UNIVERSIDAD LATINA DE PANAMÁ

FACULTAD DE CIENCIAS DE LA SALUD

DOCTOR WILLIAM C. GORGAS

ESCUELA DE TECNOLOGÍA MÉDICA

TÍTULO:

Correlación de los niveles bajos del HDL-C con los biomarcadores de disfunción renal en adultos mayores.

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UNIVERSIDAD LATINA DE PANAMÁ

FACULTAD DE CIENCIAS DE LA SALUD

Trabajo de graduación para optar por el Título de: **Licenciatura en Tecnología Médica.**

Estudiantes: **Ashley Vergara y Jhony Domínguez**

CORRELACIÓN DE LOS NIVELES BAJOS DEL HDL-C BAJO CON LOS BIOMARCADORES DE DISFUNCIÓN RENAL EN ADULTOS MAYORES.

Esta tesis fue aprobada por el Comité Asesor conformado por:

Director

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Firma

Jurado

_____

Firma

Jurado

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Firma

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DECLARACIÓN JURADA

Yo, **Ashley M. Vergara S.,** con cédula de identidad **No. 8-1019-1483**, estudiante graduando de la carrera (o programa) de **Licenciatura en Tecnología Médica**, declaro bajo la gravedad de juramento que el material que aparece en esta tesis de grado es de mi producción intelectual,

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Yo, **Jhony A. Domínguez.**, con cédula de identidad **No. 6-726-767**, estudiante graduando de la carrera (o programa) de **Licenciatura en Tecnología Médica**, declaro bajo la gravedad de juramento que el material que aparece en esta tesis de grado es de mi producción intelectual, debido a la cual asumo toda la responsabilidad sobre el uso de producción intelectual.

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Tabla de contenido

Resumen

La disfunción renal se puede definir como la condición médica en donde el paciente lucha contra un mal funcionamiento de los riñones, de manera que estos no pueden cumplir con la tarea de filtrar los desechos o excesos de líquido en la sangre.

Por consiguiente, la disfunción renal no solo se limita a la disminución a nivel del filtrado renal, sino que impacta al adecuado funcionamiento de otros analitos de importancia clínica, y algunas complicaciones sistémicas tal como el HDL (lipoproteína de alta densidad que coloquialmente se conoce como “colesterol bueno”), estas moléculas tienen la capacidad de eliminar el colesterol del torrente sanguíneo. El HDL es una pieza clave para poder transportar el exceso de colesterol de las células periféricas al hígado mediante el transporte reverso de colesterol, que participa activamente en la producción de las bilis para la disminución de estas partículas lipídicas.

El presente estudio tiene como objetivo principal evidenciar la prevalencia de niveles bajos de HDL-C y la correlación que tiene ante los biomarcadores de disfunción o daño renales que hay en pacientes con enfermedad renal crónica mayores de 50 años.

Ahora bien, la fracción C del HDL hace referencia a la porción de colesterol que está contenida en la partícula lipoproteica. A su vez, es la única fracción que se puede llegar a medir en el laboratorio dado que el “HDL libre” no se cuantifica en clínica comúnmente por métodos fotométricos que son empleados, principalmente, por la mayoría de los equipos en hospitales de segundo y de tercer nivel. Se prevé identificar la correlación entre la disminución significativa del HDL-C y la alteración de función renal.

Asimismo, se espera que la información obtenida permita fortalecer los programas de manejo de las enfermedades no transmisibles de carácter crónico, creando una referencia actualizada sobre la evolución de la enfermedad.

Palabras clave: biomarcadores, disfunción renal, transporte reverso de colesterol, torrente sanguíneo, filtrado glomerular, inhibidores

Abstract

Renal dysfunction can be defined as a medical condition in which the patient presents impaired kidney function, such that the kidneys are unable to perform the task of filtering waste products or excess fluids from the blood.

Consequently, renal dysfunction is not only limited to a decrease in glomerular filtration but also impacts the proper functioning of other clinically important analytes, as well as some systemic complications such as HDL (high-density lipoprotein, commonly known as “good cholesterol”). These molecules have the ability to remove cholesterol from the bloodstream. HDL is a key component in transporting excess cholesterol from peripheral cells to the liver through reverse cholesterol transport, which actively participates in bile production to reduce these lipid particles.

The present study has as its main objective to demonstrate the prevalence of low HDL-C levels and the correlation with biomarkers of renal dysfunction or damage in patients over 50 years of age with chronic kidney disease.

