epidemiological studies have shown that insulin resistance is associated with high concentrations of uric acid and a wide set of acute phase reactants and markers of endothelial dysfunction [147,148]. In addition, obesity, commonly present among people with T2DM, perpetuates the maintenance of a state of chronic inflammation as adipose tissue secretes a variety of proinflammatory adipocytokines such as tumour necrosis factor α, interleukins 1, 6, and 8, resistin, adiponectin, leptin, and adipsin [149].

Increased blood concentrations of different biomarkers of systemic inflammation, endothelial activation, and oxidative stress [150,151] have also been reported in FH subjects, and some authors have postulated their possible role as tools for cardiovascular risk stratification in HeFH [152]. In any case, these studies reveal that DM and FH could share

a greater predisposition to the activation of pathways leading to arterial wall inflammation and endothelial activation, promoting early mechanisms of atherosclerosis induction.

4.3. Effects on the Cardiovascular Risk

Contrary to theoretical assumptions and evidence from the general population, in which the role of DM as a cardiovascular risk factor is incontrovertible, studies that have evaluated the association between DM and cardiovascular disease in HeFH have offered contradictory results. Over the past two decades, a considerable number of studies have assessed the role of classical cardiovascular risk factors in patients with HeFH. A multi-centre retrospective cohort study performed in the Netherlands on 2400 patients (112,943 person-years) [153] found that, along with male gender, smoking, hypertension, low HDL-c and Lp(a), DM was independently associated with the presence of at least one cardiovascular event (RR 2.19; 95% CI: 1.36–3.54). Very recently, another methodologically similar study, which evaluated 1050 Japanese patients with HeFH over 19 years, also demonstrated that DM was an independent risk factor for a composite of major adverse cardiovascular events (HR 1.81; 95% CI: 1.12–2.25) [154]. However, the results of cross-sectional studies were mixed (see Table 3), and in many of them, DM was no longer significantly associated with the presence of cardiovascular disease after adjustment for other covariates. In many of the studies that found no association, either the population size was small or the prevalence of DM was very low, possibly limiting the statistical power to detect the association between DM and cardiovascular disease. In fact, a meta-analysis of 27 studies, published in 2018, aimed at assessing the association between cardiovascular disease and several classical risk factors, adding up to 41,831 subjects and 6629 cardiovascular events, found that DM was indeed an independent risk factor in HeFH (OR 1.95; 95% CI: 1.33–2.57), along with age, male sex, hypertension, body mass index, smoking, increased Lp(a), low HDL-c and a family history of cardiovascular disease [14].

In recent years, mainly due to the wide variation in established cardiovascular disease rates, even among individuals who share the same mutation and belong to the same family, there has been a growing interest in finding tools for cardiovascular risk stratification in subjects with HeFH. To this end, predictive models specifically designed for HeFH have been developed, and, strikingly, DM was not a factor to be taken into account in any of them. The first one, the Montreal-FH-SCORE, was calculated on the basis of retrospective data from a sample of 670 patients carrying a known FH-causing mutation in the *LDLR* gene, and it combines five predictor variables (age, gender, smoking, hypertension, and untreated HDL-c levels) [155]. In light of these findings, the authors conducted a specific study to investigate the impact of DM on cardiovascular disease in FH, using data from 1412 patients (73 with DM) from the FH Canada Registry. Although patients with DM had a higher prevalence of established cardiovascular disease, their results confirmed that including DM did not improve risk prediction with respect to the Montreal-FH-SCORE [146]. Subsequently, two mathematical models for cardiovascular risk prediction have been developed, but, unlike the Montreal-FH-SCORE, which had the limitation of being based on retrospective data, these were generated using prospective data from registries that collected incident cardiovascular events. The SAFEHEART Risk Equation was estimated using data from 2404 Spanish patients (104 with DM) with HeFH. Age, male sex, history of previous atherosclerotic cardiovascular disease, high blood pressure, increased body mass index, active smoking, and LDL-c and Lp(a) concentrations, but not DM, were independent predictors of incident cardiovascular events [156]. The FH-Risk SCORE was developed from a multinational prospective cohort of 3881 adults (152 with DM) with HeFH and no prior history of atherosclerotic cardiovascular disease. DM was not among the selected variables for the FH-Risk SCORE equation either, which incorporates sex, age, HDL-c, LDL-c, hypertension, smoking, and Lp(a) concentration as independent risk factors for 10-year atherosclerotic cardiovascular disease [157]. It should be noted that, until the publication of these two large studies, only a few long-term prospective studies

had been carried out to assess the occurrence of new cardiovascular events in subjects with FH and, again, DM was not a significant risk factor in any of them [36,158,159].

Overall, the information available to date suggests that the role of DM as a cardiovascular risk factor in the FH population is smaller than in the general population. However, as their authors themselves acknowledge, due to the low prevalence among the FH population, even the highest quality prospective studies included small numbers of patients with DM and may not have had sufficient statistical power to determine the true effect of the disease [156,157]. Therefore, as has already been cautioned before [160], it is probably premature to underestimate the role of DM, and clinical judgement should be applied to establish the individual risk of a person with both FH and DM, considering other specific variables related to the disease, such as type of DM, time since diagnosis, or target organ damage, as recommended in clinical practice guidelines [161].

Table 3. Cross-sectional studies that have assessed the association between diabetes and cardiovascular disease in subjects with heterozygous familial hypercholesterolemia.

Author, Year	Study Type *	Country	FH Diagnostic Criteria **	*N*	Diabetes (%)	Univariate Association OR (95% CI)	Multivariate Association OR (95% CI)	Adjusting Covariates
Hopkins, 2001 [162]	RR	USA	MEDPED criteria	262	3.0	NS	NS	Age, sex, BMI, smoking, waist to hip ratio, hypertension, HDL-c, triglycerides, small LDL, Lp(a), homocysteine, insulin, white cell count, C-reactive protein, xanthomas, intima-medial thickness, angiotensin-converting enzyme I/D polymorphism
De Sauvage, 2003 [163]	MC	Netherlands	Genetic test or definite DLCN criteria	526	2.1	17.61 (2.25–137.8)	NS	Age, sex, BMI, smoking, total-c, LDL-c, HDL-c, triglycerides, Lp(a), apo A1, apo B, homocysteine
Allard, 2014 [164]	SC	Canada	Definite DLCN criteria	409	6.4	3.2 (1.9–5.6)	3.6 (2.0–6.5)	Sex, BMI, smoking, family history of premature CVD, hypertension, LDL-c, HDL-c, triglycerides, Lp(a)
Alonso, 2014 [165]	MC	Spain	Genetic test	1960	3.9	Non reported	NS	Sex, BMI, smoking, hypertension, HDL-c, triglycerides, Lp(a), type of mutation, xanthomas
Besseling, 2014 [62]	NR	Netherlands	Genetic test	14,283	2.8	6.40 (5.21–7.86)	1.37 (1.03–1.82)	Age, sex, BMI, smoking, hypertension, lipid profile
Pereira, 2014 [166]	SC	Brazil	Definite or probable DLCN criteria	202	17.3	2.23 (1.05–4.75)	NS	Age, sex, BMI, smoking, hypertension, sedentary lifestyle, LDL-c, HDL-c, triglycerides, glucose, creatinine, xanthomas, corneal arcus, ankle-brachial index, claudication
Chan, 2015 [167]	SC	Australia	Genetic test	390	1.3	2.74 (1.06–7.08)	NS	Obesity, smoking, hypertension, CKD, LDL-c, HDL-c, triglycerides, Lp(a)
De Goma, 2016 [168]	NR	USA	Genetic test or any set of clinical criteria	1295	13	3.08 (2.04–4.64)	1.74 (1.08–2.82)	Age, smoking, hypertension, total-c, low HDL-c
Paquette, 2016 [155]	SC	Canada	Genetic test	670	3.3	3.5 (1.45–8.47)	NS	Age, sex, BMI, smoking, hypertension, prior statin use, total-c, LDL-c, HDL-c, triglycerides, VLDL-c, non-HDL-c, Lp(a), apoB
Paquette, 2017 [169]	MC	Canada	Genetic test	1388	4.5	3.28 (1.92–5.619	NS	Age, sex, BMI, smoking, hypertension, prior statin use, total-c, LDL-c, HDL-c, triglycerides, VLDL-c, non-HDL-c, Lp(a), apo B
Galema Boers, 2017 [170]	SC	Netherlands	Genetic test or definite or probable DLCN criteria	821	4	4.39 (2.15–8.97)	NS	Age, sex, BMI, smoking, hypertension, family history of CVD, previous cardiovascular disease, triglycerides, high LDL-c, low HDL-c.
Paquette, 2019 [146]	MC	Canada	Definite, probable or possible DLCN criteria	1412	5.2	2.9 (1.8–4.7)	NS	Montreal-FH-SCORE
Pérez-Calahorra, 2019 [171]	NR	Spain	Genetic test or definite or probable DLCN criteria	1958	6.5	4.99 (3.43–7.26)	NS	
Michikura, 2022 [172]	SC	Japan	Genetic test	176	12	Non reported	NS	Age, sex, BMI, smoking, hypertension, LDL-c, HDL-c, triglycerides, Achilles tendon elasticity index

* Type of study. SC: single-centre; MC: multicentre; RR: regional registry; NR: national registry. ** Diagnostic criteria. MEDPED: Make Early Diagnosis to Prevent Early Deaths System; DLCN: Dutch Lipid Clinic Network; NS: Not significant; BMI: body mass index; CVD: cardiovascular disease; c: cholesterol.

5. Knowledge Gaps and Further Research

The previous sections have highlighted the interplay between lipid and glucose metabolism, but also the controversy in this area. The inverse correlation between LDL-c concentrations and the risk of DM is supported by the low risk of DM in most populations with HF, by mendelian randomization studies, and by the increased risk of DM associated with some cholesterol-lowering agents, especially statins. However, results are inconsistent, and robust mechanistic studies are sparse. Furthermore, healthy behavior in people with FH could be associated with lower body mass index and a lower risk of T2DM.

There are several approaches that could fill in some of the existing knowledge gaps.

1. In FH populations where DM is more frequent than in the general population, family co-segregation studies could be performed, comparing the prevalence of DM and pre-DM in FH-causing mutation carriers and non-carriers in the same families;
2. Studies focused on glucose tolerance, insulin secretion, and insulin resistance in whole-body and β-cell specific *LDLR* (or other FH-related genes) knock-out animal models, as performed already for *PCSK9* [129,130];
3. FH-causing-mutation-specific studies in β-cells and islets, assessing their viability and function;
4. Larger and longer prospective studies assessing the incidence of DM in FH and non-FH populations, as well as the cardiovascular risk of the combination of FH and DM.

6. Conclusions

Both DM and FH are associated with an increased risk of cardiovascular disease. Many studies suggest that FH is protective against the development of DM and that cholesterol-lowering treatments, especially statins, increase the risk of DM. Indeed, the LDLR is hypothesized to play a role in the toxicity of (or protection from) cholesterol on the β-cells. Their reduced amount or function in HF would protect the cells against LDL particle entry, whereas their increase would promote it and, thus, damage the β-cells. Nevertheless, this hypothesis is still to be proven. Indeed, a healthy lifestyle associated with a relatively low body mass index in people with FH could also account for some of the protection against DM. On the other hand, there are also studies showing an increased prevalence of DM in people with FH, and not all cholesterol-lowering drugs are associated with an increased risk of DM. The combination of FH and DM would be expected to be associated with an especially high risk of cardiovascular disease. However, existing evidence suggests that other classical cardiovascular risk factors modulate cardiovascular risk in FH, but DM does not play a highly relevant role. Short follow-up and small numbers of people with DM advise that this conclusion should be drawn with caution. Much research is still needed to fully understand the interplay between glucose and lipid metabolism in FH and DM.

Author Contributions: Conceptualization, A.M.W., R.M.S.-H. and M.B.; writing—original draft preparation, A.M.G.-L., R.M.S.-H. and M.B.; writing—review and editing, R.M.S.-H. and A.M.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Instituto de Salud Carlos III (ISCIII), Spain with grants CM 19/00116 (AMGL), INT20/00032 (RMSH) and PI 20/0084, partially funded with European Union Regional Development Funds, "A way of doing Europe".

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We would like to thank Yeray Brito-Casillas for assistance with reference management.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Goldstein, J.L.; Schrott, H.G.; Hazzard, W.R.; Bierman, E.L.; Motulsky, A.G. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J. Clin. Investig.* **1973**, *52*, 1544–1568. [CrossRef] [PubMed]
2. Landrum, M.J.; Lee, J.M.; Benson, M.; Brown, G.; Chao, C.; Chitipiralla, S.; Gu, B.; Hart, J.; Hoffman, D.; Hoover, J.; et al. ClinVar: Public archive of interpretations of clinically relevant variants. *Nucleic Acids Res.* **2016**, *44*, D862–D868. [CrossRef] [PubMed]
3. Cenarro, A.; Etxebarria, A.; De Castro-Orós, I.; Stef, M.; Bea, A.M.; Palacios, L.; Mateo-Gallego, R.; Benito-Vicente, A.; Ostolaza, H.; Tejedor, T.; et al. The p.Leu167del Mutation in APOE Gene Causes Autosomal Dominant Hypercholesterolemia by Down-regulation of LDL Receptor Expression in Hepatocytes. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 2113–2121. [CrossRef]
4. De Ferranti, S.D.; Rodday, A.M.; Mendelson, M.M.; Wong, J.B.; Leslie, L.K.; Sheldrick, R.C. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States national health and nutrition examination surveys (NHANES). *Circulation* **2016**, *133*, 1067–1072. [CrossRef]
5. Steyn, K.; Goldberg, Y.P.; Kotze, M.J.; Steyn, M.; Swanepoel, A.S.P.; Fourie, J.M.; Coetzee, G.A.; Van Der Westhuyzen, D.R. Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. *Hum. Genet.* **1996**, *98*, 479–484. [CrossRef]
6. Couture, P.; Morissette, J.; Gaudet, D.; Vohl, M.C.; Gagné, C.; Bergeron, J.; Després, J.P.; Simard, J. Fine mapping of low-density lipoprotein receptor gene by genetic linkage on chromosome 19p13.1-p13.3 and study of the founder effect of four French Canadian low-density lipoprotein receptor gene mutations. *Atherosclerosis* **1999**, *143*, 145–151. [CrossRef]
7. Sánchez-Hernández, R.M.; Tugores, A.; Nóvoa, F.J.; Brito-Casillas, Y.; Expósito-Montesdeoca, A.B.; Garay, P.; Bea, A.M.; Riaño, M.; Pocovi, M.; Civeira, F.; et al. The island of Gran Canaria: A genetic isolate for familial hypercholesterolemia. *J. Clin. Lipidol.* **2019**, *13*, 618–626. [CrossRef]
8. Benito-Vicente, A.; Uribe, K.B.; Jebari, S.; Galicia-Garcia, U.; Ostolaza, H.; Martin, C. Familial Hypercholesterolemia: The Most Frequent Cholesterol Metabolism Disorder Caused Disease. *Int. J. Mol. Sci.* **2018**, *19*, 3426. [CrossRef]
9. Cuchel, M.; Bruckert, E.; Ginsberg, H.N.; Raal, F.J.; Santos, R.D.; Hegele, R.A.; Kuivenhoven, J.A.; Nordestgaard, B.G.; Descamps, O.S.; Steinhagen-Thiessen, E.; et al. Homozygous familial hypercholesterolaemia: New insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur. Heart J.* **2014**, *35*, 2146–2157. [CrossRef]
10. Perak, A.M.; Ning, H.; De Ferranti, S.D.; Gooding, H.C.; Wilkins, J.T.; Lloyd-Jones, D.M. Long-Term Risk of Atherosclerotic Cardiovascular Disease in US Adults with the Familial Hypercholesterolemia Phenotype. *Circulation* **2016**, *134*, 9–19. [CrossRef]
11. Di Taranto, M.D.; Giacobbe, C.; Fortunato, G. Familial hypercholesterolemia: A complex genetic disease with variable phenotypes. *Eur. J. Med. Genet.* **2020**, *63*, 103831. [CrossRef] [PubMed]
12. Masana, L.; Zamora, A.; Plana, N.; Comas-Cufí, M.; Garcia-Gil, M.; Martí-Lluch, R.; Ponjoan, A.; Alves-Cabratosa, L.; Elosua, R.; Marrugat, J.; et al. Incidence of Cardiovascular Disease in Patients with Familial Hypercholesterolemia Phenotype: Analysis of 5 Years Follow-Up of Real-World Data from More than 1.5 Million Patients. *J. Clin. Med.* **2019**, *8*, 1080. [CrossRef] [PubMed]
13. Alonso, R.; Mata, N.; Castillo, S.; Fuentes, F.; Saenz, P.; Muñiz, O.; Galiana, J.; Figueras, R.; Diaz, J.L.; Gomez-Enterría, P.; et al. Cardiovascular disease in familial hypercholesterolaemia: Influence of low-density lipoprotein receptor mutation type and classic risk factors. *Atherosclerosis* **2008**, *200*, 315–321. [CrossRef] [PubMed]
14. Akioyamen, L.E.; Genest, J.; Chu, A.; Inibhunu, H.; Ko, D.T.; Tu, J.V. Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: A systematic review and meta-analysis. *J. Clin. Lipidol.* **2019**, *13*, 15–30. [CrossRef]
15. Committee, A.D.A.P.P. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes Care* **2022**, *45*, S17–S38. [CrossRef]
16. Liu, J.; Ren, Z.H.; Qiang, H.; Wu, J.; Shen, M.; Zhang, L.; Lyu, J. Trends in the incidence of diabetes mellitus: Results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention. *BMC Public Health* **2020**, *20*, 1415. [CrossRef]
17. Saeedi, P.; Petersohn, I.; Salpea, P.; Malanda, B.; Karuranga, S.; Unwin, N.; Colagiuri, S.; Guariguata, L.; Motala, A.A.; Ogurtsova, K.; et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res. Clin. Pract.* **2019**, *157*, 107843. [CrossRef]
18. Kolb, H.; Martin, S. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. *BMC Med.* **2017**, *15*, 131. [CrossRef]
19. Boles, A.; Kandimalla, R.; Reddy, P.H. Dynamics of diabetes and obesity: Epidemiological perspective. *Biochim. Biophys. Acta. Mol. Basis Dis.* **2017**, *1863*, 1026–1036. [CrossRef]
20. Htay, T.; Soe, K.; Lopez-Perez, A.; Doan, A.H.A.; Romagosa, M.A.; Aung, K.K. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *Curr. Cardiol. Rep.* **2019**, *21*, 45. [CrossRef]
21. Morrish, N.J.; Wang, S.L.; Stevens, L.K.; Fuller, J.H.; Keen, H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* **2001**, *44* (Suppl. 2), S14–S21. [CrossRef] [PubMed]