Furthermore, the HDL-C fraction refers to the portion of cholesterol contained within the lipoprotein particle. In turn, it is the only fraction that can be measured in the laboratory, since “free HDL” is not commonly quantified in clinical practice using photometric methods, which are primarily employed by most equipment in secondary and tertiary level hospitals. It is intended to identify the correlation between a significant decrease in HDL-C and altered renal function.

Likewise, it is expected that the information obtained will help strengthen management programs for chronic non-communicable diseases, creating an updated reference on disease progression.

Keywords: high-density lipoprotein, photometric methods, reverse cholesterol transport, disease progression, glomerular filtration, bloodstream.

Introducción

Los términos colesterol bueno y colesterol malo han sido acuñados desde hace más de una década. Junto con su descubrimiento, se evidenció que, debido a su composición bioquímica, el colesterol no viaja libremente por la sangre. En su estructura, posee una porción polar que permite a las macromoléculas lipoproteicas encargadas de su transporte interactuar mediante puentes de hidrógeno con los grupos polares de los fosfolípidos y las proteínas presentes en la superficie de la lipoproteína.

Las lipoproteínas son partículas sumamente complejas que se caracterizan por poseer en su superficie una monocapa de fosfolípidos y colesterol libre. Cabe destacar que las lipoproteínas difieren tanto en su contenido lipídico como en su composición proteica.

Existe una asociación significativa entre las dislipidemias, y las alteraciones renales. En los pacientes con ERC la disminución de las lipoproteínas no solo sugiere una alteración a nivel de los lípidos. Sino que también, involucra el metabolismo de los lípidos en donde se evalúa la reducción de la producción a nivel hepático de apolipoproteínas que son de importancia química para el HDL. Además de su capacidad antiaterogénica y su función en el trasporte reverso. A partir de sus hallazgos, Rader (2006) señala que comúnmente se excluyen las características funcionales que potencian el efecto antiaterogénica, tales como:

- Inhibición de la oxidación de las lipoproteínas de baja densidad (LDL)
- La reducción de la inflamación endotelial

- La estimulación de la síntesis de óxido nítrico (NO) por las células endoteliales
- El aumento de la disponibilidad de prostaciclina.
- La disminución de la agregación plaquetaria y la coagulación sanguínea.

De acuerdo con Rader (2016), el trasfondo fisiológico no es claro, pero, se considera que la sinergia de estos mecanismos puede orientar a aumentar los niveles de HDL-C, y la disminución podría ejercer su efecto antiaterogénico, sin la necesidad de inducir el transporte reverso de colesterol.

CAPITULO I

PLANTEAMIENTO DEL PROBLEMA

1.1 PLANTEAMIENTO DEL PROBLEMA

La enfermedad renal crónica constituye un problema de salud pública a nivel mundial, y a nivel nacional. Según cifras del Ministerio de salud **MINSA (2025),** se estima que más de 150,000 panameños padecen de enfermedad renal crónica, principalmente, la población de personas mayores de 50 años.

Ante esta problemática, se plantea la siguiente interrogante ¿De qué manera se relaciona la disfunción renal con los aspectos clínicos en la población mayor de 50 años y qué alteraciones metabólicas pueden ser medidas y correlacionadas desde el laboratorio clínico?

Diversos estudios han evidenciado que la disminución significativa del HDL-C son rasgos característicos de la dislipidemia asociada a la enfermedad renal crónica. **Pavanello & Ossoli (2023)**. No obstante, la literatura expone que la relación que hay entre marcadores de función renal tales como: la creatinina sérica, la tasa de filtración glomerular (TFG), la presencia de proteinuria y el nitrógeno ureico en sangre (BUN), y las alteraciones del metabolismo lipídico están intrínsecamente asociada a procesos de inflamación crónica.

Del mismo modo, el análisis entre la función renal y los niveles de HDL-C, facilitaría a contribuir con posibles avances en el monitoreo riguroso de este analito en pacientes con mayor predisposición a la ERC u otras enfermedades crónicas no transmisibles con el componente inflamatorio; la detección temprana de la lesión renal, evaluación del estado del paciente, concientizar a la población sobre la adopción de hábitos adecuados como medicina preventiva y poder implementar estrategias para la prevención primaria

y secundaria, junto con la reducción de la progresión de la ERC y la aparición de otras posibles comorbilidades.