22. Glovaci, D.; Fan, W.; Wong, N.D. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. *Curr. Cardiol. Rep.* **2019**, *21*, 21. [CrossRef]
23. Rawshani, A.; Sattar, N.; Franzén, S.; Rawshani, A.; Hattersley, A.T.; Svensson, A.M.; Eliasson, B.; Gudbjörnsdottir, S. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: A nationwide, register-based cohort study. *Lancet* **2018**, *392*, 477–486. [CrossRef]
24. Gregg, E.W.; Cheng, Y.J.; Srinivasan, M.; Lin, J.; Geiss, L.S.; Albright, A.L.; Imperatore, G. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: An epidemiological analysis of linked national survey and vital statistics data. *Lancet* **2018**, *391*, 2430–2440. [CrossRef]
25. Dokken, B.B. The pathophysiology of cardiovascular disease and diabetes: Beyond blood pressure and lipids. *Diabetes Spectr.* **2008**, *21*, 160–165. [CrossRef]
26. Besseling, J.; Kastelein, J.J.P.; Defesche, J.C.; Hutten, B.A.; Hovingh, G.K. Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. *JAMA* **2015**, *313*, 1029–1036. [CrossRef]
27. Bruikman, C.S.; Hovingh, G.K.; Kastelein, J.J.P. Molecular basis of familial hypercholesterolemia. *Curr. Opin. Cardiol.* **2017**, *32*, 262–266. [CrossRef]
28. Soutar, A.K.; Naoumova, R.P.; Traub, L.M. Genetics, clinical phenotype, and molecular cell biology of autosomal recessive hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 1963–1970. [CrossRef]
29. Civeira, F.F.; De Castro-Orós, I.; Pocoví, M. The genetic basis of familial hypercholesterolemia: Inheritance, linkage, and mutations. *Appl. Clin. Genet.* **2010**, *3*, 53. [CrossRef]
30. Sánchez-Hernández, R.M.; Civeira, F.; Stef, M.; Perez-Calahorra, S.; Almagro, F.; Plana, N.; Novoa, F.J.; Sáenz-Aranzubía, P.; Mosquera, D.; Soler, C.; et al. Homozygous Familial Hypercholesterolemia in Spain: Prevalence and Phenotype-Genotype Relationship. *Circ. Cardiovasc. Genet.* **2016**, *9*, 504–510. [CrossRef]
31. Goldberg, A.C.; Hopkins, P.N.; Toth, P.P.; Ballantyne, C.M.; Rader, D.J.; Robinson, J.G.; Daniels, S.R.; Gidding, S.S.; de Ferranti, S.D.; Ito, M.K.; et al. Familial hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J. Clin. Lipidol.* **2011**, *5*, S1–S8. [CrossRef] [PubMed]
32. Santos, R.D.; Gidding, S.S.; Hegele, R.A.; Cuchel, M.A.; Barter, P.J.; Watts, G.F.; Baum, S.J.; Catapano, A.L.; Chapman, M.J.; Defesche, J.C.; et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: A consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol.* **2016**, *4*, 850–861. [CrossRef]
33. Hartgers, M.L.; Hovingh, G.K.; Kastelein, J.J.; Huijgen, R. Familial Hypercholesterolemia: Classification of Mutation Severity According to Percentile Low-Density Lipoprotein Cholesterol Useful for Predicting Coronary Artery Disease Risk. *Circulation* **2016**, *134*, A19939.
34. Soria, L.F.; Ludwig, E.H.; Clarke, H.R.G.; Vega, G.L.; Grundy, S.M.; McCarthy, B.J. Association between a specific apolipoprotein B mutation and familial defective apolipoprotein B-100. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 587–591. [CrossRef] [PubMed]
35. Tybjærg-Hansen, A.; Humphries, S.E. Familial defective apolipoprotein B-100: A single mutation that causes hypercholesterolemia and premature coronary artery disease. *Atherosclerosis* **1992**, *96*, 91–107. [CrossRef]
36. Futema, M.; Taylor-Beadling, A.; Williams, M.; Humphries, S.E. Genetic testing for familial hypercholesterolemia-past, present, and future. *J. Lipid Res.* **2021**, *62*, 100139. [CrossRef]
37. Abifadel, M.; Varret, M.; Rabès, J.P.; Allard, D.; Ouguerram, K.; Devillers, M.; Cruaud, C.; Benjannet, S.; Wickham, L.; Erlich, D.; et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat. Genet.* **2003**, *34*, 154–156. [CrossRef]
38. Naoumova, R.P.; Tosi, I.; Patel, D.; Neuwirth, C.; Horswell, S.D.; Marais, A.D.; Van Heyningen, C.; Soutar, A.K. Severe hypercholesterolemia in four British families with the D374Y mutation in the PCSK9 gene: Long-term follow-up and treatment response. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 2654–2660. [CrossRef]
39. Sánchez-Hernández, R.M.; Di Taranto, M.D.; Benito-Vicente, A.; Uribe, K.B.; Lamiquiz-Moneo, I.; Larrea-Sebal, A.; Jebari, S.; Galicia-Garcia, U.; Nóvoa, F.J.; Boronat, M.; et al. The Arg499His gain-of-function mutation in the C-terminal domain of PCSK9. *Atherosclerosis* **2019**, *289*, 162–172. [CrossRef]
40. Talmud, P.J.; Shah, S.; Whittall, R.; Futema, M.; Howard, P.; Cooper, J.A.; Harrison, S.C.; Li, K.; Drenos, F.; Karpe, F.; et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: A case-control study. *Lancet* **2013**, *381*, 1293–1301. [CrossRef]
41. Khera, A.V.; Chaffin, M.; Aragam, K.G.; Haas, M.E.; Roselli, C.; Choi, S.H.; Natarajan, P.; Lander, E.S.; Lubitz, S.A.; Ellinor, P.T.; et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* **2018**, *50*, 1219–1224. [CrossRef] [PubMed]
42. Loaiza, N.; Hartgers, M.L.; Reeskamp, L.F.; Balder, J.W.; Rimbert, A.; Bazioti, V.; Wolters, J.C.; Winkelmeijer, M.; Jansen, H.P.G.; Dallinga-Thie, G.M.; et al. Taking One Step Back in Familial Hypercholesterolemia: STAP1 Does Not Alter Plasma LDL (Low-Density Lipoprotein) Cholesterol in Mice and Humans. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 973–985. [CrossRef] [PubMed]
43. Lamiquiz-Moneo, I.; Restrepo-Córdoba, M.A.; Mateo-Gallego, R.; Bea, A.M.; del Pino Alberiche-Ruano, M.; García-Pavía, P.; Cenarro, A.; Martín, C.; Civeira, F.; Sánchez-Hernández, R.M. Predicted pathogenic mutations in STAP1 are not associated with clinically defined familial hypercholesterolemia. *Atherosclerosis* **2020**, *292*, 143–151. [CrossRef]

44. Wang, X.; Strizich, G.; Hu, Y.; Wang, T.; Kaplan, R.C.; Qi, Q. Genetic markers of type 2 diabetes: Progress in genome-wide association studies and clinical application for risk prediction. *J. Diabetes* **2016**, *8*, 24–35. [CrossRef] [PubMed]
45. Zhang, H.; Colclough, K.; Gloyn, A.L.; Pollin, T.I. Monogenic diabetes: A gateway to precision medicine in diabetes. *J. Clin. Investig.* **2021**, *131*, e142244. [CrossRef] [PubMed]
46. Weinreich, S.S.; Bosma, A.; Henneman, L.; Rigter, T.; Spruijt, C.M.J.; Grimbergen, A.J.E.M.A.; Breuning, M.H.; De Koning, E.J.P.; Losekoot, M.; Cornel, M.C. A decade of molecular genetic testing for MODY: A retrospective study of utilization in The Netherlands. *Eur. J. Hum. Genet.* **2015**, *23*, 29–33. [CrossRef]
47. Dong, G.; Qu, L.; Gong, X.; Pang, B.; Yan, W.; Wei, J. Effect of Social Factors and the Natural Environment on the Etiology and Pathogenesis of Diabetes Mellitus. *Int. J. Endocrinol.* **2019**, *2019*, 8749291. [CrossRef]
48. Yahaya, T.O.; Salisu, T.F. A Review of Type 2 Diabetes Mellitus Predisposing Genes. *Curr. Diabetes Rev.* **2019**, *16*, 52–61. [CrossRef]
49. Mambiya, M.; Shang, M.; Wang, Y.; Li, Q.; Liu, S.; Yang, L.; Zhang, Q.; Zhang, K.; Liu, M.; Nie, F.; et al. The Play of Genes and Non-genetic Factors on Type 2 Diabetes. *Front. Public Health* **2019**, *7*, 349. [CrossRef]
50. Sirdah, M.M.; Reading, N.S. Genetic predisposition in type 2 diabetes: A promising approach toward a personalized management of diabetes. *Clin. Genet.* **2020**, *98*, 525–547. [CrossRef]
51. Prasad, R.B.; Groop, L. Genetics of type 2 diabetes-pitfalls and possibilities. *Genes* **2015**, *6*, 87–123. [CrossRef] [PubMed]
52. Medici, F.; Hawa, M.; Ianari, A.; Pyke, D.A.; Leslie, R.D.G. Concordance rate for type II diabetes mellitus in monozygotic twins: Actuarial analysis. *Diabetologia* **1999**, *42*, 146–150. [CrossRef] [PubMed]
53. Imamura, M.; Shigemizu, D.; Tsunoda, T.; Iwata, M.; Maegawa, H.; Watada, H.; Hirose, H.; Tanaka, Y.; Tobe, K.; Kaku, K.; et al. Assessing the clinical utility of a genetic risk score constructed using 49 susceptibility alleles for type 2 diabetes in a Japanese population. *J. Clin. Endocrinol. Metab.* **2013**, *98*, E1667–E1673. [CrossRef] [PubMed]
54. Chen, X.; Liu, C.; Si, S.; Li, Y.; Li, W.; Yuan, T.; Xue, F. Genomic risk score provides predictive performance for type 2 diabetes in the UK biobank. *Acta Diabetol.* **2021**, *58*, 467–474. [CrossRef]
55. Hertel, J.K.; Johansson, S.; Midthjell, K.; Nygård, O.; Njølstad, P.R.; Molven, A. Type 2 diabetes genes—Present status and data from Norwegian studies. *Nor. Epidemiol.* **2013**, *23*, 9–22. [CrossRef]
56. Szabo, M.; Máté, B.; Csép, K.; Benedek, T. Genetic Approaches to the Study of Gene Variants and Their Impact on the Pathophysiology of Type 2 Diabetes. *Biochem. Genet.* **2018**, *56*, 22–55. [CrossRef]
57. Fall, T.; Xie, W.; Poon, W.; Yaghootkar, H.; Magi, R.; Knowles, J.W.; Lyssenko, V.; Weedon, M.; Frayling, T.M.; Ingelsson, E. Using genetic variants to assess the relationship between circulating lipids and type 2 diabetes. *Diabetes* **2015**, *64*, 2676–2684. [CrossRef]
58. Swerdlow, D.I.; Sattar, N. Blood Lipids and Type 2 Diabetes Risk: Can Genetics Help Untangle the Web? *Diabetes* **2015**, *64*, 2344–2345. [CrossRef]
59. White, J.; Swerdlow, D.I.; Preiss, D.; Fairhurst-Hunter, Z.; Keating, B.J.; Asselbergs, F.W.; Sattar, N.; Humphries, S.E.; Hingorani, A.D.; Holmes, M.V. Association of Lipid Fractions with Risks for Coronary Artery Disease and Diabetes. *JAMA Cardiol.* **2016**, *1*, 692–699. [CrossRef]
60. Klimentidis, Y.C.; Wineinger, N.E.; Vazquez, A.I.; De Los Campos, G. Multiple metabolic genetic risk scores and type 2 diabetes risk in three racial/ethnic groups. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E1814–E1818. [CrossRef]
61. Klimentidis, Y.C.; Chougule, A.; Arora, A.; Frazier-Wood, A.C.; Hsu, C.H. Triglyceride-Increasing Alleles Associated with Protection against Type-2 Diabetes. *PLoS Genet.* **2015**, *11*, e1005204. [CrossRef] [PubMed]
62. Besseling, J.; Kindt, I.; Hof, M.; Kastelein, J.J.P.; Hutten, B.A.; Hovingh, G.K. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: A study of a cohort of 14,000 mutation carriers. *Atherosclerosis* **2014**, *233*, 219–223. [CrossRef]
63. Neil, H.A.W.; Betteridge, D.J.; Broome, K.; Durrington, P.N.; Hawkins, M.M.; Humphries, S.E.; Mann, J.I.; Miller, J.P.; Thompson, G.R.; Thorogood, M.; et al. Mortality in treated heterozygous familial hypercholesterolaemia: Implications for clinical management. *Atherosclerosis* **1999**, *142*, 105–112. [CrossRef]
64. Ferriéres, J.; Lambert, J.; Lussier-Cacan, S.; Davignon, J. Coronary artery disease in heterozygous familial hypercholesterolemia patients with the same LDL receptor gene mutation. *Circulation* **1995**, *92*, 290–295. [CrossRef] [PubMed]
65. Climent, E.; Pérez-Calahorra, S.; Marco-Benedí, V.; Plana, N.; Sánchez, R.; Ros, E.; Ascaso, J.F.; Puzo, J.; Almagro, F.; Lahoz, C.; et al. Effect of LDL cholesterol, statins and presence of mutations on the prevalence of type 2 diabetes in heterozygous familial hypercholesterolemia. *Sci. Rep.* **2017**, *7*, 5596. [CrossRef]
66. Sánchez-Hernández, R.M.; González-Lleó, A.M.; Tugores, A.; Brito-Casillas, Y.; Civeira, F.; Boronat, M.; Wägner, A. Familial hypercholesterolemia in Gran Canaria: Founder mutation effect and high frequency of diabetes. *Clin. E Investig. En Arterioscler.* **2021**, *33*, 247–253. [CrossRef] [PubMed]
67. Lalić, K.; Rajković, N.; Popović, L.; Lukač, S.S.; Stošić, L.; Rasulić, I.; Lalić, N.M. The effects of 3-year statin therapy and the achievement of LDL cholesterol target values in familial hypercholesterolemia patients: An experience from Serbia. *Atherosclerosis* **2018**, *277*, 298–303. [CrossRef]
68. Sun, D.; Cao, Y.X.; You, X.D.; Zhou, B.Y.; Li, S.; Guo, Y.L.; Zhang, Y.; Wu, N.Q.; Zhu, C.G.; Gao, Y.; et al. Clinical and genetic characteristics of familial hypercholesterolemia patients with type 2 diabetes. *J. Endocrinol. Investig.* **2019**, *42*, 591–598. [CrossRef]
69. Vuorio, A.F.; Turtola, H.; Piilahti, K.-M.; Repo, P.; Kanninen, T.; Kontula, K. Familial Hypercholesterolemia in the Finnish North Karelia. *Arterioscler. Thromb. Vasc. Biol.* **1997**, *17*, 3127–3138. [CrossRef]

70. Fuentes, F.; Alcala-Diaz, J.F.; Watts, G.F.; Alonso, R.; Muñiz, O.; Díaz-Díaz, J.L.; Mata, N.; Sanchez Muñoz-Torrero, J.F.; Brea, Á.; Galiana, J.; et al. Statins do not increase the risk of developing type 2 diabetes in familial hypercholesterolemia: The SAFEHEART study. *Int. J. Cardiol.* **2015**, *201*, 79–84. [CrossRef]
71. Saavedra, Y.G.L.; Dufour, R.; Baass, A. Familial hypercholesterolemia: PCSK9 InsLEU genetic variant and prediabetes/diabetes risk. *J. Clin. Lipidol.* **2015**, *9*, 786–793. [CrossRef] [PubMed]
72. Skoumas, I.; Ioakeimidis, N.; Vlachopoulos, C.; Chrysohoou, C.; Michalakeas, C.; Georgakopoulos, C.; Katsi, V.; Panagiotakos, D.; Tousoulis, D. Statin Therapy and Risk of Diabetes Mellitus in Aging Patients with Heterozygous Familial Hypercholesterolemia or Familial Combined Hyperlipidemia: A 10-Year Follow-Up. *Angiology* **2018**, *69*, 242–248. [CrossRef] [PubMed]
73. Mehta, R.; Martagon, A.J.; Galan Ramirez, G.A.; Antonio-Villa, N.E.; Vargas-Vázquez, A.; Elias-Lopez, D.; Gonzalez-Retana, G.; Rodríguez-Encinas, B.; Ceballos-Macías, J.J.; Romero-Zazueta, A.; et al. Familial hypercholesterolemia in Mexico: Initial insights from the national registry. *J. Clin. Lipidol.* **2021**, *15*, 124–133. [CrossRef] [PubMed]
74. Climent, E.; Pérez-Calahorra, S.; Benaiges, D.; Pintó, X.; Suárez-Tembra, M.; Plana, N.; Sánchez-Hernández, R.M.; Valdivielso, P.; Ascaso, J.F.; Pedro-Botet, J. Clinical and genetic differences between heterozygous familial hypercholesterolemia patients with and without type 2 diabetes. *Rev. Esp. Cardiol.* **2020**, *73*, 718–724. [CrossRef] [PubMed]
75. Xu, H.; Ryan, K.A.; Jaworek, T.J.; Southam, L.; Reid, J.G.; Overton, J.D.; Baras, A.; Puurunen, M.K.; Zeggini, E.; Taylor, S.I.; et al. Familial Hypercholesterolemia and Type 2 Diabetes in the Old Order Amish. *Diabetes* **2017**, *66*, 2054–2058. [CrossRef] [PubMed]
76. Sattar, N.; Preiss, D.; Murray, H.M.; Welsh, P.; Buckley, B.M.; de Craen, A.J.; Seshasai, S.R.K.; McMurray, J.J.; Freeman, D.J.; Jukema, J.W.; et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet* **2010**, *375*, 735–742. [CrossRef]
77. Waters, D.D.; Ho, J.E.; Boekholdt, S.M.; Demicco, D.A.; Kastelein, J.J.P.; Messig, M.; Breazna, A.; Pedersen, T.R. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: Effect of baseline risk factors for diabetes. *J. Am. Coll. Cardiol.* **2013**, *61*, 148–152. [CrossRef]
78. Cederberg, H.; Stančáková, A.; Yaluri, N.; Modi, S.; Kuusisto, J.; Laakso, M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: A 6 year follow-up study of the METSIM cohort. *Diabetologia* **2015**, *58*, 1109–1117. [CrossRef]
79. Khan, S.U.; Rahman, H.; Okunrintemi, V.; Riaz, H.; Khan, M.S.; Sattur, S.; Kaluski, E.; Lincoff, A.M.; Martin, S.S.; Blaha, M.J. Association of Lowering Low-Density Lipoprotein Cholesterol with Contemporary Lipid-Lowering Therapies and Risk of Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.* **2019**, *8*, e011581. [CrossRef]
80. Ko, M.J.; Jo, A.J.; Kim, Y.J.; Kang, S.H.; Cho, S.; Jo, S.H.; Park, C.Y.; Yun, S.C.; Lee, W.J.; Park, D.W. Time- and Dose-Dependent Association of Statin Use with Risk of Clinically Relevant New-Onset Diabetes Mellitus in Primary Prevention: A Nationwide Observational Cohort Study. *J. Am. Heart Assoc.* **2019**, *8*, e011320. [CrossRef]
81. Choi, J.Y.; Choi, C.U.; Hwang, S.Y.; Choi, B.G.; Jang, W.Y.; Kim, D.Y.; Kim, W.; Park, E.J.; Lee, S.; Na, J.O.; et al. Effect of Pitavastatin Compared with Atorvastatin andRosuvastatin on New-Onset Diabetes Mellitus in PatientsWith Acute Myocardial Infarction. *Am. J. Cardiol.* **2018**, *122*, 922–928. [CrossRef] [PubMed]
82. Freeman, D.J.; Norrie, J.; Sattar, N.; Neely, R.D.G.; Cobbe, S.M.; Ford, I.; Isles, C.; Lorimer, A.R.; Macfarlane, P.W.; McKillop, J.H.; et al. Pravastatin and the development of diabetes mellitus: Evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* **2001**, *103*, 357–362. [CrossRef] [PubMed]
83. Hiramitsu, S.; Ishiguro, Y.; Matsuyama, H.; Yamada, K.; Kato, K.; Noba, M.; Uemura, A.; Yoshida, S.; Matsubara, Y.; Kani, A.; et al. The effects of ezetimibe on surrogate markers of cholesterol absorption and synthesis in Japanese patients with dyslipidemia. *J. Atheroscler. Thromb.* **2010**, *17*, 106–114. [CrossRef] [PubMed]
84. Dagli, N.; Yavuzkir, M.; Karaca, I. The effects of high dose pravastatin and low dose pravastatin and ezetimibe combination therapy on lipid, glucose metabolism and inflammation. *Inflammation* **2007**, *30*, 230–235. [CrossRef]
85. Her, A.Y.; Kim, J.Y.; Kang, S.M.; Choi, D.; Jang, Y.; Chung, N.; Manabe, I.; Lee, S.H. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. *J. Cardiovasc. Pharmacol. Ther.* **2010**, *15*, 167–174. [CrossRef]
86. Takeshita, Y.; Takamura, T.; Honda, M.; Kita, Y.; Zen, Y.; Kato, K.I.; Misu, H.; Ota, T.; Nakamura, M.; Yamada, K.; et al. The effects of ezetimibe on non-alcoholic fatty liver disease and glucose metabolism: A randomised controlled trial. *Diabetologia* **2014**, *57*, 878–890. [CrossRef]
87. Sabatine, M.S.; Leiter, L.A.; Wiviott, S.D.; Giugliano, R.P.; Deedwania, P.; De Ferrari, G.M.; Murphy, S.A.; Kuder, J.F.; Gouni-Berthold, I.; Lewis, B.S.; et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: A prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol.* **2017**, *5*, 941–950. [CrossRef]
88. De Carvalho, L.S.F.; Campos, A.M.; Sposito, A.C. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors and Incident Type 2 Diabetes: A Systematic Review and Meta-analysis With Over 96,000 Patient-Years. *Diabetes Care* **2018**, *41*, 364–367. [CrossRef]
89. Chen, Q.; Wu, G.; Li, C.; Qin, X.; Liu, R.; Zhang, M. Safety of Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibodies in Regard to Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Am. J. Cardiovasc. Drugs* **2020**, *20*, 343–353. [CrossRef]

90. Leiter, L.A.; Banach, M.; Catapano, A.L.; Duell, P.B.; Gotto, A.M.; Laufs, U.; Mancini, G.B.J.; Ray, K.K.; Hanselman, J.C.; Ye, Z.; et al. Bempedoic acid in patients with type 2 diabetes mellitus, prediabetes, and normoglycaemia: A post hoc analysis of efficacy and glycaemic control using pooled data from phase 3 clinical trials. *Diabetes. Obes. Metab.* **2022**. [CrossRef]
91. Masson, W.; Lobo, M.; Lavalle-Cobo, A.; Masson, G.; Molinero, G. Effect of bempedoic acid on new onset or worsening diabetes: A meta-analysis. *Diabetes Res. Clin. Pract.* **2020**, *168*, 108369. [CrossRef] [PubMed]
92. Handelsman, Y.; Goldberg, R.B.; Garvey, W.T.; Fonseca, V.A.; Rosenstock, J.; Jones, M.R.; Lai, Y.L.; Jin, X.; Misir, S.; Nagendran, S.; et al. Colesevelam hydrochloride to treat hypercholesterolemia and improve glycemia in prediabetes: A randomized, prospective study. *Endocr. Pract.* **2010**, *16*, 617–628. [CrossRef] [PubMed]
93. Kazi, D.S.; Penko, J.M.; Bibbins-Domingo, K. Statins for Primary Prevention of Cardiovascular Disease: Review of Evidence and Recommendations for Clinical Practice. *Med. Clin. N. Am.* **2017**, *101*, 689–699. [CrossRef] [PubMed]
94. Tramacere, I.; Boncoraglio, G.B.; Banzi, R.; Del Giovane, C.; Kwag, K.H.; Squizzato, A.; Moja, L. Comparison of statins for secondary prevention in patients with ischemic stroke or transient ischemic attack: A systematic review and network meta-analysis. *BMC Med.* **2019**, *17*, 67. [CrossRef] [PubMed]
95. Karlson, B.W.; Palmer, M.K.; Nicholls, S.J.; Lundman, P.; Barter, P.J. Doses of rosuvastatin, atorvastatin and simvastatin that induce equal reductions in LDL-C and non-HDL-C: Results from the VOYAGER meta-analysis. *Eur. J. Prev. Cardiol.* **2016**, *23*, 744–747. [CrossRef] [PubMed]
96. Adhyaru, B.B.; Jacobson, T.A. Safety and efficacy of statin therapy. *Nat. Rev. Cardiol.* **2018**, *15*, 757–769. [CrossRef] [PubMed]
97. Goodarzi, M.O.; Li, X.; Krauss, R.M.; Rotter, J.I.; Chen, Y.D.I. Relationship of sex to diabetes risk in statin trials. *Diabetes Care* **2013**, *36*, e100–e101. [CrossRef]
98. Preiss, D.; Seshasai, S.R.K.; Welsh, P.; Murphy, S.A.; Ho, J.E.; Waters, D.D.; DeMicco, D.A.; Barter, P.; Cannon, C.P.; Sabatine, M.S.; et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: A meta-analysis. *JAMA* **2011**, *305*, 2556–2564. [CrossRef]
99. Cholesterol Treatment Trialists' (CTT) Collaborators Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: A meta-analysis. *Lancet* **2008**, *371*, 117–125. [CrossRef]
100. Mach, F.; Ray, K.K.; Wiklund, O.; Corsini, A.; Catapano, A.L.; Bruckert, E.; De Backer, G.; Hegele, R.A.; Hovingh, G.K.; Jacobson, T.A.; et al. Adverse effects of statin therapy: Perception vs. the evidence—Focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur. Heart J.* **2018**, *39*, 2526–2539. [CrossRef]
101. Sasaki, J.; Iwashita, M.; Kono, S. Statins: Beneficial or adverse for glucose metabolism. *J. Atheroscler. Thromb.* **2006**, *13*, 123–129. [CrossRef] [PubMed]
102. Garcia-Calvo, M.; Lisnock, J.M.; Bull, H.G.; Hawes, B.E.; Burnett, D.A.; Braun, M.P.; Crona, J.H.; Davis, H.R.; Dean, D.C.; Detmers, P.A.; et al. The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 8132–8137. [CrossRef] [PubMed]
103. Tsunoda, T.; Nozue, T.; Yamada, M.; Mizuguchi, I.; Sasaki, M.; Michishita, I. Effects of ezetimibe on atherogenic lipoproteins and glucose metabolism in patients with diabetes and glucose intolerance. *Diabetes Res. Clin. Pract.* **2013**, *100*, 46–52. [CrossRef] [PubMed]
104. Hiramitsu, S.; Miyagishima, K.; Ishii, J.; Matsui, S.; Naruse, H.; Shiino, K.; Kitagawa, F.; Ozaki, Y. Effect of ezetimibe on lipid and glucose metabolism after a fat and glucose load. *J. Cardiol.* **2012**, *60*, 395–400. [CrossRef] [PubMed]
105. Wu, H.; Shang, H.; Wu, J. Effect of ezetimibe on glycemic control: A systematic review and meta-analysis of randomized controlled trials. *Endocrine* **2018**, *60*, 229–239. [CrossRef] [PubMed]
106. Lee, Y.-B.; Kim, B.; Han, K.; Kim, J.A.; Roh, E.; Hong, S.H.; Choi, K.M.; Baik, S.H.; Yoo, H.J. Combination of Statin and Ezetimibe versus Statin Monotherapy on Cardiovascular Disease and Type 2 Diabetes Incidence among Adults with Impaired Fasting Glucose: A Propensity-Matched Nationwide Cohort Study. *J. Lipid Atheroscler.* **2021**, *10*, 303–312. [CrossRef]
107. Kikuchi, K.; Nezu, U.; Inazumi, K.; Miyazaki, T.; Ono, K.; Orime, K.; Shirakawa, J.; Sato, K.; Koike, H.; Wakasugi, T.; et al. Double-blind randomized clinical trial of the effects of ezetimibe on postprandial hyperlipidaemia and hyperglycaemia. *J. Atheroscler. Thromb.* **2012**, *19*, 1093–1101. [CrossRef]
108. Ascaso, J.F. Inhibition of proprotein convertase subtilisin/kexin type 9 in the treatment of hypercholesterolemia. *Endocrinol. Nutr.* **2016**, *63*, 255–257. [CrossRef]
109. Ganda, O.P.; Plutzky, J.; Sanganalmath, S.K.; Bujas-Bobanovic, M.; Koren, A.; Mandel, J.; Letierce, A.; Leiter, L.A. Efficacy and safety of alirocumab among individuals with diabetes mellitus and atherosclerotic cardiovascular disease in the ODYSSEY phase 3 trials. *Diabetes. Obes. Metab.* **2018**, *20*, 2389–2398. [CrossRef]
110. Lotta, L.A.; Sharp, S.J.; Burgess, S.; Perry, J.R.B.; Stewart, I.D.; Willems, S.M.; Luan, J.; Ardanaz, E.; Arriola, L.; Balkau, B.; et al. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis Supplemental content. *JAMA* **2016**, *316*, 1383–1391. [CrossRef]
111. Malik, S.; Kashyap, M.L. Niacin, lipids, and heart disease. *Curr. Cardiol. Rep.* **2003**, *5*, 470–476. [CrossRef] [PubMed]
112. Zafrir, B.; Jain, M. Lipid-lowering therapies, glucose control and incident diabetes: Evidence, mechanisms and clinical implications. *Cardiovasc. Drugs Ther.* **2014**, *28*, 361–377. [CrossRef] [PubMed]
113. Garg, A.; Sharma, A.; Krishnamoorthy, P.; Garg, J.; Virmani, D.; Sharma, T.; Stefanini, G.; Kostis, J.B.; Mukherjee, D.; Sikorskaya, E. Role of Niacin in Current Clinical Practice: A Systematic Review. *Am. J. Med.* **2017**, *130*, 173–187. [CrossRef] [PubMed]

114. Vega, G.L.; Dunn, F.L.; Grundy, S.M. Effect of colesevelam hydrochloride on glycemia and insulin sensitivity in men with the metabolic syndrome. *Am. J. Cardiol.* **2011**, *108*, 1129–1135. [CrossRef] [PubMed]
115. Ritz-Laser, B.; Meda, P.; Constant, I.; Klages, N.; Charollais, A.; Morales, A.; Magnan, C.; Ktorza, A.; Philippe, J. Glucose-induced preproinsulin gene expression is inhibited by the free fatty acid palmitate. *Endocrinology* **1999**, *140*, 4005–4014. [CrossRef] [PubMed]
116. Briaud, I.; Harmon, J.S.; Kelpe, C.L.; Segu, V.B.G.; Poitout, V. Lipotoxicity of the pancreatic beta-cell is associated with glucose-dependent esterification of fatty acids into neutral lipids. *Diabetes* **2001**, *50*, 315–321. [CrossRef]
117. Lu, X.; Liu, J.; Hou, F.; Liu, Z.; Cao, X.; Seo, H.; Gao, B. Cholesterol induces pancreatic β cell apoptosis through oxidative stress pathway. *Cell Stress Chaperones* **2011**, *16*, 539–548. [CrossRef]
118. Cnop, M.; Hannaert, J.C.; Grupping, A.Y.; Pipeleers, D.G. Low density lipoprotein can cause death of islet β-cells by its cellular uptake and oxidative modification. *Endocrinology* **2002**, *143*, 3449–3453. [CrossRef]
119. Villarreal-Molina, M.T.; Aguilar-Salinas, C.A.; Rodríguez-Cruz, M.; Riaño, D.; Villalobos-Comparan, M.; Coral-Vazquez, R.; Menjivar, M.; Yescas-Gomez, P.; Königsoerg-Fainstein, M.; Romero-Hidalgo, S.; et al. The ATP-binding cassette transporter A1 R230C variant affects HDL cholesterol levels and BMI in the Mexican population: Association with obesity and obesity-related comorbidities. *Diabetes* **2007**, *56*, 1881–1887. [CrossRef]
120. Haghvirdizadeh, P.; Ramachandran, V.; Etemad, A.; Heidari, F.; Ghodsian, N.; Bin Ismail, N.; Ismail, P. Association of ATP-Binding Cassette Transporter A1 Gene Polymorphisms in Type 2 Diabetes Mellitus among Malaysians. *J. Diabetes Res.* **2015**, *2015*, 289846. [CrossRef]
121. Dullaart, R.P.F.; Annema, W.; de Boer, J.F.; Tietge, U.J.F. Pancreatic β-cell function relates positively to HDL functionality in well-controlled Type 2 diabetes mellitus. *Atherosclerosis* **2012**, *222*, 567–573. [CrossRef] [PubMed]
122. Sokooti, S.; Flores-Guerrero, J.L.; Kieneker, L.M.; Heerspink, H.J.L.; Connelly, M.A.; Bakker, S.J.L.; Dullaart, R.P.F. HDL Particle Subspecies and Their Association with Incident Type 2 Diabetes: The PREVEND Study. *J. Clin. Endocrinol. Metab.* **2021**, *106*, 1761–1772. [CrossRef] [PubMed]
123. Perego, C.; Da Dalt, L.; Pirillo, A.; Galli, A.; Catapano, A.L.; Norata, G.D. Cholesterol metabolism, pancreatic β-cell function and diabetes. *Biochim. Biophys. Acta Mol. Basis Dis.* **2019**, *1865*, 2149–2156. [CrossRef] [PubMed]
124. Paolisso, G.; Ferrannini, E.; D'Amore, A.; Volpe, C.; Varricchio, M.; D'Onofrio, F. Effects of physiological plasma insulin levels on glucose turnover parameters in familial hypercholesterolemia. *Atherosclerosis* **1993**, *101*, 111–115. [CrossRef]
125. Galvan, A.Q.; Santoro, D.; Natali, A.; Sampietro, T.; Boni, C.; Masoni, A.; Buzzigoli, G.; Ferrannini, E. Insulin sensitivity in familial hypercholesterolemia. *Metabolism* **1993**, *42*, 1359–1364. [CrossRef]
126. Karhapää, P.; Voutilainen, E.; Kovanen, P.T.; Laakso, M. Insulin resistance in familial and nonfamilial hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.* **1993**, *13*, 41–47. [CrossRef]
127. Koks, N.; de Vries, M.A.; Birnie, E.; Alipour, A.; Castro Cabezas, M. Glucose-dependent leucocyte activation in familial hypercholesterolemia. *Eur. J. Clin. Investig.* **2017**, *47*, 839–846. [CrossRef]
128. Oliveira, R.B.d.; Carvalho, C.P.d.F.; Polo, C.C.; Dorighello, G.d.G.; Boschero, A.C.; Oliveira, H.C.F.d.; Collares-Buzato, C.B. Impaired compensatory beta-cell function and growth in response to high-fat diet in LDL receptor knockout mice. *Int. J. Exp. Pathol.* **2014**, *95*, 296–308. [CrossRef]
129. Da Dalt, L.; Ruscica, M.; Bonacina, F.; Balzarotti, G.; Dhyani, A.; Di Cairano, E.; Baragetti, A.; Arnaboldi, L.; De Metrio, S.; Pellegatta, F.; et al. PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: The role of the low-density lipoprotein receptor. *Eur. Heart J.* **2019**, *40*, 357–368. [CrossRef]
130. Peyot, M.L.; Roubtsova, A.; Lussier, R.; Chamberland, A.; Essalmani, R.; Murthy Madiraju, S.R.; Seidah, N.G.; Prentki, M.; Prat, A. Substantial PCSK9 inactivation in β-cells does not modify glucose homeostasis or insulin secretion in mice. *Biochim. Biophys. Acta. Mol. Cell Biol. Lipids* **2021**, *1866*, 158968. [CrossRef]
131. Tada, H.; Kawashiri, M.A.; Yoshida, T.; Teramoto, R.; Nohara, A.; Konno, T.; Inazu, A.; Mabuchi, H.; Yamagishi, M.; Hayashi, K. Lipoprotein(A) in familial hypercholesterolemia with proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutations. *Circ. J.* **2016**, *80*, 512–518. [CrossRef] [PubMed]
132. Paige, E.; Masconi, K.L.; Tsimikas, S.; Kronenberg, F.; Santer, P.; Weger, S.; Willeit, J.; Kiechl, S.; Willeit, P. Lipoprotein(a) and incident type-2 diabetes: Results from the prospective Bruneck study and a meta-analysis of published literature. *Cardiovasc. Diabetol.* **2017**, *16*, 38. [CrossRef] [PubMed]
133. Perez-Calahorra, S.; Civeira, F.; Guallar-Castillón, P.; Pinto, X.; Banegas, J.R.; Pedro-Botet, J.; Suarez-Tembra, M.; Mauri, M.; Soler, C.; Rodriguez-Artalejo, F.; et al. Behavioural cardiovascular risk factors and prevalence of diabetes in subjects with familial hypercholesterolaemia. *Eur. J. Prev. Cardiol.* **2020**, *27*, 1649–1660. [CrossRef] [PubMed]
134. Fox, C.S.; Coady, S.; Sorlie, P.D.; D'agostino, R.B.; Pencina, M.J.; Vasan, R.S.; Meigs, J.B.; Levy, D.; Savage, P.J. Increasing Cardiovascular Disease Burden Due to Diabetes Mellitus the Framingham Heart Study. *Circulation* **2007**, *115*, 1544–1550. [CrossRef]
135. Raghavan, S.; Vassy, J.L.; Ho, Y.L.; Song, R.J.; Gagnon, D.R.; Cho, K.; Wilson, P.W.F.; Phillips, L.S. Diabetes Mellitus-Related All-Cause and Cardiovascular Mortality in a National Cohort of Adults. *J. Am. Heart Assoc.* **2019**, *8*, e011295. [CrossRef]
136. Katakami, N. Mechanism of Development of Atherosclerosis and Cardiovascular Disease in Diabetes Mellitus. *J. Atheroscler. Thromb.* **2018**, *25*, 27–39. [CrossRef]
137. Wu, L.; Parhofer, K.G. Diabetic dyslipidemia. *Metabolism.* **2014**, *63*, 1469–1479. [CrossRef]

138. Tribble, D.L.; Rizzo, M.; Chait, A.; Lewis, D.M.; Blanche, P.J.; Krauss, R.M. Enhanced oxidative susceptibility and reduced antioxidant content of metabolic precursors of small, dense low-density lipoproteins. *Am. J. Med.* **2001**, *110*, 103–110. [CrossRef]
139. Paiker, J.E.; Raal, F.J.; Waisberg, R.; Buthelezi, E.P. Quantity versus quality of LDL cholesterol in patients with familial hypercholesterolemia-which is more important? *Clin. Chim. Acta* **2001**, *314*, 167–173. [CrossRef]
140. Kolovou, G.D.; Kostakou, P.M.; Anagnostopoulou, K.K. Familial hypercholesterolemia and triglyceride metabolism. *Int. J. Cardiol.* **2011**, *147*, 349–358. [CrossRef]
141. Chemello, K.V.; García-Nafría, J.; Gallo, A.; Martín, C.; Lambert, G.; Blom, D. Lipoprotein metabolism in familial hypercholesterolemia. *J. Lipid Res.* **2021**, *62*, 100062. [CrossRef] [PubMed]
142. Chan, D.C.; Watts, G.F. Postprandial lipoprotein metabolism in familial hypercholesterolemia: Thinking outside the box. *Metabolism* **2012**, *61*, 3–11. [CrossRef] [PubMed]
143. Wittekoek, M.E.; Pimstone, S.N.; Reymer, P.W.; Feuth, L.; Botma, G.J.; Defesche, J.C.; Prins, M.; Hayden, M.R.; Kastelein, J.J. A common mutation in the lipoprotein lipase gene (N291S) alters the lipoprotein phenotype and risk for cardiovascular disease in patients with familial hypercholesterolemia. *Circulation.* **1998**, *97*, 729–735. [CrossRef] [PubMed]
144. Ganjali, S.; Momtazi, A.A.; Banach, M.; Kovanen, P.T.; Stein, E.A.; Sahebkar, A. HDL abnormalities in familial hypercholesterolemia: Focus on biological functions. *Prog. Lipid Res.* **2017**, *67*, 16–26. [CrossRef] [PubMed]
145. Pedro-Botet, J.; Climent, E.; Benaiges, D. Familial Hypercholesterolemia: Do HDL Play a Role? *Biomedicines* **2021**, *9*, 810. [CrossRef] [PubMed]
146. Paquette, M.; Bernard, S.; Ruel, I.; Blank, D.W.; Genest, J.; Baass, A. Diabetes is associated with an increased risk of cardiovascular disease in patients with familial hypercholesterolemia. *J. Clin. Lipidol.* **2019**, *13*, 123–128. [CrossRef]
147. Spiga, R.; Marini, M.A.; Mancuso, E.; Di Fatta, C.; Fuoco, A.; Perticone, F.; Andreozzi, F.; Mannino, G.C.; Sesti, G. Uric Acid Is Associated with Inflammatory Biomarkers and Induces Inflammation via Activating the NF-κB Signaling Pathway in HepG2 Cells. *Arterioscler. Thromb. Vasc. Biol.* **2017**, *37*, 1241–1249. [CrossRef]
148. Mirza, S.; Hossain, M.; Mathews, C.; Martinez, P.; Pino, P.; Gay, J.L.; Rentfro, A.; McCormick, J.B.; Fisher-Hoch, S.P. Type 2-diabetes is associated with elevated levels of TNF-alpha, IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: A cross-sectional study. *Cytokine* **2012**, *57*, 136–142. [CrossRef]
149. Derosa, G.; Fogari, E.; D'Angelo, A.; Bianchi, L.; Bonaventura, A.; Romano, D.; Maffioli, P. Adipocytokine levels in obese and non-obese subjects: An observational study. *Inflammation* **2013**, *36*, 914–920. [CrossRef]
150. Rahman, T.; Hamzan, N.S.; Mokhsin, A.; Rahmat, R.; Ibrahim, Z.O.; Razali, R.; Thevarajah, M.; Nawawi, H. Enhanced status of inflammation and endothelial activation in subjects with familial hypercholesterolaemia and their related unaffected family members: A case control study. *Lipids Health Dis.* **2017**, *16*, 81. [CrossRef]
151. Ganjali, S.; Keshavarz, R.; Hosseini, S.; Mansouri, A.; Mannarino, M.R.; Pirro, M.; Jamialahmadi, T.; Sahebkar, A. Evaluation of Oxidative Stress Status in Familial Hypercholesterolemia. *J. Clin. Med.* **2021**, *10*, 5867. [CrossRef] [PubMed]
152. Bahrami, A.; Liberale, L.; Reiner, Ž.; Carbone, F.; Montecucco, F.; Sahebkar, A. Inflammatory Biomarkers for Cardiovascular Risk Stratification in Familial Hypercholesterolemia. *Rev. Physiol. Biochem. Pharmacol.* **2020**, *177*, 25–52. [CrossRef] [PubMed]
153. Jansen, A.C.M.; Van Aalst-Cohen, E.S.; Tanck, M.W.; Trip, M.D.; Lansberg, P.J.; Liem, A.H.; Roeters Van Lennep, H.W.O.; Sijbrands, E.J.G.; Kastelein, J.J.P. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: Data in 2400 patients. *J. Intern. Med.* **2004**, *256*, 482–490. [CrossRef] [PubMed]
154. Tada, H.; Okada, H.; Nohara, A.; Yamagishi, M.; Takamura, M.; Kawashiri, M.A. Effect of Cumulative Exposure to Low-Density Lipoprotein-Cholesterol on Cardiovascular Events in Patients with Familial Hypercholesterolemia. *Circ. J.* **2021**, *85*, 2073–2078. [CrossRef] [PubMed]
155. Paquette, M.; Dufour, R.; Baass, A. The Montreal-FH-SCORE: A new score to predict cardiovascular events in familial hypercholesterolemia. *J. Clin. Lipidol.* **2017**, *11*, 80–86. [CrossRef]
156. Pérez De Isla, L.; Alonso, R.; Mata, N.; Fernández-Pérez, C.; Muñiz, O.; Díaz-Díaz, J.L.; Saltijeral, A.; Fuentes-Jiménez, F.; De Andrés, R.; Zambón, D.; et al. Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation* **2017**, *135*, 2133–2144. [CrossRef]
157. Paquette, M.; Bernard, S.; Cariou, B.; Hegele, R.A.; Genest, J.; Trinder, M.; Brunham, L.R.; Béliard, S.; Baass, A. Familial Hypercholesterolemia-Risk-Score: A New Score Predicting Cardiovascular Events and Cardiovascular Mortality in Familial Hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.* **2021**, *41*, 2632–2640. [CrossRef]
158. Panagiotakos, D.B.; Pitsavos, C.; Skoumas, J.; Chrysohoou, C.; Toutouza, M.; Stefanadis, C.I.; Toutouzas, P.K. Importance of LDL/HDL cholesterol ratio as a predictor for coronary heart disease events in patients with heterozygous familial hypercholesterolaemia: A 15-year follow-up (1987–2002). *Curr. Med. Res. Opin.* **2003**, *19*, 89–94.
159. Humphries, S.E.; Cooper, J.A.; Capps, N.; Durrington, P.N.; Jones, B.; McDowell, I.F.W.; Soran, H.; Neil, A.H.W. Coronary heart disease mortality in severe vs. non-severe familial hypercholesterolaemia in the Simon Broome Register. *Atherosclerosis* **2019**, *281*, 207. [CrossRef]
160. Gidding, S.S. Diabetes and familial hypercholesterolemia: An unhealthy marriage. *Rev. Española Cardiol.* **2020**, *73*, 705–706. [CrossRef]
161. Cosentino, F.; Grant, P.J.; Aboyans, V.; Bailey, C.J.; Ceriello, A.; Delgado, V.; Federici, M.; Filippatos, G.; Grobbee, D.E.; Hansen, T.B.; et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur. Heart J.* **2020**, *41*, 255–323. [CrossRef] [PubMed]