Esta situación evidencia una diversidad de enfoques, lo cual dificulta la interpretación específica y la aplicación clínica de los resultados obtenidos en los distintos métodos y poblaciones analizadas. Asimismo, muchos de los estudios no presentan conclusiones suficientes o específicas sobre la correlación renal, lo que ofrece una visión poco unificada del tema. En este contexto, se sustenta la necesidad de sintetizar la información disponible en la literatura mediante una revisión sistemática de la evidencia científica.

1.2 NECESIDAD DEL ESTUDIO

Incursionar en el aumento de la biblioteca de datos científicos en Panamá es fundamental, dado que este sector se encuentra rezagado en el desarrollo de la ciencia y la tecnología. En este contexto, esta revisión surge ante a la necesidad que hay actualmente en el país debido a la carencia de evidencia científica actualizada y sólida que contextualice la problemática de las enfermedades metabólicas. Esta permitirá reforzar las escasas evidencias existentes y contribuir a la consolidación del conocimiento científico en el ámbito de la salud.

Los principales beneficiarios de esta revisión serán los estudiantes y las instituciones de salud. Para los estudiantes, permitirá contar con información más actualizada sobre la situación poblacional y el abordaje de la enfermedad renal crónica desde el laboratorio clínico. Para las instituciones de salud, facilitará una mejor orientación hacia investigaciones de carácter científico, fortaleciendo la toma de decisiones basadas en evidencia. De manera indirecta, la población panameña también se verá beneficiada, ya

que esta revisión permitirá ampliar el conocimiento contextualizado a la realidad nacional, contribuyendo a mejorar el manejo clínico, la implementación de nuevas tecnologías, la detección temprana y el tratamiento oportuno.

Se espera que los datos obtenidos contribuyan a impulsar la producción científica a nivel nacional. Asimismo, se prevé que esta revisión promueva el fortalecimiento del sistema de salud pública en aspectos relacionados con el análisis e interpretación de resultados de laboratorio, favoreciendo el desarrollo de una medicina preventiva y no meramente reactiva.

El aporte de esta investigación también radica en la educación sobre los riesgos de las enfermedades que se originan a nivel metabólico y que desencadenan una serie de eventos capaces de comprometer la vida del paciente. La identificación temprana de estas alteraciones permite la referencia oportuna a un especialista antes de alcanzar etapas avanzadas de daño renal, lo que favorece una mejor planificación, intervención y control de la progresión de la enfermedad.

El impacto esperado de esta revisión es de carácter multidimensional, ya que contribuye tanto al fortalecimiento del conocimiento del personal de salud como al de los pacientes, especialmente en lo referente a las dislipidemias, su prevención y los riesgos asociados a las enfermedades metabólicas.

1.3 JUSTIFICACIÓN

Según datos de la Organización Panamericana de la Salud (OPS, 2019), durante ese mismo año se registraron alrededor de 250,000 defunciones en la región de las Américas, siendo las enfermedades renales la octava causa de mortalidad. En Panamá,

la prevalencia de la enfermedad renal crónica (ERC) se estima en 12.6% y es responsable del 2.8% de las defunciones anuales (Borrero et al., 2023); esta creciente prevalencia representa un importante desafío para la salud pública nacional.

Usualmente, la ERC suele ser detectada en etapas avanzadas, debido a la ausencia de manifestaciones clínicas en sus estadios iniciales. En los últimos años se ha evidenciado un incremento significativo en el número de casos de ERC. Aunado a ello, la presencia de comorbilidades contribuye a acelerar la progresión del daño renal. La solución definitiva implicaría promover un cambio integral en el estilo de vida de la población panameña, lo cual constituye un objetivo a largo plazo. Sin embargo, como alternativa temporal frente a esta problemática, resulta fundamental fortalecer los métodos diagnósticos e implementar guías de detección temprana de la lesión renal, con el fin de disminuir la población de pacientes con ERC.

Asimismo, es necesario reducir los sesgos derivados de las distintas comorbilidades presentes en la población, las cuales pueden interferir en el análisis del valor real de los biomarcadores. Esto es especialmente relevante en la población adulta mayor, donde la interpretación de los biomarcadores renales y metabólicos debe realizarse en conjunto con una valoración clínica integral y no como valores analíticos aislados.