162. Hopkins, P.N.; Stephenson, S.; Wu, L.L.; Riley, W.A.; Xin, Y.; Hunt, S.C. Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia. *Am. J. Cardiol.* **2001**, *87*, 547–553. [CrossRef]
163. De Sauvage Nolting, P.R.W.; Defesche, J.C.; Buirma, R.J.A.; Hutten, B.A.; Lansberg, P.J.; Kastelein, J.J.P. Prevalence and significance of cardiovascular risk factors in a large cohort of patients with familial hypercholesterolaemia. *J. Intern. Med.* **2003**, *253*, 161–168. [CrossRef]
164. Allard, M.D.; Saeedi, R.; Yousefi, M.; Frohlich, J. Risk stratification of patients with familial hypercholesterolemia in a multi-ethnic cohort. *Lipids Health Dis.* **2014**, *13*, 65. [CrossRef] [PubMed]
165. Alonso, R.; Andres, E.; Mata, N.; Fuentes-Jiménez, F.; Badimón, L.; López-Miranda, J.; Padró, T.; Muñiz, O.; Díaz-Díaz, J.L.; Mauri, M.; et al. Lipoprotein(a) levels in familial hypercholesterolemia: An important predictor of cardiovascular disease independent of the type of LDL receptor mutation. *J. Am. Coll. Cardiol.* **2014**, *63*, 1982–1989. [CrossRef] [PubMed]
166. Pereira, C.; Miname, M.; Makdisse, M.; Filho, R.K.; Santos, R.D. Association of Peripheral Arterial and Cardiovascular Diseases inFamilial Hypercholesterolemia. *Arq. Bras. Cardiol.* **2014**, *103*, 118. [CrossRef]
167. Chan, D.C.; Pang, J.; Hooper, A.J.; Burnett, J.R.; Bell, D.A.; Bates, T.R.; Van Bockxmeer, F.M.; Watts, G.F. Elevated lipoprotein(a), hypertension and renal insufficiency as predictors of coronary artery disease in patients with genetically confirmed heterozygous familial hypercholesterolemia. *Int. J. Cardiol.* **2015**, *201*, 633–638. [CrossRef]
168. Degoma, E.M.; Ahmad, Z.S.; O'Brien, E.C.; Kindt, I.; Shrader, P.; Newman, C.B.; Pokharel, Y.; Baum, S.J.; Hemphill, L.C.; Hudgins, L.C.; et al. Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States. *Circ. Cardiovasc. Genet.* **2016**, *9*, 240–249. [CrossRef]
169. Paquette, M.; Brisson, D.; Dufour, R.; Khoury, É.; Gaudet, D.; Baass, A. Cardiovascular disease in familial hypercholesterolemia: Validation and refinement of the Montreal-FH-SCORE. *J. Clin. Lipidol.* **2017**, *11*, 1161–1167. [CrossRef]
170. Galema-Boers, A.M.; Lenzen, M.J.; Engelkes, S.R.; Sijbrands, E.J.; Roeters van Lennep, J.E. Cardiovascular risk in patients with familial hypercholesterolemia using optimal lipid-lowering therapy. *J. Clin. Lipidol.* **2018**, *12*, 409–416. [CrossRef]
171. Perez-Calahorra, S.; Laclaustra, M.; Marco-Benedí, V.; Lamiquiz-Moneo, I.; Pedro-Botet, J.; Plana, N.; Sanchez-Hernandez, R.M.; Amor, A.J.; Almagro, F.; Fuentes, F.; et al. Effect of lipid-lowering treatment in cardiovascular disease prevalence in familial hypercholesterolemia. *Atherosclerosis* **2019**, *284*, 245–252. [CrossRef] [PubMed]
172. Michikura, M.; Ogura, M.; Hori, M.; Matsuki, K.; Makino, H.; Hosoda, K.; Harada-Shiba, M. Association between Achilles Tendon Softness and Atherosclerotic Cardiovascular Disease in Patients with Familial Hypercholesterolemia. *J. Atheroscler. Thromb.* **2022**, 63151. [CrossRef] [PubMed]

Cardiovascular Diabetology

RESEARCH

Open Access

Impact of PCSK9 inhibitors in glycaemic control and new-onset diabetes

Ana M. González-Lleó[1,2*], Rosa M. Sánchez-Hernández[1,2], Núria Plana[3], Daiana Ibarretxe[3], Pere Rehues[3], Josep Ribalta[3], Dídac Llop[3], Ana M. Wägner[1,2], Lluís Masana[3] and Mauro Boronat[1,2]

Abstract

Background The diabetogenic effect of statins has been well established by clinical trials, Mendelian randomisation studies and meta-analyses. According to large clinical trials, PCSK9 inhibitors (PCSK9i) have no deleterious impact on glucose metabolism. However, few real-life studies have yet evaluated the long-term effects of these drugs on glucose homeostasis and their impact on new-onset diabetes (NODM).

Methods We studied 218 patients treated with either alirocumab or evolocumab (70% with familial hypercholesterolemia) for at least three years (PCSK9iG). We studied the NODM rate in the nondiabetic group at baseline (168) and overall glucose metabolism control in the whole group. Incidental DM was compared with two groups. The first was a propensity score matching (PSM)-selected group (n = 168) from the database of patients attending the Reus lipid unit (Metbank, n = 745) who were not on PCSK9i (PSMG). The second was a subgroup with a similar age range (n = 563) of the Di@bet.es study (Spanish prospective study on diabetes development n = 5072) (D@G). The incidence was reported as the percentage of NODM cases per year.

Results The fasting glucose (FG) level of the subjects with normoglycaemia at baseline increased from 91 (86-95.5) to 93 (87–101) mg/dL ($p = 0.014$). There were 14 NODM cases in the PCSK9i group (2.6%/y), all among people with prediabetes at baseline. The incidence of NODM in PSMG and D@G was 1.8%/y ($p = 0.69$ compared with the PCSK9iG). The incidence among the subjects with prediabetes was 5.1%/y in the PCSK9iG, 4.8%/y in the PSMG and 3.9%/y in the D@G ($p = 0.922$ and $p = 0.682$, respectively). In the multivariate analysis, only the FG level was associated with the development of NODM in the PCSK9iG (OR 1.1; 95% CI: 1.0-1.3; $p = 0.027$). Neither FG nor A1c levels changed significantly in patients with DM at baseline.

Conclusion A nonsignificant increase in NODM occurred in the PCSK9iG, particularly in patients with prediabetes, compared with the PSMG and D@G groups. Baseline FG levels were the main variable associated with the development of DM. In the subjects who had DM at baseline, glucose control did not change. The impact of PCSK9i on glucose metabolism should not be of concern when prescribing these therapies.

Keywords New-onset Diabetes Mellitus, Prediabetes, PCSK9 inhibitors, Real-life study, Hyperglycaemia, Familial hypercholesterolemia

*Correspondence:
Ana M. González-Lleó
anamaria.gonzalez@salutsantjoan.cat
[1]Sección de Endocrinología y Nutrición. Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria (CHUIMI), Las Palmas de Gran Canaria, España
[2]Instituto Universitario de Investigaciones Biomédicas y Sanitarias (IUIBS), Universidad de Las Palmas de Gran Canaria (ULPGC), Las Palmas de Gran Canaria, España
[3]Universitat Rovira i Virgili. Unidad de Medicina Vascular y Metabolismo. Unitat de Recerca Lipids i Arteriosclerosi. Hospital Universitari Sant Joan, IISPV: CIBERDEM., Reus, España

Background

The interest in proprotein convertase subtilisin/kexin type 9 (PCSK9) as a lipid-lowering target arose at the beginning of the present century after the identification of several families with familial hypercholesterolemia (FH) who carried gain-of-function mutations in the gene encoding PCSK9. The subsequent observation that loss-of-function gene variants were associated with reduced low-density lipoprotein (LDL) cholesterol (C) levels and fewer cardiovascular events led to its consideration as a potential drug target [1, 2].

Circulating LDL binds to the LDL receptor (LDLR) to form a complex that is internalised in the cell, where the LDL particles are degraded and the LDLR is recycled. PCSK9 is synthesised in the liver and released into plasma, where it also binds LDLR. When internalisation of the LDL-LDLR complex occurs in the presence of PCSK9, LDLR is also degraded, preventing recycling and reducing the expression of LDLR on the cell surface, mainly in hepatocytes.

In 2015, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved the clinical use of alirocumab and evolocumab, two PCSK9 inhibitor monoclonal antibodies (PCSK9i). These drugs block the circulating PCSK9 protein, allowing the recycling of the receptors, thus increasing the availability of LDLR. These therapies lower LDL-C concentrations by approximately 60% and significantly reduce cardiovascular risk when added to statin therapy [3, 4].

Data from the Jupiter study [5], various subsequent meta-analyses [6] and results from Mendelian randomisation studies [7] have demonstrated the diabetogenic potential of statins, the cornerstone of lipid-lowering treatment, although the exact mechanism through which this phenomenon is produced is unknown. Various hypotheses have been formulated, such as their association with the decrease in LDL concentrations, the disturbed intracellular metabolism in pancreatic beta-cells induced by the hyperexpression of LDLR on the cell membrane and the subsequent increase in intracellular cholesterol [8, 9], or even body weight increase associated with statin treatment [10]. Given that PCSK9i notably raise LDLR expression and achieve much higher LDL-C reductions than statins, it would be reasonable to think that these new drugs might also have effects on glucose metabolism [11]. Large-scale clinical studies conducted to date have not observed a higher incidence of diabetes mellitus (DM) among participants treated with PCSK9i [12, 13]. However, Mendelian randomisation studies [7, 9], some meta-analyses [14, 15] and real-life studies [16] published in recent years have found a slight deterioration in glycaemic control among users of these drugs.

The aim of this study was to examine the development of glucose metabolism disorders and new-onset DM in patients with hypercholesterolemia receiving treatment with PCSK9i.

Methods

Study design and population

This is a retrospective observational study based on real clinical practice. Two hundred eighteen patients over 18 years of age on PCSK9i, because of clinical indication, for a mean follow-up of 3.2 years, from two lipid units at University Hospitals in Las Palmas de Gran Canaria and Reus (Spain), were included in the study (PCSK9iG). Subjects who discontinued treatment before the first year and those who were lost to follow-up were excluded. To compare the incidence of new-onset diabetes, the non-diabetic patients at baseline (n=168) were compared to a similar group of patients not taking PCSK9i selected by a propensity score matching technique (PSM) from the database (Metbank, n=745) of patients enrolled in the Reus Lipid Unit because of metabolic disturbance. The mean follow-up of this group was 6.6 years. The incidence of new-onset DM was also compared with that of the Di@bet.es study, a prospective, population-based study including 5072 participants, aimed at estimating the prevalence and incidence of DM in Spain (D@G) [17]. For comparison with the PCSK9iG, a subgroup of 563 subjects with a similar age were selected with a mean follow-up of 7.5 years.

Medical records of PCSK9iG participants were reviewed, and demographic data, personal history of DM and cardiovascular disease (CVD) (defined as acute myocardial infarction, angina pectoris, coronary revascularization, ischaemic stroke or peripheral vascular disease), type of hypercholesterolemia (FH, polygenic hypercholesterolemia or mixed dyslipidaemia), and time and characteristics of lipid-lowering treatment were compiled. Anthropometric data (height and weight) were also recorded at baseline and at the end of follow-up. Initial and final body mass index (BMI) and weight change during the time of exposure to PCSK9i were obtained. Standard biochemical data, including LDL-C, lipoprotein (a) and glycaemic profile [fasting glucose (FG) and glycated haemoglobin (A1c)] were recorded at baseline and follow-up. The new-onset DM rate was determined according to the American Diabetes Association (ADA) guidelines and expressed as a percentage per year (%/y) in the PCSK9iG, PSMG and D@G groups.

PCSK9iG patients received alirocumab 75 or 150 mg or evolocumab 140 mg every two weeks at the discretion of their physicians. Depending on the status of their glucose metabolism prior to PCSK9i treatment, participants were classified into three categories according to ADA definitions: normoglycaemia (FG<100 mg/dl and A1c<5.7%), prediabetes (pre-DM) (FG between 100 and 125 mg/dL and/or A1c between 5.7 and 6.4%) and DM (FG≥126 mg/

dL and/or A1c ≥ 6.5% on two or more occasions, or use of hypoglycaemic medication). The same criteria, observed in at least one blood test, were used to determine category changes of the patients during treatment.

Statistical analysis

Descriptive data are presented as the mean +/- standard deviation or median (interquartile range) for quantitative variables and as percentages for categorical variables. The groups were compared using ANOVA/Student's 't' test or the Kruskal–Wallis/Mann–Whitney test for quantitative variables, depending on whether the distribution was normal or not and according to the number of groups analysed. To compare follow-up with baseline results, Student's 't' test for related data or Wilcoxon's test was used, depending on whether the distribution was normal or not.

A propensity score matching (PSM) is a statistical technique that was designed to control for potential clinically relevant confounding variables and effectively balance the distribution of covariates between the groups to minimize bias and enhance the validity of our comparative analysis. The propensity score is the probability of receiving the treatment given a set of observed covariates of each individual selected, which is obtained using logistic regression analysis. The idea is to create a pseudo-randomised group not on PCSK9 inhibitors that is comparable to the treatment group based on the observed covariates. Thus, PSM involves pairing individuals from the treatment group with similar propensity scores to individuals from the control group. The matching process was carried out with the MatchIt R package. Patients were selected from the database (Metbank, n > 745) of patients attending the lipid units because of dyslipidaemia and/or associated disturbances, such as DM, obesity or metabolic syndrome. Subjects without baseline DM from the Metbank and PCSK9iG cohorts were matched at a 1:1 ratio. The covariates used as predictors in this matching process included age, sex, BMI, FG levels, statin use and FH diagnosis. A1c was not included in the matching process because measurements were unavailable for a considerable number of patients, and its inclusion would compromise the optimality of the process. These covariates were selected because they were identified as potential confounders, and, moreover, they were measured in all patients.To compare the proportion of patients who developed DM during follow-up, in the PCSK9iG, PSMG and D@G groups, a two-proportion z test, which assesses whether there is a significant difference between two known proportions, was used. It is a test commonly employed when dealing with categorical data, and the goal is to assess whether the proportions in the two groups are significantly different from each other.

Finally, to identify the factors associated with the development of DM, a multivariate logistic regression analysis was performed in the non-DM PCSK9iG. FG, A1c, age, sex, baseline BMI, FH diagnosis, PCSK9i type, exposure to treatment time, centre of origin, concomitant treatment with statins, and percentage reduction in LDL-C were included as independent variables. Odds ratios (OR) along with their corresponding confidence intervals (CI) were calculated to assess the impact of the mentioned variables on the onset of new DM. SPSS version 21.0 for Windows (IBM Corporation, Armonk, NY, USA) and RStudio (version 4.0.1) were used to perform the analyses. A p value less than 0.05 was considered significant.

Table 1 Characteristics of the PCSK9iG subjects according to their initial glucose metabolism status

	Total n = 218	Normoglycaemia n = 91	Pre-DM n = 77	DM n = 50	*p*
Age (years)	62 (54–69)	59 (51–67)	62 (54–69)	66 (58–72)	**0.001**
Sex (male, %)	53.2	58.2	45.5	56	0.230
Baseline BMI (kg/m^2)	29 ± 4.6	27.7 ± 4.5	29.8 ± 4.8	30.4 ± 3.9	0.001
Final BMI (kg/m^2)	29 ± 4.7	27.8 ± 4.7	29.7 ± 4.8	30.1 ± 4.3	0.004
CVD (%)	53.2	45.1	48.1	76	**0.001**
FH (%)	70.6	69.2	76.6	64	0.289
Ezetimibe (%)	62.8	56	68.8	66	0.202
Statins (%)	73.4	70.3	77.9	72	0.523
PCSK9i starting dose (%)					**0.005**
Al 75 mg	37.6	34.1	40.3	40	
Al 150 mg	31.2	23.1	31.2	46	
E 140 mg	31.2	42.9	28.6	14	
Lp(a) (mg/dL)	40.6 (11.2–98.8)	57.4 (10.6-100.6)	23 (9.2–84)	48 (14–108)	0.509
LDL-C (mg/dL)	158.1 (130.8-191.1)	157 (129–190)	173.3 (141.9-202.6)	153.1 (127.5-172.2)	**0.009**
Fasting glucose (mg/dL)	100 (91–114)	91 (86-95.5)	107 (100–112)	130 (114–160)	**< 0.001**
A1c (%) N = 151	5.9 (5.6–6.4)	5.5 (5.3–5.6)	5.8 (5.6–6.1)	6.7 (6.4–7.8)	**< 0.001**

BMI: body mass index; CVD: cardiovascular disease; FH: familial hypercholesterolemia; Lp(a): lipoprotein A; LDL-C: LDL cholesterol; A1c: glycated haemoglobin; preDM: prediabetes; DM2: type 2 diabetes mellitus

Results

Two hundred eighteen patients were included in the PCSK9iG group, and 53.2% of these patients were men. The patients were overweight, and the median age was 62 years (54–69). Table 1 shows the clinical characteristics of the PCSK9iG patients sorted by glycaemic status at baseline. A total of 70.6% of patients had FH, and more

than half already had established CVD. Over two-thirds (68.8%) of the population used alirocumab (37.6% were on the 75 mg dose), and 31.2% used evolocumab. The rates were different between the two centres (Supplementary Table 1). The mean follow-up was 38.2 months [21.3–61.6]. After starting PCSK9i, a reduction in LDL-C of 57% [40.5–67.8] was achieved at six months of follow-up, and a reduction of 60% [43.5–70.7] was achieved after three years. One hundred and sixty-eight participants did not have DM (though 77 had pre-DM) at baseline. Participants with DM at the beginning (n=50) were older and had a higher prevalence of ECV and BMI than non-DM subjects. Table 2 compares the main clinical characteristics of the non-DM PCSK9iG, PSMG and D@G groups.

After a mean follow-up of 3.2 years, the non-DM patients at baseline in the PCSK9iG group experienced a slight nonsignificant increase in FG (97 (90–107) vs. 99 (90.3–107) mg/dL, $p=0.058$). Twenty-six of the 91 subjects with normoglycaemia (28.6%) progressed to pre-DM, but none developed DM.

Fourteen out of 168 non-DM patients in the PCSK9iG group at baseline developed overt DM (8.3%), representing an incidence rate of 2.6%/y. The incidence in both the PSMG and D@G comparison groups was 1.8%/y ($p=0.69$ vs. PCSK9iG). Importantly, all 14 patients from the PCSK9iG group that transitioned to overt DM had pre-DM at baseline. The new-onset DM incidence among the 77 pre-DM patients in the PCSK9iG group was 5.1%/y, and this value was 4.8%/y and 3.9%/y among the pre-DM patients in the PSMG and D@G groups, respectively ($p=0.922$ and 0.682) (Fig. 1).

Table 2 Matching baseline characteristics of the non-DM subjects from the three compared groups

	PCSK9iG (n=168)	PSMG (n=168)	Di@bet.es study (n=563)
Age (years)	59.5±10.6	65.4±11.8	64.5±10.5
Sex (male, %)	52.4	50.8	39.7
BMI (kg/m2)	28.6±4.7	28±4.5	27.5±4.7
Fasting glucose (mg/dL)	98.2±12.4	95.6±11.2	91.9±12.6
A1c (%)	5.7±0.4	6.2±6.3 (n=96)	N/A
FH (%)	72.6	72.6	N/A

BMI: body mass index, FH: familial hypercholesterolemia; A1c: glycated haemoglobin; DM2: type 2 diabetes mellitus

Patients with pre-DM who developed DM had higher baseline FG levels than those without diabetes, but there were no differences in the lipid-lowering treatment received, the LDL-C reduction or the time on PCSK9i (Supplementary Table 2). Regarding subjects with DM at baseline, they had a slight but significant decrease of BMI at the end of follow-up, without changes in either FG or A1 (Fig. 2).

As expected from the clinical settings (specialised lipid units), more than 70% of the patients had FH. The incidence of DM was 2.2%/y and 1.4%/y in the PCSK9iG and PSMG FH patients, respectively ($p=0.67$) (Fig. 1). According to the multivariant logistic regression analysis (Table 3), baseline FG was the only variable significantly associated with the development of DM (OR 1.1; 95% CI: 1.0-1.3; $p=0.027$).

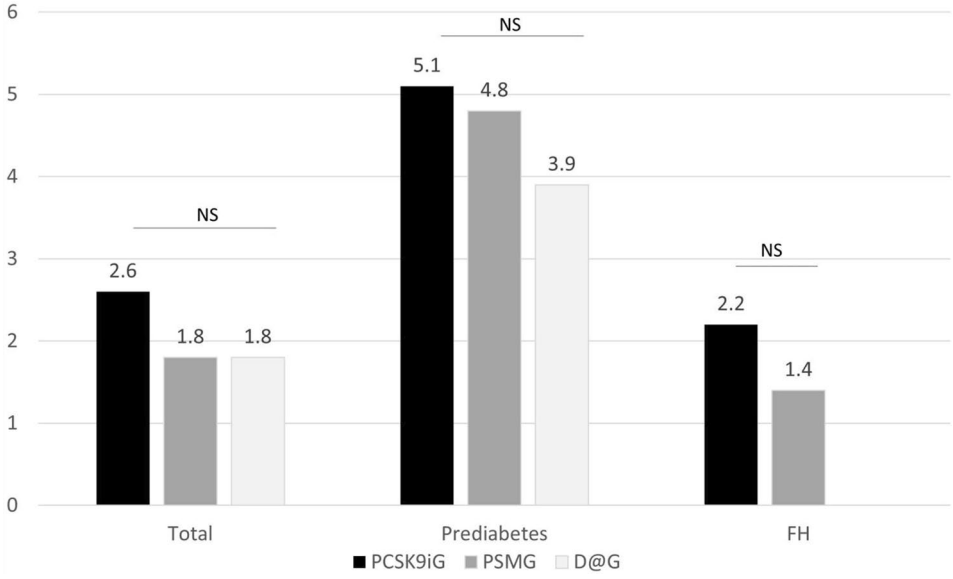


Fig. 1 Incidence (%/year) of new onset Diabetes Mellitus according to their original group
PCSK9iG: PCSK9i users; PSMG: Propensity score matching group (control group 1); D@G: di@bet.es cohort (control group 2); FH: familial hypercholesterolemia group

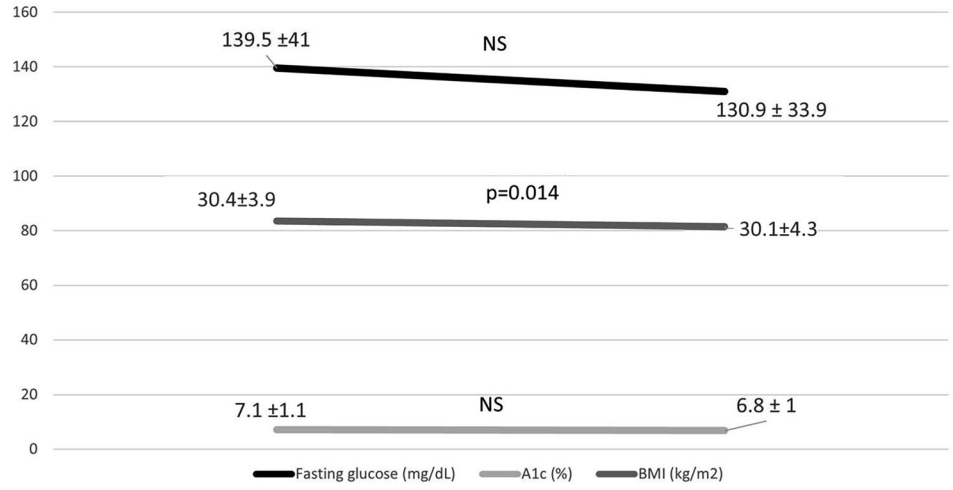


Fig. 2 Evolution of fasting glucose, A1c and BMI in DM patients at baseline on PCSK9i
Follow-up 3.2 years. Only significant differences were found in BMI
A1c: glycated haemoglobin. BMI: body mass index. NS: not significant

Table 3 Multivariant logistic regression analysis of non-DM PCSK9i-treated patients. Dependent variable: new-onset DM (compared with baseline characteristics)

	OR	CI 95%	sig
Fasting glucose	1.1	1-1.3	**0.027**
BMI	1	0.9–1.2	0.773
Statin	1.5	0.7–35.1	0.791
Ezetimibe	2.4	0.1–40.6	0.531
Age	1	0.9–1.1	0.642
Male sex	1.4	0.2–9.9	0.731
Alirocumab	1	0.03–31.6	0.995
LDL-C reduction at 1y	1	0.9-1	0.590
FH	2.4	0.1–45.1	0.565
Treatment duration (months)	1	1-1.1	0.313

LDL-C: LDL cholesterol; BMI: body mass index; FH: familial hypercholesterolemia

Discussion

We analysed the effects of treatment with PCSK9i (alirocumab and evolocumab) on the development of *de novo* DM in real-life practice. In general, mild alterations in glycaemic control parameters were recorded during treatment with PCSK9i among the non-DM patients. Approximately a quarter (28.6%) of the patients with normoglycaemia had FG level increases that reclassified them as pre-DM. Although the change in the FG level was statistically significant, it was of little clinical relevance, as it increased from 91 (86-95.5) to 93 (87–101) mg/dL. The incidence of new-onset DM in this cohort was 2.6%/y, which is higher than that of a matched group of patients with metabolic alterations (PSMG, 1.8%/y) and the incidence observed in the general population in the same range of age from the Di@bet.es study (1.8%/y). Although these results did not reach statistical significance (probably because of its low incidence), the difference between the two control groups was consistent. Interestingly, only those patients with baseline pre-DM developed overt DM, suggesting that any diabetogenic effects associated with PCSK9i could play an acceleration effect in DM-prone patients.

Another aspect to be considered is that 70% of the patients in the PCSK9iG had FH. In general, it is believed that FH patients have a lower prevalence of DM [8, 11]; however, the main gene variation [p.(Tyr400_Phe402del)], causing 68% of FH in Gran Canaria Island, is associated with a paradoxical 25% increased prevalence of diabetes [18]. Therefore, the higher incidence of DM in the PCSK9iG group could be expected, as this group of patients had a wide representation of FH when compared to the general population or to metabolic patients, including FH patients from other parts of the country (D@G and PSMG groups, respectively). However, our results do not support this possibility. The new-onset DM in the PCSK9iG and PSMG FH groups was similar to that of the non-FH groups, and there were no differences between them. Moreover, the multilevel multivariate study, which was adjusted for the possible impact of the origin of the subjects on the evolution of their glucose metabolism, showed that the development of DM was only related to baseline FG levels, excluding factors associated with treatment, such as the type of inhibitor, the length of exposure and the percentage reduction in LDL-C levels, as shown in previous studies [12, 13]. As previously mentioned, in the PCSK9iG group, new-onset DM was only diagnosed in subjects who already had baseline pre-DM. These subjects had higher weight gains (although the difference was not significant) than the pre-DM subjects who did not progress to DM, a finding consistent with the results recently published by Merino et al. [10]. This study showed that the diabetogenic effect

related to lipid-lowering therapies and LDL-C reduction could be partially mediated by the increase in BMI (38% of the total effect, $p=0.003$). Interestingly, in the group of patients with DM at baseline in the PCSK9iG group, anthropometric parameters and glucose metabolism control did not worsen, which is probably because of the absence of relevant effects. Moreover, in this group of patients, physicians tend to adapt DM therapies promptly according to clinical practice. Overall, our data suggest that the impact of PCSK9i on glycaemic control, if any, would be moderate, perhaps slightly accelerating the transition to DM in predisposed subjects [19, 20]. Moreover, the efficacy and safety of PCSK9i were demonstrated in clinical trials carried out during their development in patients with and without DM [13, 21]. Neither the ODYSSEY OUTCOMES (alirocumab) nor FOURIER (evolocumab) studies found any deterioration in glycaemic control when compared with placebo, during 2.8 and 2.2 years, respectively [19, 20]. Moreover, most cases of *de novo* DM occurred among subjects with pre-DM, as in our study [20]. The recently published FOURIER-OLE study found no increased risk of *de novo* DM after a median follow-up of five years. The short follow-up time and the fact that most participants in the clinical trials were undergoing statin treatment are factors that could mask a hypothetical risk of DM associated with PCSK9i.

Most meta-analyses published to date have also failed to show an increased risk of DM among patients treated with PCSK9i [22]. In 2020, Chen et al. [14] found an increased risk of DM with alirocumab only when they adjusted for the use of statins, reinforcing the idea that the metabolic repercussions of the inhibitors probably depend to a great extent on the baseline treatment the patient is receiving.

In 2018, Carvalho et al. [15] published a meta-analysis that included more than 68,000 patients with a mean follow-up of 78 weeks. Compared with placebo, subjects treated with PCSK9i experienced a slight but significant increase in FG and A1c levels. However, this did not translate into a significant increase in the incidence of DM, with an association between DM risk and PCSK9i power and duration. These results are consistent with those obtained by Goldman et al. [16] in a recently published real-life study. Hyperglycaemic events were more frequent in PCSK9i users, without higher levels of DM. These effects were observed in the first six months of treatment and were reversible after PCSK9i withdrawal. Analysis according to the type of iPCKS9 indicated that only evolocumab was significantly associated with hyperglycaemia.

Mendelian randomisation studies have analysed gene variants of the *HMGCR, PCSK9 and NPC1L1* genes as a model of the pharmacological action of statins, PCSK9i and ezetimibe. This approach suggested an impact of these three genes on glycaemic metabolism and increased risk of DM, especially among patients who already had altered FG levels [7, 9]. However, it is not known whether the metabolic repercussions of these genetic variants, present from birth, can be assimilated to those of a treatment habitually initiated in adulthood.

The pathophysiological mechanism involved in diabetogenesis associated to PCSK9i is not known. It has been speculated that LDLR upregulation in beta cells could play a role. Higher intracellular cholesterol levels have been related to cell toxicity in animal models [23, 24]. The lower prevalence of DM in FH patients whit less LDLR expression has been postulated to reinforce this theory [8]. Moreover a recent mendelian randomization study including more than 900,000 patients suggest that lower genetically driven LDL-C concentrations are partially mediated by a higher BMI [10].

This study has several limitations; the main ones are its retrospective nature, the small sample size, a relatively short follow-up period and the lack of data availability for some variables of interest, such as A1c, HDL cholesterol or triglycerides levels in non-DM patients. Lifestyle (diet, physical activity), socioeconomic status, race or family background were not taken into account in the PSM and we cannot exclude some impact in DM development. Pre-DM were defined by FG or A1c but glucose tolerance test was not performed, so we could lose some pre-DM patients.

Finally, the initial dose and subsequent adjustments of statins were not assessed although all our patients were on high intensity statins. Moreover, the impact of DM therapy changes was not analysed. The strengths of the study lie on its real life nature, and the comparison with a similar metabolic population and a general population cohort with robust data, which provide a reliable comparison for the main variable of the study: the incidence of new-onset DM.

Conclusions

Our study has shown that PCSK9i therapy is associated with minute alterations in glucose metabolism control of nonclinical impact. The incidence of new-onset DM was higher in the PCSK9i-treated patients than in both the ad hoc control group and the observed rates in the general population; however, the difference did not reach statistical significance. No changes in glucose parameters were found in subjects with baseline DM. The development of new-onset diabetes was limited to subjects with prediabetes at baseline with higher FG levels and BMI values, so in these cases, closer monitoring of glucose parameters could be important for making an early diagnosis of DM.

In summary, our results do not support a clinically relevant effect of PCSK9i on the risk of DM. In any case, the impact of PCSK9i on glucose homeostasis, if any, should

not modify the clinical decision-making process regarding the prescription of these therapies.

List of Abbreviations

DM	Diabetes mellitus
NODM	New-onset diabetes mellitus
pre-DM	Prediabetes
PCSK9i	PCSK9 inhibitors
LDL-C	LDL cholesterol
FG	Fasting glucose
A1c	Glycated haemoglobin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-023-02077-y.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contribution
AMGLL, RMSH, AW and MB contributed to the conception and initial design of the study. AMGLL and NP were the main individuals responsible for the acquisition of PCSK9iG data. AMGLL performed the statistical analyses that were completed and reviewed by DLL, PR and JR. PR, JR, DLL and LM analysed and selected the comparator data (PSMG and D@G). AMGLL, RMSH, AW, MB, DI and LM contributed to the interpretation of the results. AMGLL, RMSH, AW and MB performed the initial drafting of the manuscript, which was corrected and revised by DI and LM.All the authors have read and approved the final manuscript.

Funding
This research was funded by Instituto de Salud Carlos III (ISCIII), Spain, with grants Rio Hortega 2019 (AMGL) exp CM19/00116, INT20/00032 (RMSH) and PI 20/00846, partially funded with European Union Regional Development Funds, "A way of doing Europe". We have also received fundings of FIISC (Canarian Foundation of Health Research) (PIFIISC 20/16).

Data Availability
The PCSK9iG and PSMG datasets used and analysed during the current study are available from the corresponding author upon reasonable request. Dates of the Di@bet.es study are available, but restrictions apply to the availability of these data. They were used under licence for the current study and are thus not publicly available. The data are, however, available from the authors upon reasonable request and with permission of Dr. Josep Ribalta.

Declarations

Ethics approval and consent to participate
This study complied with international recommendations on clinical research and was approved by the local ethics committee (CEIC Reference: CEI/CEIM Hospital Universitario de Gran Canaria Dr. Negrín, CEIm HUGCDN Code: 2021-210-1, protocol V 0.1–04/25/2021). Given the semianonymized retrospective nature of the study, informed consent was not requested from PCSK9iG participants. The Metbank and Di@betes cohorts had been previously approved by the ethical committees, and all participants signed a written agreement to participate and provide confidential data.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 5 October 2023 / Accepted: 27 November 2023
Published online: 03 January 2024

References

1. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34:154–6.
2. Ascaso JF. Inhibición De La proproteína convertasa subtilisina/kexina tipo 9 en El Tratamiento De La Hipercolesterolemia. Endocrinol Y Nutr. 2016;63:255–7.
3. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical outcomes in patients with Cardiovascular Disease. N Engl J Med. 2017;376:1713–22.
4. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of Alirocumab in reducing lipids and Cardiovascular events. N Engl J Med. 2015;372:1489–99.
5. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-Reactive protein. N Engl J Med [Internet]. 2008;359:2195–207.
6. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident Diabetes among patients treated with statins: Population based study. BMJ. 2013;346.
7. Lotta LA, Sharp SJ, Burgess S, Perry JRB, Stewart ID, Willems SM, et al. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 Diabetes: a meta-analysis. JAMA - J Am Med Assoc. 2016;316:1383–91.
8. Besseling J, Kastelein JJP, Defesche JC, Hutten BA, Hovingh GK. Association between familial hypercholesterolemia and prevalence of type 2 Diabetes Mellitus. JAMA - J Am Med Assoc. 2015;313:1029–36.
9. Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, et al. Variation in PCSK9 and HMGCR and risk of Cardiovascular Disease and Diabetes. N Engl J Med. 2016;375:2144–53.
10. Wu P, Moon JY, Daghlas I, Franco G, Porneala BC, Ahmadizar F, et al. Obesity partially mediates the Diabetogenic Effect of lowering LDL cholesterol. Diabetes Care. 2022;45:232–40.
11. González-Lleó AM, Sánchez-Hernández RM, Boronat M, Wägner AM. Diabetes and familial hypercholesterolemia: interplay between lipid and glucose metabolism. Nutrients. MDPI; 2022.
12. Colhoun HM, Ginsberg HN, Robinson JG, Leiter LA, Müller-Wieland D, Henry RR, et al. No effect of PCSK9 inhibitor alirocumab on the incidence of Diabetes in a pooled analysis from 10 ODYSSEY phase 3 studies. Eur Heart J. 2016;37:2981–9.
13. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet. 2017;390:1962–71.
14. Chen Q, Wu G, Li C, Qin X, Liu R, Zhang M. Safety of Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibodies in Regard to Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am. J. Cardiovasc. Drugs. Adis; 2020. p. 343–53.
15. De Carvalho LSF, Campos AM, Sposito AC. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and incident type 2 Diabetes: a systematic review and meta-analysis with over 96,000 patient-years. Diabetes Care. American Diabetes Association Inc.; 2018. pp. 364–7.
16. Goldman A, Raschi E, Cukierman-Yaffe T, Dankner R, Shouval R, Shechter M, et al. Hyperglycaemic disorders associated with PCSK9 inhibitors: a real-world, pharmacovigilance study. Eur J Prev Cardiol. 2022;29:1334–42.
17. Rojo-Martínez G, Valdés S, Soriguer F, Vendrell J, Urrutia I, Pérez V, et al. Incidence of Diabetes Mellitus in Spain as results of the nation-wide cohort di@bet.es study. Sci Rep. 2020;10:1–9.
18. Sánchez-Hernández RM, González-Lleó AM, Tugores A, Brito-Casillas Y, Civeira F, Boronat M, et al. Hipercolesterolemia familiar en Gran Canaria: mutación con efecto fundador y alta frecuencia de Diabetes. Clínica E Investig en Arterioscler. 2021;33:247–53.
19. Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, et al. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without Diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7:618–28.
20. Deedwania P, Murphy SA, Scheen A, Badariene J, Pineda AL, Honarpour N, et al. Efficacy and safety of PCSK9 inhibition with evolocumab in reducing cardiovascular events in patients with metabolic syndrome receiving statin therapy: secondary analysis from the FOURIER randomized clinical trial. JAMA Cardiol. 2021;6:139–47.

21. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO i study. Am Heart J. 2015;169:906–915e13.
22. Marouf BH, Iqbal Z, Mohamad JB, Bashir B, Schofield J, Syed A, et al. Efficacy and safety of PCSK9 monoclonal antibodies in patients with Diabetes. Clin. Ther. Elsevier Inc.; 2022. pp. 331–48.
23. Mbikay M, Sirois F, Mayne J, Wang GS, Chen A, Dewpura T, et al. PCSK9-deficient mice exhibit impaired glucose tolerance and pancreatic islet abnormalities. FEBS Lett. 2010;584:701–6.
24. Da Dalt L, Ruscica M, Bonacina F, Balzarotti G, Dhyani A, Di Cairano E, et al. PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor. Eur Heart J. 2019;40:357–68.

Publisher's Note

Cardiovascular Diabetology

RESEARCH

Open Access

Glucose metabolism in heterozygous familial hypercholesterolemia with a founder effect and a high diabetes prevalence: a cross-sectional study

Ana María González-Lleó[1,2,3,4*], Yeray Brito-Casillas[3], Virginia Martín-Santana[5], Yaiza Gil-Quintana[3], Antonio Tugores[6], Roberto Scicali[7], Marta Riaño[8], Luisa Hernández-Baraza[3], Roberto Jiménez-Monzón[3], Josefa Girona[1], Francesco Di Giacomo Barbagallo[7,9], Luis Masana[1,2], Mauro Boronat[3,4], Ana M. Wägner[3,4] and Rosa M. Sánchez-Hernández[3,4]

Abstract

Background Heterozygous familial hypercholesterolemia (HeFH) is typically associated with a lower prevalence of type 2 diabetes mellitus (T2DM). However, individuals carrying the *p.[Tyr400_Phe402del]LDLR* mutation, which is prevalent in Gran Canaria, exhibit an unexpectedly high prevalence of T2DM. This study aimed to investigate whether the *p.[Tyr400_Phe402del] LDLR* mutation co-segregates with T2DM and other glucose metabolism abnormalities.

Methods A total of 226 individuals were recruited, with 196 included in the final analysis. This included 90 HeFH patients from Gran Canaria (HeFH-GC) carrying the *p.[Tyr400_Phe402del]LDLR* mutation, 76 first-degree relatives (non-HeFH), and 30 HeFH patients from Italy (HeFH-It) with other *LDLR* mutations. Clinical, anthropometric, biochemical, and hematological parameters, including insulin resistance and sensitivity**,** were assessed via oral glucose tolerance tests (OGTT), and indices such as HOMA-IR, HOMA-beta, QUICKI, and the triglyceride–glucose ratio were measured.

Results Among HeFH-GC participants, 20% had T2DM, similar to 18.4% in the non-HeFH group (p = NS). HOMA-beta was significantly greater in HeFH-GC patients (86.2 vs. 68.4; $p = 0.046$). Normoglycemic HeFH-GC individuals had elevated HOMA-IR [2.0 (1.3–2.9) vs. 1.3 (1.0–1.9); $p = 0.008$]. Compared with HeFH-It patients, HeFH-GC individuals had higher fasting glucose levels (99 vs. 92.5 mg/dL; $p = 0.004$) and lower 120-min post-OGTT glucose levels (115 vs. 136.5 mg/dL; $p = 0.001$). Lipid-lowering therapy, hypertension, hypertriglyceridemia, and increased waist circumference were associated with T2DM.

Conclusions HeFH patients from Gran Canaria exhibit a high prevalence of T2DM. The *p.[Tyr400_Phe402del]LDLR* mutation does not co-segregate with T2DM, but normoglycemic HeFH-GC individuals have greater insulin resistance.

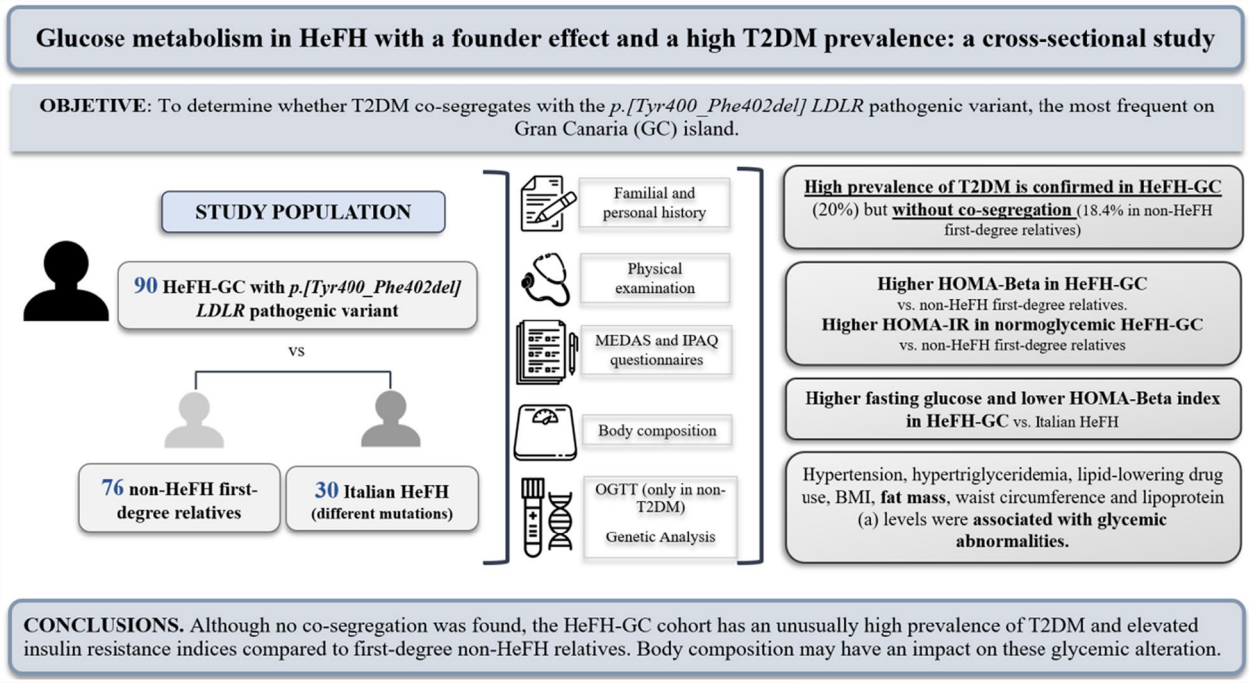
*Correspondence:
Ana María González-Lleó
anamaria.gonzalez@salutsantjoan.cat

Full list of author information is available at the end of the article

Additionally, lipid-lowering therapy, hypertension, hypertriglyceridemia, and increased waist circumference are factors associated with the prevalence of T2DM.

Keywords Heterozygous familial hypercholesterolemia, Type 2 diabetes, Founder effect, Glucose metabolism, Insulin resistance index, Oral glucose tolerance test

Graphical abstract



Research insights

What is currently known about this topic?

- Despite HeFH usually being linked to low diabetes prevalence, a founder effect in Gran Canaria has led to a high frequency of a specific mutation and an unexpectedly high diabetes prevalence in local HeFH patients.

What is the key research question?

- Does the prevalent mutation co-segregate with diabetes and other glucose issues?

What is new?

- This study examines the link between HeFH and high diabetes prevalence by analyzing glucose metabolism and body composition, comparing results with non-HeFH individuals and HeFH patients with other mutations.

How might this study influence clinical practice?

- The results could lead to earlier monitoring and treatment of glucose disorders in this HeFH group.

Introduction

Heterozygous familial hypercholesterolemia (HeFH) is one of the most common monogenic disorders, with a prevalence of 1 in 313 individuals [1]. It is inherited in an autosomal codominant manner and is characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels from childhood, the presence of distinctive physical signs (such as corneal arcus, xanthomas, and xanthelasmas), and an increased risk of early-onset cardiovascular disease (CVD) [2]. In HeFH patients, additional cardiovascular risk factors (CVRFs), including male sex, hypertension, and type 2 diabetes mellitus (T2DM), significantly increase the likelihood of developing CVD [3]. Despite the well-documented diabetogenic effects of statins [4], the prevalence of T2DM among HeFH individuals, who are almost universally treated with this medication, remains markedly lower (1.75–2.3%) [5] than

that in the general population (10.5%) [6]. This discrepancy may be partly explained by better adherence to a healthy lifestyle and maintenance of an optimal body weight [7]. In vitro studies have demonstrated that intracellular cholesterol accumulation induces apoptosis in pancreatic beta cells [5, 8]. These findings form the basis of the pancreatic lipotoxicity hypothesis, suggesting that excessive cellular cholesterol uptake could contribute to the pathogenesis of diabetes. This theory is further supported by Mendelian randomization studies showing that individuals with genetic variants that increase cellular cholesterol uptake (e.g., NPC1L1, HMGCR, PCSK9, and ABCG5/G8) have a higher prevalence of T2DM, in direct proportion to reductions in LDL-C levels [9]. Consequently, HeFH patients, who inherently have reduced cellular cholesterol uptake, might be considered partially protected from developing T2DM. This hypothesis also provides a plausible explanation for the diabetogenic effects of statins.

In contrast, individuals from Gran Canaria who carry the *p.[Tyr400_Phe402del] LDLR* pathogenic variant exhibit an unusually high T2DM prevalence of 25% [10], which is twice the prevalence reported in the local (10.4%) [11] and national (13.8%) [12] background populations. The geographic isolation of the Canary Islands until the mid-twentieth century facilitated consanguinity and genetic isolation, leading to the expansion of specific genetic traits and diseases [13, 14]. As a result, nearly 70% of HeFH individuals in Gran Canaria share this particular *LDLR* genetic variant, which is classified as a founder effect mutation [13].

The p.[Tyr400_Phe402del] variant in the *LDLR* leads to the deletion of three consecutive amino acids—tyrosine 400, serine 401, and phenylalanine 402—resulting in the production of immature LDL receptor proteins that are retained in the endoplasmic reticulum. Consequently, their expression on the cell surface is reduced, impairing the receptor's ability to mediate LDL-C uptake [15]. Notably, the loss of the tyrosine residue affects the highly conserved YWTD domain, a region critical for proper folding and function of the LDL receptor, and potentially important for its interaction with PCSK9, particularly in the recycling process and return of the receptor to the plasma membrane. Recent Mendelian randomization and meta-analyses involving PCSK9 inhibitors have reported associations with altered glucose metabolism [9, 16]. Together, these findings suggest that shared molecular mechanisms—possibly involving PCSK9 activity—may contribute not only to hypercholesterolemia, but also to insulin resistance and impaired glucose homeostasis [10].

The primary objective of this study was to determine whether T2DM co-segregates with the *p.[Tyr400_Phe402del] LDLR* pathogenic variant. Additionally, we evaluated glucose metabolism in HeFH affected individuals without T2DM, comparing them with their unaffected first-degree relatives and with an Italian cohort of HeFH patients carrying different *LDLR* genetic variants.

Materials and methods

Study design and subjects

This was a cross-sectional study that included HeFH patients aged ≥ 18 years who carried the *p.[Tyr400_Phe402del] LDLR* genetic variant and who were regularly followed at the Lipid Unit of the Maternal–Child Insular University Hospital Complex of Gran Canaria (CHUIMI) between 2020 and 2022 (HeFH-GC). First-degree relatives (parents, siblings, and offspring) aged ≥ 18 years were invited to participate. Those with a negative genetic test for HeFH were classified into the control group (non-HeFH). Subjects with poorly controlled thyroid disease, liver or kidney disorders, or active cancer were excluded.

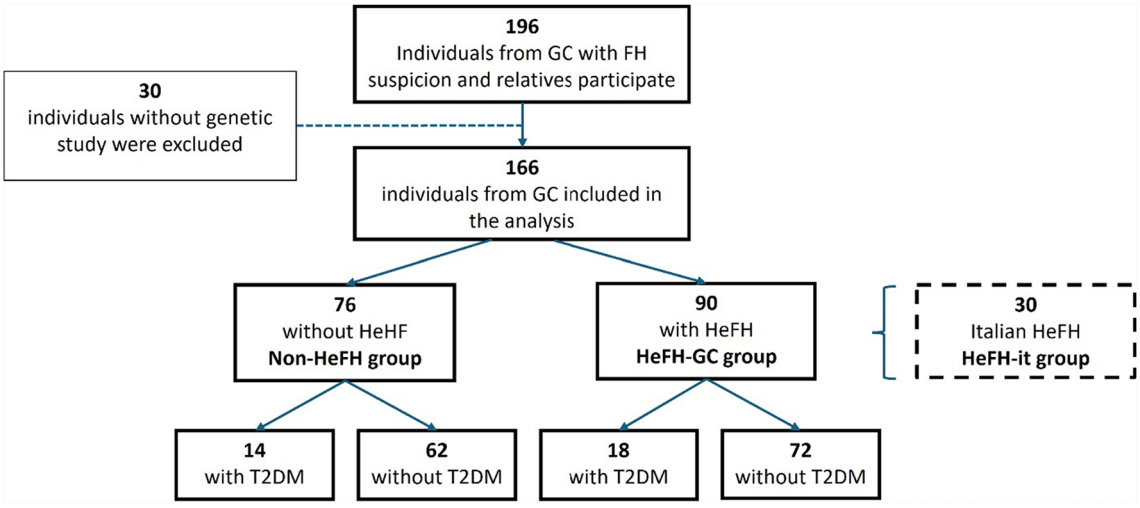


Fig. 1 Flow diagram

Additionally, a cohort of Italian HeFH patients without T2DM, carrying *LDLR* mutations distinct from the prevalent in Gran Canaria, was included for comparative analysis (HeFH-It) (Fig. 1).

Study protocol

For Gran Canaria patients, data collection included family history of early-onset cardiovascular disease (CVD), demographic characteristics (age, sex, place of birth, family history), lifestyle factors (smoking, alcohol consumption), and personal history of hypertension, T2DM, and/or CVD. CVD was defined as acute myocardial infarction (AMI), coronary revascularization, ischemic stroke, or peripheral vascular disease (intermittent claudication symptoms or an ankle-brachial index < 0.9).

Lipid-lowering therapy was recorded and classified on the basis of intensity (low, moderate, or high) [17]. Adherence to a healthy lifestyle was assessed via the Mediterranean Diet Adherence Screener (MEDAS) [18] and the International Physical Activity Questionnaire (IPAQ) [19].

A comprehensive physical examination was conducted, including weight, height, body mass index (BMI), waist and hip circumference, blood pressure (BP), and hypercholesterolemia stigmata (xanthomas, xanthelasmas, or corneal arcus). Hypertension was diagnosed in patients receiving antihypertensive treatment. Hypercholesterolemia was defined as LDL-C ≥ 160 mg/dL on two or more occasions and/or current lipid-lowering therapy. Hypertriglyceridemia was defined as a triglyceride level > 200 mg/dL on two or more occasions and/or ongoing treatment for hypertriglyceridemia. Medications affecting glycemic metabolism (e.g., glucocorticoids, estrogens, and antipsychotics) were also recorded.

The participants also underwent body composition analysis using bioelectrical impedance (Nutrilab™ Akern ®, Pisa, Italy) to determine fat mass, fat-free mass, muscle mass, and total body water.

After a 12-h overnight fast, blood samples were collected for general biochemical profiling, including complete blood count; fasting glucose, glycosylated hemoglobin (HbA1c); renal, hepatic, and thyroid function tests; urine analysis; vitamin D levels; and lipid panels (total cholesterol, HDL cholesterol [HDL-C], triglycerides, LDL-C [calculated via the Friedewald formula], apolipoprotein B [ApoB], and lipoprotein (a)).

Participants without a prior T2DM diagnosis underwent an oral glucose tolerance test (OGTT) with 75 g of glucose, and glucose, insulin, and C-peptide levels were measured at 0, 30, 90, and 120 min. On the basis of these results, glucose metabolism status was reclassified according to the 2024 American Diabetes Association (ADA) criteria [20], and surrogate markers of insulin resistance and beta-cell function were calculated. The homeostasis model assessment for insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI) and the triglyceride–glucose index (TyG) were used to evaluate insulin resistance [21, 22]. HOMA-Beta was employed as a proxy for pancreatic beta-cell function [21], and the oral glucose insulin sensitivity (OGIS) index was used as an estimator of insulin sensitivity [23].

Biochemical methods

Glucose concentrations were determined using a hexokinase-based method (Beckman Coulter AU analyzers), whereas the Italian cohort employed a glucose oxidase technique. HbA1c levels were measured via high-performance liquid chromatography (HPLC) with a Bio-Rad D-100 hemoglobin testing system (Gran Canaria) and an HLC-723G7 hemoglobin HPLC analyzer (Tosoh Corp.) (Italy). All measurements were standardized to the National Glycohemoglobin Standardization Program and aligned with the Diabetes Control and Complications Trial (DCCT) reference assay. Insulin levels were quantified using chemiluminescent immunoassay (Beckman Coulter Access Immunoassay Systems), while C-peptide levels were measured via an electrochemiluminescence immunoassay (ECLIA) on Cobas e 411 analyzer (Roche Diagnostics). In the Italian cohort, insulin was measured via microparticle enzyme immunoassay (Axsym System, Abbott Laboratories), and C-peptide was quantified using ELISA (Millipore Corporation, Billerica, MA, USA), with inter-assay and intra-assay coefficients of variation (CVs) ranging from 5.0–8.7% and 1.6–4.0%, respectively.

Plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) levels were measured in duplicate using a PCSK9 ELISA kit (Human PCSK9 Simple Step ELISA Kit, ABCAM, model ab209884). Concentrations were determined via 4-parameter logistic regression curve analysis (Prism 9, GraphPad Software).

The remaining analytical variables were determined using standard, routine laboratory methods. All laboratory analyses for the Canarian samples were conducted at the same facility.

Genetic analysis

Genomic DNA was extracted from blood samples collected in EDTA-containing tubes using a salt precipitation protocol [24]. Primer BLAST was used to design the following specific oligonucleotide primers: LDLR_e9_1F (5'-AGGCACTCTTGGTTCCATCG-3'), labeled with 6-carboxyfluorescein (FAM); and LDLR_e9_1R (GAGGAGAGAAGGGCATCAGC). PCR amplification was performed using 35 cycles (95 °C, 1 min; 55 °C, 1 min; 72 °C, 1 min) with 50 ng of genomic DNA and Taq polymerase (Promega Biotech, Madison, WI, USA). The PCR

products were denatured, combined with deionized formamide, heated at 95 °C for 5 min, and separated via 4% acrylamide:bis-acrylamide (19:1) denaturing gels with 50% urea in 1 × TBE buffer (89 mM Tris–borate, 2 mM EDTA, pH 8.2). Fluorescence detection was performed via a FUJI FLA 9000 Starion (Fujifilm Corporation, Tokyo, Japan) following the manufacturer's protocol.

Italian cohort

The results from the Gran Canaria cohort were compared with those from a cohort of 30 Italian HeFH patients (HeFH-It) from Catania, Sicily, who did not have T2DM. These individuals were diagnosed with HeFH and carried genetic variants distinct from the *p.[Tyr400_Phe402del] LDLR* mutation. Data collection included personal medical history, physical examinations, current lipid-lowering treatments, and laboratory results.

An oral glucose tolerance test (OGTT) with 75 g of glucose was performed in these patients at three time points (0, 60, and 120 min). These data were used to calculate the HOMA-IR, HOMA-beta, and QUICKI indices.

Statistical analysis

Descriptive data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and as frequencies (%) for categorical variables.

Comparisons between groups were performed using appropriate statistical tests: the chi-square (χ^2) test was used for categorical variables. Student's t test or the Mann–Whitney U test was used for continuous variables, depending on the normality of the data distribution. Multivariate logistic regression analyses were conducted to identify variables associated with the primary outcomes, using T2DM and a composite variable of impaired fasting glucose, glucose intolerance, and T2DM as dependent variables. The independent variables were those that reached statistical significance in the bivariate analyses.

A p value < 0.05 was considered statistically significant.

All the statistical analyses were conducted via SPSS version 21.0 for Windows (IBM Corporation, Armonk, NY, USA).

Results

From the 226 individuals recruited, 196 were included in the final analysis because they had a FH genetic testing performed. Among them, 90 were HeFH patients from Gran Canaria (HeFH-GC group) from 32 different families carrying the *p.[Tyr400_Phe402del] LDLR* mutation; 76 were first-degree relatives who had a negative genetic test (non-HeFH group); and 30 were HeFH patients from an Italian cohort (HeFH-It group) carrying other *LDLR* mutations (Fig. 1).

Regarding the characteristics of the entire Canarian cohort, classified by HeFH status, more than 50% of the participants were male, with a mean age of 55 years (47.8–62) and a mean BMI in the overweight range (Supplementary Material, Table 1).

Among HeFH Canarian patients, 40% (n = 36) who carried the *p.[Tyr400_Phe402del] LDLR* mutation were diagnosed de novo during the study. Compared with non-HeFH controls, HeFH-GC patients were younger, but there were no significant differences in sex distribution, hypertension prevalence, or hypertriglyceridemia.

As expected, HeFH-GC patients had an earlier diagnosis of hypercholesterolemia and a higher prevalence of established CVD, primarily AMI. The use of antiplatelet agents and lipid-lowering therapies, including high-intensity statins and PCSK9 inhibitors (PCSK9i), was significantly greater among HeFH-GC patients.

There were no significant differences in lipid profiles between HeFH-GC and non-HeFH participants, except for triglycerides, which were higher in the control group.

Additionally, no significant differences were observed in BMI, waist circumference, fat mass, fat-free mass, or muscle mass between the groups (body composition data were available for 79.9% of the participants).

With respect to glucose metabolism parameters, 36.7% of HeFH-GC patients had prediabetes (pre-DM), whereas 38.2% of non-HeFH controls did. 20% of HeFH-GC group had T2DM, compared to 18.4% of non-HeFH controls ($p = 0.962$). The fasting glucose and HbA1c levels were similar between the groups [99 (92–105) mg/dL (HeFH-GC) vs 98 (92–107) mg/dL (non-HeFH); ($p = 0.982$)] and [5.8 ± 0.8% (HeFH-GC) vs. 6.1 ± 1.4% (non-HeFH); ($p = 0.163$)], respectively. Only 8.6% of the participants were taking medications known to affect glucose metabolism.

The general characteristics of the participants without T2DM were comparable to those of the entire study cohort (Table 1). The prevalence of pre-DM was similar between HeFH-GC and non-HeFH individuals (70.8% vs. 66.1%; $p = 0.580$). No significant differences were observed in the glucose metabolism results between the HeFH-GC and non-HeFH groups.

Prior to the OGTT, there were no known cases of T2DM in the Italian cohort (Table 1). Compared with HeFH-GC patients without T2DM, Italian subjects were older, had a higher prevalence of hypertension, and presented worse HbA1c levels. However, there were no significant differences between the two groups regarding CVD prevalence, weight, or BMI.

Although the use of lipid-lowering therapy was similar between the groups, the Italian cohort had a better lipid profile. Conversely, impaired fasting glucose was more prevalent in HeFH-GC patients than in Italian HeFH patients (48.6% vs. 20%; $p = 0.019$).

Table 1 Characteristics of patients without diabetes mellitus (n = 134) with and without familial hypercholesterolemia from the Gran Canaria (HeFH-GC and non-HeFH) and Italian cohorts (HeFH-It)

	non-HeFH (n = 62, 37.8%)	HeFH-GC(n = 72, 43.9%)	*p* value *	HeFH-It (n = 30, 18.3%)	*p* value **
Age (years)	56 (51–61)	50 (42–58)	**0.017**	61 (57–66)	**< 0.001**
Sex (male,%)	54.8	48.6	0.493	36.7	0.285
Smoking (%)	18	22.2	0.776	36.7	**0.014**
IPAQ (%)			**0.005**	N/A	N/A
Low	35.7	10.9			
Moderate	35.7	48.4			
High	28.6	40.6			
MEDAS	7.3 ± 2	8.2 ± 2	**0.011**	N/A	N/A
Hypertension (%)	35	23.9	0.181	46.7	**0.033**
Hypercholesterolemia (%)	54.8	100	**< 0.001**	N/A	N/A
Age of diagnosis of hypercholesterolemia (years)	41.9 ± 11.9	21.1 ± 11.1	**< 0.001**	N/A	N/A
Hypertriglyceridemia (%)	23.3	22.2	1.000	N/A	N/A
Glucose metabolism post OGTT (%)			0.580		0.205
Normoglycemia	33.9	29.2		20	
PreDM	66.1	70.8		76.7	
T2DM	0	0		3.3	
Impaired fasting glucose (%)	48.4	48.6	0.994	20	**0.019**
Glucose intolerance by OGTT (%)	26.2	19.4	0.626	36.7	0.095
HbA1c 5.7–6.4%	37.1	43.1	0.458	63.3	**0.038**
Gestational DM (%)	36.4	9.1	0.311	N/A	N/A
CVD (%)	1.6	15.3	**0.006**	26.7	0.263
Antiplatelet drug (%)	3.2	16.7	**0.012**	26.7	0.279
Lipid lowering drugs (%)	29	95.8	**< 0.001**	100	0.553
Statins	29	88.9	**< 0.001**	100	0.101
Low intensity	0	1.6	1.000	6.7	
Moderate intensity	72.2	17.2	**< 0.001**	46.7	
High intensity	27.8	81.3	**< 0.001**	46.7	
Ezetimibe	11.3	66.2	**< 0.001**	76.7	0.351
PCSK9i	0	31	**< 0.001**	26.7	0.813
Medications that can alter glucose metabolism (%)	8.2	8.4	0.269	N/A	N/A
Antipsychotic	3.3	2.8			
Glucocorticoid	4.9	1.4			
Weight (kg)	76.3 ± 18.1	74.5 ± 13.3	0.534	71.8 ± 8.9	0.306
Height (cm)	167.3 ± 10.5	166.2 ± 8.5	0.514	165 ± 8.3	**< 0.001**
BMI (kg/m2)	25.9 (23.1–30.5)	26.3 (24.4–28.9)	0.728	25.4 (24.2–28.4)	0.386
Waist circumference (cm)	96.8 ± 13.7	94.3 ± 13.1	0.309	91.6 ± 12.1	0.338
Fat mass (%)	28.2 ± 10.7	26.7 ± 8.6	0.447	N/A	N/A
Fat free mass (%)	71.8 ± 10.7	73.3 ± 8.6	0.447	N/A	N/A
Muscular mass (%)	33.1 ± 9.4	35.3 ± 6.7	0.189	N/A	N/A
CRP mg/dL	0.2 (0.1–0.5)	0.1 (0.1–0.3)	**0.017**	N/A	N/A
HbA1c (%)	5.6 ± 0.4	5.6 ± 0.3	0.163	5.8 ± 0.4	**0.016**
Total cholesterol (mg/dL)	210.5 ± 44	210.4 ± 73.6	0.988	173.9 ± 44.3	**0.013**
HDL-C (mg/dL)	56.5 ± 10.4	55 ± 13	0.483	52.7 ± 12.1	0.406
LDL-C (mg/dL)	132.4 ± 36	135.3 ± 66.2	0.746	101.1 ± 39.1	**0.002**
ApoB (mg/dL)	99.8 ± 23.2	103.1 ± 38	0.542	84.2 ± 23.9	**0.013**
Lp(a) (mg/dL)	45.3 ± 36.4	57 ± 52.1	0.129	48 ± 37.9	0.390
Triglycerides (mg/dL)	115 ± 53.9	100.9 ± 49.5	0.117	100.7 ± 37.4	0.988
Untreated total cholesterol (mg/dL)	238 (210–278)	337 (298–406)	**< 0.001**	323 (313–356)	0.347

Table 1 (continued)

	non-HeFH (n = 62, 37.8%)	HeFH-GC(n = 72, 43.9%)	*p* value *	HeFH-It (n = 30, 18.3%)	*p* value **
Untreated LDL-C (mg/dL)	162.7 (132–195.1)	266.2 (217.8–321.1)	**< 0.001**	242 (232–271)	0.197
Duration of lipid-lowering treatment (years)	9.5 ± 7.1	21.1 ± 10.9	**< 0.001**	N/A	N/A

The bolded values indicate statistically significant results

MEDAS, Mediterranean Diet Adherence Screener; IPAQ, International Physical Activity Questionnaire; T2DM, type 2 diabetes; CVD, cardiovascular disease; PCSK9i, PCSK9 inhibitors; BMI, body mass index; HbA1c, glycosylated hemoglobin; CRP, C-reactive protein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Apo-B, apolipoprotein B; Lp(a), lipoprotein(a)

p value * comparison between HeFH-GC vs. non-HeFH patients

p value ** comparison between HeFH-GC vs. HeFH-It patients

Table 2 Comparison of OGTT results in patients with familial hypercholesterolemia from the Gran Canaria and Italian cohorts (HeFH-GC and HeFH-It)

	non-HeFH (n = 62, 37.8%)	HeFH-GC (n = 72, 43.9%)	*p* value *	HeFH-It (n = 30, 18.3%)	*p* value **
Glucose 0 min (mg/dL)	98 (92–107)	99 (92–105)	0.982	92.5 (86–97)	**0.004**
Glucose 90 min (mg/dL)	137 (112–167)	135 (106–167)	0.811	N/A	N/A
Glucose 120 min (mg/dL)	116 (92–144)	115 (97–135.5)	0.820	136.5 (117–172)	**0.001**
Insulin 0 min (µU/ml)	6.2 (3.9–9.9)	8.5 (5.4–11.5)	0.052	7.4 (6.8–12.3)	0.623
Insulin 90 min (µU/ml)	49 (33.1–80.4)	58.8 (34–104.9)	0.585	N/A	N/A
Insulin 120 min (µU/ml)	40.9 (27.9–82.3)	50.1 (30.2–82.7)	0.357	57.4 (37–75.6)	0.537
HOMA-IR	1.5 (1–2.7)	2.1 (1.4–2.9)	0.068	1.7 (1.5–3.1)	0.843
HOMA-beta	68.4 (49–99)	86.2 (51.5–118.8)	**0.046**	97 (84.4–175.1)	**0.017**
QUICKI	0.4 (0.3–0.4)	0.3 (0.3–0.4)	0.066	N/A	N/A
OGIS	405 (342–442)	393.5 (336.5–423)	0.550	N/A	N/A
Tg/glucose index	8.6 ± 0.5	8.4 ± 0.5	0.080	8.4 ± 0.4	0.825

The bolded values indicate statistically significant results

OGTT, oral glucose tolerance test with 75 g glucose; HOMA, homeostatic model assessment; IR, insulin resistance; QUICKI, quantitative insulin sensitivity check index; OGIS, oral glucose insulin sensitivity; Tg, triglycerides

p value * comparison between HeFH-GC vs. non-HeFH patients

p value ** comparison between HeFH-GC vs. HeFH-It patients

The comparison of the results of the OGTT, which was conducted only in participants without a known T2DM diagnosis, is presented in Table 2. Compared with that in the control group, the HOMA-beta index was significantly higher in HeFH-GC subjects. Although the differences did not reach statistical significance, both fasting insulin and HOMA-IR tended to be higher in the HeFH-GC group. In a subgroup analysis of 84 normoglycemic individuals (excluding pre-DM patients; Supplementary Material, Table 2), the HeFH-GC group presented significantly higher fasting insulin levels, 30-min insulin levels, HOMA-IR index, HOMA-beta index and a lower QUICKI index.

Compared with Italian patients, Canarian HeFH subjects had higher fasting glucose levels, lower 120-min glucose levels after the OGTT and a lower HOMA-beta index. No significant differences were observed in the TyG index between HeFH-GC patients and their unaffected relatives or the Italian cohort.

Following the OGTT, one Italian patient was newly diagnosed with T2DM according to ADA criteria.

The multivariate logistic regression analysis conducted to identify factors associated with T2DM in the HeFH-GC cohort revealed that, after adjusting for age, T2DM was significantly associated with the use of lipid-lowering drugs, hypertension, hypertriglyceridemia, and waist circumference. No association was found between T2DM and the prevalent mutation (Fig. 2).

When a composite outcome of impaired fasting glucose, glucose intolerance (based on the OGTT), and T2DM was used as the dependent variable, we identified associations with hypertension, hypertriglyceridemia, lipid-lowering drug use, BMI, fat mass, waist circumference and lipoprotein (a) levels (Fig. 3).

Discussion

This study confirms an unusually high prevalence of diabetes (20%) among HeFH patients from Gran Canaria carrying the *p.[Tyr400_Phe402del] LDLR* mutation. In comparison, the prevalence of T2DM in individuals within the same age range from the reference hospital's health area ranges between 8.1 and 13.7% [11].

This finding is particularly noteworthy given previous suggestions that HeFH patients might be somewhat protected against T2DM. Globally, the prevalence of T2DM among individuals with HeFH is estimated at 5.7%, and even lower—around 4.1%—among those with a confirmed genetic diagnosis [25]. Similarly, in Spain, the prevalence among HeFH patients is 6.7% [7], but drops to below 2% in cohorts with genetically confirmed *LDLR* mutations [5]. One proposed explanation for this lower prevalence has been the adoption of healthier lifestyles and lower BMI among HeFH patients [7] due to early

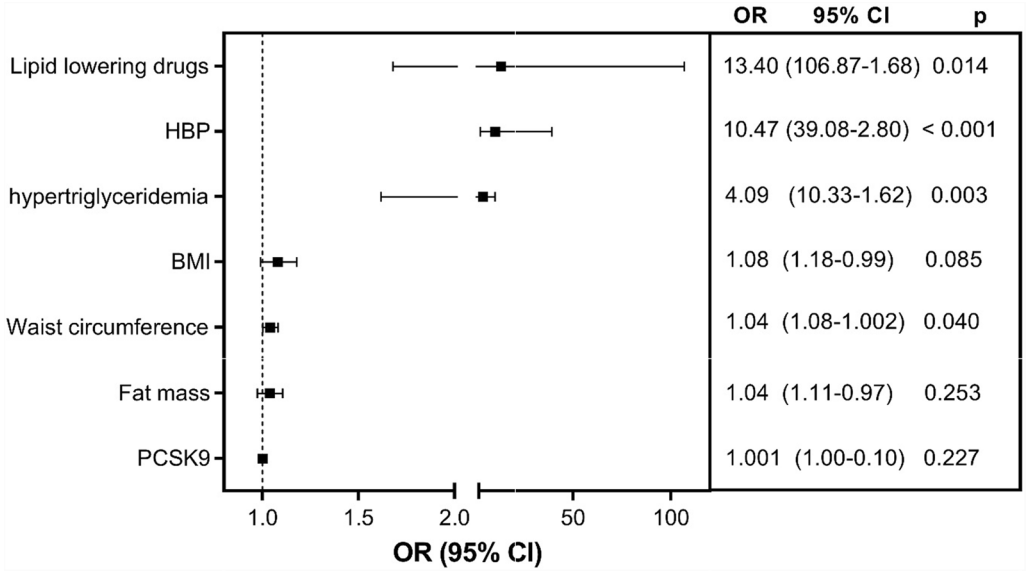


Fig. 2 Multivariate logistic regression analysis in patients with familial hypercholesterolemia from the Gran Canaria cohort using type 2 diabetes mellitus (T2DM) as the dependent variable. Abbreviations: HBP: high blood pressure; BMI: body mass index; PCSK9i: PCSK9 inhibitors

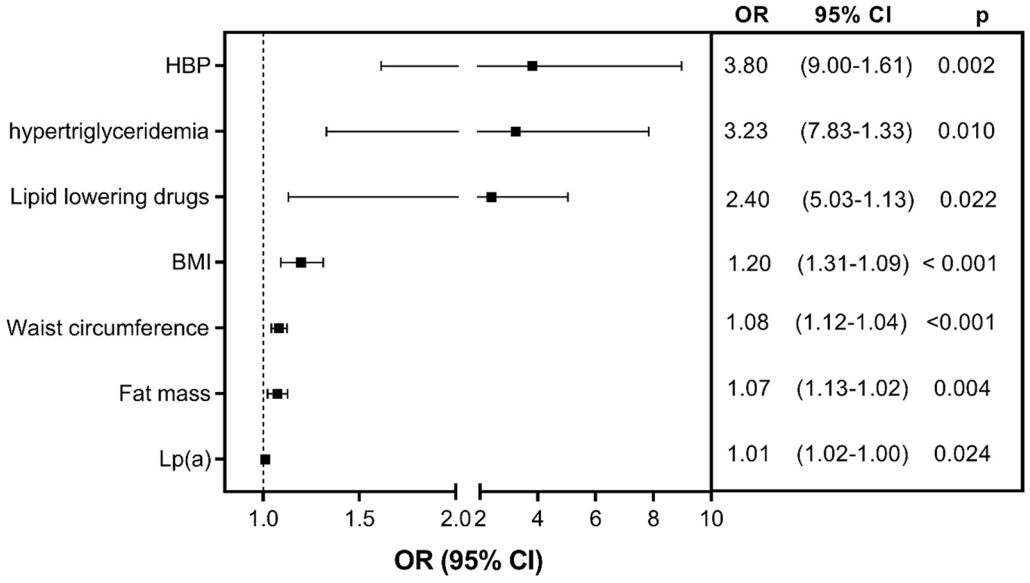


Fig. 3 Multivariate logistic regression analysis in patients with familial hypercholesterolemia from the Gran Canaria cohort using the composite of impaired fasting glucose, glucose intolerance (by OGTT) and type 2 diabetes mellitus (T2DM) as the dependent variable. Abbreviations: HBP: high blood pressure; BMI: body mass index; Lp(a): lipoprotein(a)

medical follow-up and preventive care. However, our findings do not support this hypothesis. Despite reporting healthier lifestyle habits than their non-HeFH first-degree relatives—as assessed by dietary and physical activity questionnaires—no significant differences were observed in anthropometric measures, and the HeFH-GC cohort still exhibited a similarly high prevalence of T2DM. These findings suggest that additional, non-traditional factors may be contributing to this unexpected metabolic profile.

Our initial hypothesis was that the highly prevalent pathogenic variant *p.[Tyr400_Phe402del] LDLR* observed in Gran Canaria might co-segregate with a predisposition to T2DM. However, no significant differences in T2DM or pre-diabetes prevalence were found when comparing HeFH-GC patients with their first-degree relatives who did not carry the mutation. Notably, even in this control group, the prevalence of glucose metabolism disorders (pre-DM or T2DM) was higher than in the general population. Furthermore, multivariate logistic regression analysis revealed no associations between

the *p.[Tyr400_Phe402del] LDLR* mutation and T2DM or the composite variable of impaired glucose metabolism, glucose intolerance, and T2DM. These findings suggest a strong genetic predisposition to impaired glucose metabolism regulation within these families but no association with the pathogenic HeFH variant.

Although the *p.[Tyr400_Phe402del] LDLR* mutation was not a determinant of the high prevalence of T2DM in these patients, it also did not serve as a protective factor against T2DM or other glucose metabolism disorders observed in this population. In participants without previously known T2DM, insulin resistance and pancreatic beta-cell secretory capacity were evaluated. While the euglycemic clamp technique is considered the gold standard for assessing insulin resistance [26], we used HOMA-IR, HOMA-Beta, the QUICKI index, the OGIS index, and the triglyceride-glucose (TyG) index [27–31], which are more suitable for epidemiological studies.

Among HeFH-GC patients without T2DM, HOMA-Beta was significantly greater than that of non-HeFH participants. Basal insulin and HOMA-IR showed a trend toward higher values, although these differences were not statistically significant. This pattern suggests increased insulin resistance in HeFH-GC patients, accompanied by a compensatory increase in insulin secretion, potentially identifying those at higher risk of developing T2DM [31].

Interestingly, when individuals with pre-DM were excluded—leaving only normoglycemic participants presumed to have normal carbohydrate metabolism—insulin levels (fasting and at 30 min), HOMA-IR, and HOMA-Beta were significantly higher in HeFH-GC participants, whereas the QUICKI index was lower, reaching statistical significance in all cases.

After the OGTT, nearly 50% of HeFH-GC patients without T2DM exhibited altered fasting glucose levels, and 30% showed OGTT-defined glucose intolerance, a prevalence similar to that observed in non-HeFH individuals. These findings suggest a strong genetic or environmental predisposition to diabetes within these families.

A comparison of glucose metabolism test results between HeFH-GC patients and an Italian cohort carrying different *LDLR* mutations suggested that different FH mutations do not influence insulin secretion, as assessed by HOMA-Beta. This finding does not support the hypothesis that LDL cellular uptake plays a role in pancreatic beta-cell function.

The complex interplay between glucose and lipid metabolism remains incompletely understood [5], although insulin is known to play a central role in regulating LDL receptor (LDLR) function [32, 33]. Certain lipid disorders -such as hypertriglyceridemia and familial combined hyperlipidemia- can induce hyperinsulinemia and reduce insulin sensitivity independently of BMI [34–36]. However, this relationship appears to be less pronounced in HeFH subjects [37–42].

Our findings suggest that insulin resistance, particularly reduced hepatic insulin sensitivity, is the primary mechanism contributing to impaired glucose metabolism in the HeFH-GC population. In addition, multivariate analysis identified several traditional metabolic factors—including lipid-lowering treatment (mainly statins), hypertension, triglyceride levels, BMI and increased fat mass—as significant contributors to diabetes risk and glucose dysregulation. The detrimental impact of these metabolic risk factors is well recognized, and their presence in individuals with HeFH may further exacerbate cardiometabolic risk. Indeed, in this population, both metabolic syndrome [43] and T2DM [44] are established, independent risk factors for CVD [45, 46].

A recent study involving over 24,000 adults with HeFH from 44 countries identified age, lipid-lowering therapy, and—most prominently—BMI as significant predictors of T2DM risk [25]. In line with these findings, and compared to the national Spanish HeFH cohort [7], individuals in the HeFH-GC group were older, had higher BMI and waist circumference, and more frequently received lipid-lowering treatment.

The elevated use of high-intensity statins—known for their diabetogenic effect—[4, 47] -, may partially explain the unexpectedly high prevalence of T2DM in the HeFH-GC population. However, previous evidence suggests that this adverse effect may be mediated, at least in part, by statin-associated weight gain [48]. In patients with FH, the diabetogenic influence of statins appears to be attenuated, with BMI remaining the most consistent factor associated with metabolic disturbances [49]. Contrary to this, no differences in BMI or waist circumference were observed between HeFH-GC patients and their non-affected relatives, with values comparable to those reported for the general population of Gran Canaria [50, 51]. Interestingly, despite similar anthropometric profiles, the prevalence of T2DM in both groups within our cohort was significantly higher than the regional averages.

The Canary Islands report the highest prevalence of T2DM in Spain [52]. Moreover, the population exhibits disproportionately high rates of both macrovascular complications—such as diabetes-related mortality [53] and lower limb major amputations [54]—and microvascular complications, including chronic kidney disease and diabetes-related end-stage renal disease [55].

These significant disparities between the Canarian population and other Spanish regions remain poorly understood. The elevated prevalence of cardiovascular risk factors in the Canary Islands—including metabolic syndrome, hypertension, obesity, and insulin resistance—may contribute to this phenomenon [55, 56].

Social and environmental determinants also play a significant role. Lower educational levels, particularly among women [50], and the limited economic resources that often accompany this may restrict access to healthy foods, further promoting the development of T2DM in this population. The high consumption of saturated fats, simple sugars, and alcohol, along with irregular adherence to diabetes treatment regimens [57–59] likely contributes to both the elevated rates of metabolic diseases and the poor clinical outcomes observed in the Canary Islands.

Finally, the distinct ethnic origins of the Canary Islands population, which differ from the rest of Spain, may contribute to a unique genetic background. Although phenotypically Caucasian, the inhabitants descend from a mixture of indigenous peoples from North Africa and Spanish colonists who arrived from the fifteenth century onward [60]. This distinct ancestry, combined with the region's geographic isolation, could explain a genetic predisposition that differs from that of other Spanish populations. It is likely that this genetic background, together with classical metabolic, therapeutic, and environmental factors, contributes to the clinical profiles observed in the HeFH-GC cohort.

In any case, it is evident that HeFH individuals are not protected from the development of glycemic disorders, highlighting the importance of addressing all risk factors and initiating early treatment when necessary.

Our study has some limitations. Although the euglycemic clamp is the gold standard for assessing insulin resistance and sensitivity, we relied on surrogate markers such as HOMA-IR, HOMA-Beta, QUICKI, and the triglyceride–glucose index. Additionally, the Italian HeFH group was older than the Canarian HeFH patients, and methodological differences in laboratory measurements between countries may limit the generalizability of some findings. The use of alternative diagnostic criteria for T2DM [61] may also have influenced the results. Our study also presents several strengths. Although the sample size of the HeFH-GC group may seem limited, to the best of our knowledge, this represents the largest cohort of individuals carrying the same *LDLR* mutation in which glucose metabolism has been specifically evaluated, including comparisons with first-degree relatives without the mutation. This genetic homogeneity enhances the internal validity of the findings and enables a more precise metabolic characterization.

Furthermore, the HeFH-GC cohort shows an unusually high prevalence of T2DM [5], making it particularly relevant for the study of glucose homeostasis. To our knowledge, this is also the first study comparing OGTT responses between HeFH cohorts from two different countries (Spain and Italy) carrying distinct genetic mutations.

Conclusion

This study confirms a high prevalence of T2DM in HeFH families from Gran Canaria carrying the *p.[Tyr400_Phe402del] LDLR* variant. However, our findings indicate that T2DM does not co-segregate with this founder mutation.

Furthermore, the prevalent mutation in Canarian HeFH does not provide protection against T2DM. Instead, similar to the general population, genetic and environmental factors such as hypertension, fat mass, waist circumference, and others play decisive roles in determining glycemic alterations among HeFH individuals.

Routine assessment of body composition, glycemic profiles, and cardiovascular risk factors in non-diabetic HeFH patients is essential for personalized monitoring of carbohydrate metabolism, predicting diabetes progression, and early implementation of lipid- and glucose-lowering therapies with proven cardiovascular benefits.

Abbreviations

HeFH	Heterozygous familial hypercholesterolemia
T2DM	Type 2 diabetes mellitus
OGTT	Oral glucose tolerance test
HOMA	Homeostatic model assessment
LDL-C	LDL cholesterol
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factor
AMI	Acute myocardial infarction
MEDAS	Mediterranean Diet Adherence Screener
IPAQ	International Physical Activity Questionnaire
BMI	Body mass index
HbA1c	Glycosylated hemoglobin
HDL-C	HDL cholesterol
Apo-B	Apolipoprotein B
Lp(a)	Lipoprotein(a)
QUICKI	Quantitative insulin sensitivity check index
TyG	Triglyceride-glucose index
OGIS	Oral glucose insulin sensitivity
PCSK9i	PCSK9 inhibitors

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02857-8.

Supplementary Material 1

Acknowledgements

We extend our gratitude to Dra. Yaiza García Delgado for her valuable insights and guidance on body composition techniques.

Author contributions

AMGLL, RMSH, AW and MB contributed to the conception and initial design of the study. AMGLL recruited Canarian patients with HeFH and their first-degree relatives, entered the data into the database, and performed the initial statistical analysis. AMGLL, YBC, RJM, LHB, and AT were responsible for sample processing and preservation and for performing the PCR and ELISA assays. MR, VMS, and YGQ coordinated and performed the blood extractions in the laboratory. RS and FDGB recruited the Italian sample used as the comparator group. JG reviewed the statistical analysis and prepared the corresponding figures. The results were interpreted by AMGLL, MB, AW, and RMSH. AMGLL performed the initial drafting of the manuscript, which was subsequently

revised and edited by AW, MB, RMSH, MR, YBC, LM, and FDGB. All the authors have read and approved the final manuscript.

Funding
This research was funded by Instituto de Salud Carlos III (ISCIII), Spain, with grants Rio Hortega 2019 (AMGL) exp CM19/00116, INT20/00032 (RMSH) and PI 20/00846, partially funded with European Union Regional Development Funds, "A way of doing Europe". We have also received funding from the FIISC (Canarian Foundation of Health Research) (PIFIISC 20/16).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Gran Canaria ethics committee (Committee on Ethics and Research with Drugs of the Province of Las Palmas, Las Palmas de Gran Canaria, Spain; approval code: CEIm H.U.G.C. Dr. Negrín: 2020–164-1) and by the local Italian Ethics Committee, in accordance with the ethical standards of the institutional and national research committees. This study was conducted following the ethical principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Vascular Medicine and Metabolism Unit, Lipids and Atherosclerosis Research Unit, Sant Joan University Hospital, Avenida del Dr. Josep Laporte, 2, 43204 Reus, Tarragona, Spain
[2]University Rovira i Virgili, Reus, Spain
[3]University Institute of Biomedical and Health Research (IUIBS), University of Las Palmas de Gran Canaria (ULPGC), Las Palmas de Gran Canaria, Spain
[4]Section of Endocrinology and Nutrition, Maternal-Child Insular University Hospital Complex of Gran Canaria (CHUIMI), Las Palmas de Gran Canaria, Spain
[5]Prudencio Guzmán Specialized Care Center, Maternal-Child Insular University Hospital Complex of Gran Canaria (CHUIMI), Las Palmas de Gran Canaria, Spain
[6]Research Support Unit, Maternal-Child Insular University Hospital Complex of Gran Canaria (CHUIMI), Las Palmas de Gran Canaria, Spain
[7]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[8]Biochemistry Service, Maternal-Child Insular University Hospital Complex of Gran Canaria (CHUIMI), Las Palmas de Gran Canaria, Spain
[9]Department of Medicine and Surgery, "Kore" University of Enna, Enna, Italy

Received: 25 March 2025 / Accepted: 10 July 2025
Published online: 06 August 2025

References

1. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. J Am Coll Cardiol. 2020;75:2553–66.
2. Bouhairie VE, Goldberg AC. Familial hypercholesterolemia. In: Cardiol Clin. Philadelphia: W.B. Saunders; 2015. p. 169–79.
3. Akioyamen LE, Genest J, Chu A, Inibhunu H, Ko DT, Tu JV. Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: a systematic review and meta-analysis. J Clin Lipidol. 2019;13:15–30.
4. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012;380:565–71.
5. González-Lleó AM, Sánchez-Hernández RM, Boronat M, Wägner AM. Diabetes and familial hypercholesterolemia: interplay between lipid and glucose metabolism. Nutrients. 2022;14(3):600.
6. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
7. Perez-Calahorra S, Civeira F, Guallar-Castillón P, Pinto X, Banegas JR, Pedro-Botet J, et al. Behavioural cardiovascular risk factors and prevalence of diabetes in subjects with familial hypercholesterolemia. Eur J Prev Cardiol. 2020;27:1649–60.
8. Lu X, Liu J, Hou F, Liu Z, Cao X, Seo H, et al. Cholesterol induces pancreatic β cell apoptosis through oxidative stress pathway. Cell Stress Chaperones. 2011;16:539–48.
9. Lotta LA, Sharp SJ, Burgess S, Perry JRB, Stewart ID, Willems SM, et al. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 diabetes: a meta-analysis. JAMA. 2016;316:1383–91.
10. Sánchez-Hernández RM, González-Lleó AM, Tugores A, Brito-Casillas Y, Civeira F, Boronat M, et al. Familial hypercholesterolemia in Gran Canaria: founder mutation effect and high frequency of diabetes. Clínica e Investigación en Arteriosclerosis (English Edition). 2021;33:247–53.
11. Atlas for monitoring diabetes care in the Canary Islands, 2022 [Internet]. Available from: https://cienciadedatosysalud.org/atlas/cuidados-diabetes-canarias.
12. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es study. Diabetologia. 2012;55:88–93.
13. Sánchez-Hernández RM, Tugores A, Nóvoa FJ, Brito-Casillas Y, Expósito-Montesdeoca AB, Garay P, et al. The island of Gran Canaria: a genetic isolate for familial hypercholesterolemia. J Clin Lipidol. 2019;13:618–26.
14. García-Villarreal L, Daniels S, Shaw SH, Cotton D, Galvin M, Geskes J, et al. High prevalence of the very rare Wilson disease gene mutation Leu708Pro in the island of Gran Canaria (Canary Islands, Spain): a genetic and clinical study. Hepatology. 2000;32:1329–36.
15. Suárez NM, Jebari-Benslaiman S, Jiménez-Monzón R, Benito-Vicente A, Brito-Casillas Y, Garcés L, et al. Age, origin and functional study of the prevalent LDLR mutation causing familial hypercholesterolemia in Gran Canaria. Int J Mol Sci. 2023;24(21):15605.
16. De Carvalho LSF, Campos AM, Sposito AC. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and incident type 2 diabetes: a systematic review and meta-analysis with over 96,000 patient-years. Diabetes Care. 2018;41:364–7.
17. Djoussé L, Song RJ, Cho K, Gaziano JM, Gagnon DR. Association of statin therapy with incidence of type 2 diabetes among US veterans. J Clin Cardiol Cardiovasc Ther. 2019;1(1): 1001.
18. Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvadó J, Buil-Cosiales P, Corella D, et al. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLoS ONE. 2012;7(8): e43134.
19. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381–95.
20. American Diabetes Association. Diagnosis and classification of diabetes: standards of care in diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S20-42.
21. Placzkowska S, Pawlik-Sobecka L, Kokot I, Piwowar A. Indirect insulin resistance detection: current clinical trends and laboratory limitations. Biomed Pap. 2019;163:187–99.
22. Park HM, Lee HS, Lee YJ, Lee JH. The triglyceride–glucose index is a more powerful surrogate marker for predicting the prevalence and incidence of type 2 diabetes mellitus than the homeostatic model assessment of insulin resistance. Diabetes Res Clin Pract. 2021;180: 109042.
23. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care. 2001;24(3):539–48.
24. Longmire J, Albright K, Lewis A, Meincke L, Hildebrand C, Leadon S, et al. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. C I R L Press Limited; 1987).
25. Elshorbagy A, Lyons ARM, Vallejo-Vaz AJ, Stevens CAT, Dharmayat KI, Brandts J, et al. Association of BMI, lipid-lowering medication, and age with prevalence of type 2 diabetes in adults with heterozygous familial hypercholesterolemia: a worldwide cross-sectional study. Lancet Diabetes Endocrinol. 2024;12(11):811–23.

26. Heise T, Zijlstra E, Nosek L, Heckermann S, Plum-Mörschel L, Forst T. Euglycaemic glucose clamp: what it can and cannot do, and how to do it. Diabetes Obes Metab. 2016;18:962–72.
27. de Fátima Haueisen Sander Diniz M, Beleigoli AMR, Schmidt MI, Duncan BB, Ribeiro ALP, Vidigal PG, et al. Homeostasis model assessment of insulin resistance (HOMA-IR) and metabolic syndrome at baseline of a multicentric Brazilian cohort: ELSA-Brasil study. Cad Saude Publica. 2020;36:e00044119.
28. da Silva CdC, Zambon MP, Vasques ACJ, Camilo DF, de Góes Monteiro Antonio MÂR, Geloneze B. The threshold value for identifying insulin resistance (HOMA-IR) in an admixed adolescent population: a hyperglycemic clamp validated study. Arch Endocrinol Metab. 2023;67:119–25.
29. Khalili D, Khayamzadeh M, Kohansal K, Ahanchi NS, Hasheminia M, Hadaegh F, et al. Are HOMA-IR and HOMA-B good predictors for diabetes and prediabetes subtypes? BMC Endocr Disord. 2023;23:4.
30. Færch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? Diabetologia. 2009;52:1714–23.
31. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet. 2009;373:2215–21.
32. Chait A, Bierman EL, Albers JJ. Low-density lipoprotein receptor activity in cultured human skin fibroblasts: mechanism of insulin-induced stimulation. J Clin Invest. 1982;70(1):26–34.
33. Chandra NC. A comprehensive account of insulin and LDL receptor activity over the years: a highlight on their signaling and functional role. J Biochem Mol Toxicol. 2021;35(8): e22830.
34. Veerkamp MJ, de Graaf J, Stalenhoef AFH. Role of insulin resistance in familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol. 2005;25(5):1026–31.
35. Paolisso G, Ferrannini E, Sgambato S, Varricchio M, D'Onofrio F. Hyperinsulinemia in patients with hypercholesterolemia. J Clin Endocrinol Metab. 1992;74(1):141–5.
36. Sheu WH, Shieh S, Fuh MM, Shen DD, Jeng C, Chen YI, et al. Insulin resistance, glucose intolerance, and hyperinsulinemia. Diabetes Care. 1995;18(3):367–71.
37. Karhapää P, Voutilainen E, Kovanen PT, Laakso M. Insulin resistance in familial and nonfamilial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 1993;13(4):497–504.
38. Galvan AQ, Santoro D, Natali A, Sampietro T, Boni C, Masoni A, et al. Insulin sensitivity in familial hypercholesterolemia. Metabolism. 1993;42(12):1583–7.
39. Paolisso G, Ferrannini E, D'Amore A, Volpe C, Varricchio M, D'Onofrio F. Effects of physiological plasma insulin levels on glucose turnover parameters in familial hypercholesterolemia. Atherosclerosis. 1993;101(1):111–5.
40. Galvan AQ, Natali A, Baldi S, Frascerra S, Sampietro T, Galetta F, et al. Effect of reduced-fat diet with or without pravastatin on glucose tolerance and insulin sensitivity in patients with primary hypercholesterolemia. J Cardiovasc Pharmacol. 1996;28(4):595–602.
41. Xu H, Ryan KA, Jaworek TJ, Southam L, Reid JG, Overton JD, et al. Familial hypercholesterolemia and type 2 diabetes in the Old Order Amish. Diabetes. 2017;66(8):2054–8.
42. Koks N, de Vries MA, Birnie E, Alipour A, Castro CM. Glucose-dependent leucocyte activation in familial hypercholesterolemia. Eur J Clin Invest. 2017;47(10):839–46.
43. Paquette M, Bernard S, Cariou B, Hegele RA, Genest J, Trinder M, et al. Metabolic syndrome predicts cardiovascular risk and mortality in familial hypercholesterolemia. J Clin Lipidol. 2023;17(3):376–83.
44. Jansen ACM, van Aalst-Cohen ES, Tanck MW, Trip MD, Lansberg PJ, Liem AH, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med. 2004;256(6):482–90.
45. Paquette M, Cariou B, Bernard S, Hegele RA, Gallo A, Genest J, et al. Increased FH-risk-score and diabetes are cardiovascular risk equivalents in heterozygous familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2024;44(2):505–12.
46. Howard BV, Mayer-Davis EJ, Goff D, Zaccaro DJ, Laws A, Robbins DC, et al. Relationships between insulin resistance and lipoproteins in nondiabetic African Americans, Hispanics, and non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. Metabolism. 1998;47(1):1–10.
47. Alvarez-Jimenez L, Morales-Palomo F, Moreno-Cabañas A, Ortega JF, Mora-Rodríguez R. Effects of statin therapy on glycemic control and insulin resistance: a systematic review and meta-analysis. Eur J Pharmacol. 2023;947: 175672.
48. Wu P, Moon JY, Daghlas I, Franco G, Porneala BC, Ahmadizar F, et al. Obesity partially mediates the diabetogenic effect of lowering LDL cholesterol. Diabetes Care. 2022;45(1):232–40.
49. Panz V, Immelman A, Paiker J, Pilcher G, Raal F. High-dose statin therapy does not induce insulin resistance in patients with familial hypercholesterolemia. Metab Syndr Relat Disord. 2012;10(5):351–7.
50. Boronat M, Varillas VF, Saavedra P, Suárez V, Bosch E, Carrillo A, et al. Diabetes mellitus and impaired glucose regulation in the Canary Islands (Spain): prevalence and associated factors in the adult population of Telde, Gran Canaria. Diabet Med. 2006;23(2):148–55.
51. de Pablos-Velasco P, Martínez-Martín F, Rodríguez-Pérez F. Prevalence of obesity in a Canarian community. Association with type 2 diabetes mellitus: the Guía Study. Eur J Clin Nutr. 2002;56(6):557–60.
52. Cebrián Cuenca AM, Escalada J. Prevalence of obesity and diabetes in Spain. Evolution in the last 10 years. Aten Primaria. 2025;57(1): 101502.
53. Marcelino-Rodríguez I, Elosua R, Pérez MdelCR, Fernández-Bergés D, Guembe MJ, Alonso TV, et al. On the problem of type 2 diabetes-related mortality in the Canary Islands, Spain: the DARIOS study. Diabetes Res Clin Pract. 2016;111:74–82.
54. Rodríguez Pérez MC, Chines C, Pedrero García AJ, Sousa D, Cuevas Fernández FJ, Marcelino-Rodríguez I, et al. Major amputations in type 2 diabetes between 2001 and 2015 in Spain: regional differences. BMC Public Health. 2020;20(1):54.
55. Lorenzo V, Boronat M, Saavedra P, Rufino M, Maceira B, Novoa FJ, et al. Disproportionately high incidence of diabetes-related end-stage renal disease in the Canary Islands: an analysis based on estimated population at risk. Nephrol Dial Transplant. 2010;25(7):2283–8.
56. Boronat M, Chirino R, Varillas VF, Saavedra P, Marrero D, Fabregas M, et al. Prevalence of the metabolic syndrome in the island of Gran Canaria: comparison of three major diagnostic proposals. Diabet Med. 2005;22(12):1751–6.
57. Núñez-González E, Serra-Majem L, Fika-Hernándo M, Fernández-Vallhonrat B, Bravo-Martínez J, Martín-Ferrer JM, et al. Determinants of specific food consumption in the Canary Islands (Spain). Food Funct. 2011;2(10):627–32.
58. Godenau D, Martin-Rodriguez G, Gonzalez-Gomez JI, Caceres-Hernandez JJ. Food consumption in the Canary Islands: nutritional implications of food imports and local production. BMC Public Health. 2022;22: 1187.
59. Cabrera de León A, Castillo Rodríguez JC, Domínguez Coello S, Rodríguez Pérez MC, Brito Díaz B, Borges Álamo C, et al. Estilo de vida y adherencia al tratamiento de la población canaria con diabetes mellitus tipo 2. Rev Esp Salud Publica. 2009;83(4):567–75.
60. Serrano JG, Ordóñez AC, Santana J, Sánchez-Cañadillas E, Arnay M, Rodríguez-Rodríguez A, et al. The genomic history of the indigenous people of the Canary Islands. Nat Commun. 2023;14(1): 7610.
61. World Health Organization. Classification of Diabetes Mellitus [Internet]. Geneva: WHO; 2019. Available from: http://apps.who.int/bookorders

Publisher's Note

Conclusiones

1. La interacción entre el metabolismo glucémico y el lipídico es compleja y está influida por factores genéticos, ambientales y terapéuticos. Tanto la DM2 como la HF se asocian a un mayor riesgo cardiovascular, que se incrementa cuando ambas patologías coinciden en un mismo individuo.

2. La prevalencia de DM2 en personas con HF parece ser inferior a la de la población general, posiblemente debido a que una menor actividad del r-LDL atenúa la lipotoxicidad sobre las células β pancreáticas.

3. El tratamiento con iPCSK9 no se asocia a un efecto clínicamente relevante sobre el metabolismo glucémico, por lo que no se justifica modificar su indicación terapéutica por un potencial riesgo de DM2.

4. La aparición de nuevos casos de DM2 en pacientes tratados con iPCSK9 se limitó a personas con prediabetes y sobrepeso, lo que sugiere que, en individuos predispuestos, podría ser útil una monitorización glucémica más estrecha.

5. La prevalencia de DM2 entre individuos con HFHe portadores de la variante p.[Tyr400_Phe402del] en el gen *LDLR* en Gran Canaria es superior a la publicada tanto en población general como en otras cohortes de HFHe.

6 Esta variante genética no mostró co-segregación con la DM2.

7 Los individuos con HFHe portadores de esta variante no están protegidos frente a las alteraciones de la homeostasis glucémica y presentan los mismos factores de riesgo clásicos asociados al desarrollo de DM2 en la población general.

Anexos

Servicio Canario de la Salud
Complejo hospitalario Materno Insular de Gran Canaria

CUESTIONARIO DE ADHERENCIA A LA DIETA MEDITERRÁNEA

Nombre:

Edad:

1. ¿Usa el aceite de oliva como principal grasa para cocinar?

☐ No

☐ Sí

2. ¿Cuánto aceite de oliva consume en total al día? (incluyendo el usado para freír, comidas fuera de casa, ensaladas, etc.…)

☐ Menos de 2 cucharadas al día

☐ 2 o más cucharadas al día

3. ¿Cuántas raciones de verduras u hortalizas consume al día? (1 ración = 200 g. Las guarniciones o acompañamientos = ½ ración)

☐ Menos de 2 raciones al día

☐ 2 o más raciones al día (al menos una de ellas en ensaladas o crudas)

4. ¿Cuántas piezas de fruta (incluyendo zumo natural) consume al día?

☐ Menos de 3 raciones al día

☐ 3 o más raciones al día

5. ¿Cuántas raciones de carnes rojas, hamburguesas, salchichas o embutidos consume al día? (1 ración = 100-150 g)

☐ Menos de 1 ración al día

☐ 1 o más raciones al día

6. ¿Cuántas raciones de mantequilla, margarina o nata consume al día? (porción individual = 12 g)

☐ Menos de 1 ración al día

☐ 1 o más raciones al día

7. ¿Cuántas bebidas carbonatadas y/o azucaradas consume al día? (refrescos, colas, tónicas, bitter)

☐ Menos de 1 bebida al día

☐ 1 o más bebidas al día

8. ¿Bebe vino? ¿Cuánto consume a la semana?

☐ Menos de 3 vasos a la semana

☐ 3 o más vasos a la semana

9. ¿Cuántas raciones de legumbres consume a la semana? (1 plato o ración = 150 g)

☐ Menos de 3 raciones a la semana

☐ 3 o más raciones a la semana

10. ¿Cuántas raciones de pescado/mariscos consume a la semana? (1 plato, pieza o ración = 100-150 g de pescado o 4-5 piezas o 200 g de marisco)

☐ Menos de 3 raciones a la semana

☐ 3 o más raciones a la semana

11. ¿Cuántas veces consume repostería comercial a la semana? (no casera, como: galletas, flanes, dulces, bollería, pasteles)

☐ Menos de 3 raciones a la semana

☐ 3 o más raciones a la semana

12. ¿Cuántas veces consume frutos secos a la semana (1 ración = 30 g)?

☐ Menos de 1 ración a la semana

☐ 1 o más raciones a la semana

13. ¿Consume preferentemente carne de pollo, pavo o conejo en vez de ternera, cerdo, hamburguesas o salchichas? (carne de pollo, pavo o conejo: 1 pieza o ración de 100-150 g)

☐ No

☐ Sí

14. ¿Cuántas veces a la semana consume los vegetales cocinados, la pasta, arroz u otros platos aderezados con salsa de tomate, ajo, cebolla o puerro elaborada a fuego lento con aceite de oliva? (sofrito)

☐ Menos de 2 a la semana

☐ 2 o más a la semana

CUESTIONARIO INTERNACIONAL DE ACTIVIDAD FÍSICA (IPAQ)

Nombre:

Edad:

Las preguntas que se le plantean a continuación se refieren al tiempo que usted ha empleado a estar físicamente activo **en los últimos 7 días.** Por favor responda a cada pregunta incluso si no se considera una persona activa.

Piense en todas las actividades INTENSAS que usted ha realizado en los últimos 7 días. Las actividades físicas intensas se refieren a aquellas que implican un esfuerzo físico intenso y que lo hacen respirar mucho más intensamente que lo normal y que realizó durante por lo menos 10 minutos seguidos.

1. Durante los últimos 7 días, ¿en cuántos realizó actividades físicas intensas tales como levantar pesos pesados, cavar, hacer ejercicios aeróbicos o andar rápido en bicicleta?

_____ días por semana

☐ Ninguna actividad física intensa → *Vaya a la pregunta 3*

2. Habitualmente, ¿cuánto tiempo en total dedicó a una actividad física intensa en uno de esos días?

_____ horas por día

_____ minutos por día

☐ No sabe/No está seguro

Piense en todas las actividades MODERADAS que usted realizó en los últimos 7 días. Las actividades moderadas son aquellas que requieren un esfuerzo físico moderado que lo hace respirar algo más intensamente que lo normal. Piense solo en aquellas actividades físicas que realizó durante por lo menos 10 minutos seguidos.

3. Durante los últimos 7 días, ¿en cuántos días hizo actividades físicas moderadas como transportar pesos livianos, andar en bicicleta a velocidad regular o jugar al tenis? **No incluya caminar.**

_____ días por semana

☐ Ninguna actividad física moderada → *Vaya a la pregunta 5*

4. Habitualmente, ¿cuánto tiempo en total dedicó a una actividad física moderada en uno de esos días?

_____ horas por día

_____ minutos por día

□ No sabe/No está seguro

Piense en el tiempo que usted dedicó a <u>CAMINAR</u> en los últimos 7 días. Esto incluye caminar en el trabajo o en la casa, para trasladarse de un lugar a otro, o cualquier otra caminata que usted podría hacer solamente para la recreación, el deporte, el ejercicio o el ocio.

5. Durante los últimos 7 días, ¿En cuántos caminó por lo menos 10 minutos seguidos?

_____ días por semana

□ Ninguna caminata → *Vaya a la pregunta 7*

6. Habitualmente, ¿cuánto tiempo en total dedicó a caminar en uno de esos días?

_____ horas por día

_____ minutos por día

□ No sabe/No está seguro

La última pregunta es acerca del tiempo que pasó usted <u>SENTADO</u> durante los días hábiles de los últimos 7 días. Esto incluye el tiempo dedicado al trabajo, en la casa, en una clase, y durante el tiempo libre.

7. Durante los últimos 7 días ¿cuánto tiempo pasó sentado durante un día hábil?

_____ horas por día

_____ minutos por día

□ No sabe/No está seguro

Maria Pilar Gayoso Diz
Subdirectora General de Evaluación y Fomento de la Investigación

CERTIFICA

Que según los antecedentes que obran en poder de esta Subdirección General, **Dña. ANA MARIA GONZALEZ LLEÓ,** ha participado como Personal Contratado (Doctor) en los Contratos Rio Hortega que se relacionan:

Título del Proyecto: **"CONTRATOS RIO HORTEGA"**
- Número de Expediente: CM19/00116
- Duración: 2 años.
- Jefe de Grupo: WAGNER FAHLIN, ANA MARIA.
- Fecha de inicio: 31/01/2020
- Fecha fin: 30/01/2022.

Y para que así conste, firmo el presente certificado en Madrid,

La Subdirectora General de Evaluación y fomento de la Investigación.

Maria Pilar Gayoso Díz

UNIVERSIDAD DE LAS PALMAS
DE GRAN CANARIA