La realización de una revisión sistemática permitirá establecer sólidas bases teóricas a partir de la literatura científica disponible, orientando el desarrollo de futuras investigaciones sobre enfermedades crónicas no transmisibles que afectan cada vez más a la población nacional. Además, el análisis integral de la evidencia facilitará la consolidación del vínculo entre las alteraciones del metabolismo lipídico y la disfunción

renal, excluyendo necesariamente las comorbilidades de origen cardiovascular para obtener una perspectiva más precisa y relevante sobre la relación entre estos factores.

En virtud de lo anterior, para el personal de salud que atiende a esta población con enfermedades renales resulta fundamental el manejo de información actualizada y basada en evidencia científica. De manera conjunta, médicos y tecnólogos médicos desempeñan un rol clave en la educación

1.4 OBJETIVOS

1.4.1 Objetivo general:

Evidenciar la correlación existente entre las alteraciones renales y las modificaciones en el metabolismo lipídico, a partir de los hallazgos científicos reportados en la literatura especializada.

1.4.2 Objetivos específicos:

1. Analizar la relación entre los principales biomarcadores de función renal (creatinina sérica, tasa de filtración glomerular, presencia de proteinuria y nitrógeno ureico en sangre) y las alteraciones lipídicas a nivel del HDL-C.
2. Comparar los niveles de HDL-C y los biomarcadores de función renal considerando factores externos comunes que puedan influir en estos parámetros.
3. Determinar las causas asociadas a la alteración del metabolismo lipídico en pacientes con disfunción renal.

CAPÍTULO II

MARCO TEÓRICO

Marco Teórico

2.1 Antecedentes de la investigación

Kronenberg et al. (2019) evidenciaron a la comunidad médica que la disminución de las lipoproteínas de alta densidad está directamente asociadas a el desarrollo de la enfermedad renal crónica (ERC).

Por su parte **Bowe et al. (2016)** expusieron las incongruencias presentes, si se compara el aspecto teórico junto con lo experimental. Este expone la hipótesis con respecto a que la disminución del HDL-C puede estar asociado a un mayor riesgo de desarrollo o progresión de la ERC. Los resultados de este estudio revelaron la asociación que existe entre algunos biomarcadores de daño renal. Junto con la disminución del HDL-C se observó la duplicación de la creatinina sérica, y la disminución de la tasa de filtración glomerular (TFG).

En Panamá la enfermedad renal crónica representa una carga agravante para el sistema de salud público. Los altos porcentajes de panameños con ERC refleja una situación preocupante. Esto evidencia que contamos con una gran población padeciente de enfermedades renales, y metabólicas. Sin dejar de lado que muchos de los panameños ya presentan riesgo de desarrollar una problemas cardio-metabólicos.

Moreno Velásquez et al. (2017) describieron que para el periodo de 2001 a 2014, se registraron 4,646 muertes de las cuales 57.6% eran hombres y 42.4% eran mujeres. Asimismo, el Registro Nacional de Mortalidad describe que hubo un aumento sostenido en la mortalidad por ERC hasta el año 2006, y seguido a ello una disminución en años posteriores. Este evento ha sido correlacionado con el envenenamiento masivo por dietilenglicol, que no solo representó un punto de inflexión en el ámbito de salud pública

nacional, sino que también, gracias a sus propiedades nefrotóxicas, pudo contribuir al aumento progresivo de pacientes con alteraciones renales.

2.1.1 ESTUDIO 1

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Association of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and chronic kidney disease in elderly insights from NHANES

Yifan Sun[1,4], Zhou Li[2,4] & Ninghan Feng[1,2,3]✉

The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) is a novel lipid index. Prior research has established a connection between lipid irregularities and chronic kidney disease (CKD). This study aims to establish a possible link between NHHR and CKD. Data from the National Health and Nutrition Examination Survey (NHANES) spanning from 2003 to 2016 was used to examine the relationship between NHHR and CKD among the elderly population. This research utilized weighted logistic regression, smoothed curve fitting and subgroup analyses along with interaction tests to evaluate the association between NHHR and CKD. The findings reveal a positive correlation between NHHR and CKD in fully adjusted Model 3. Besides, NHHR had a J-curve relationship with CKD. Subgroup analysis indicated that compared with those with lower body mass index (BMI), individuals with higher BMI are more prone to CKD. Research has shown that increased NHHR levels are associated with a higher likelihood of developing CKD in individuals aged above 60 in the United States. NHHR's role in lipid metabolism suggests it might be an effective marker for tracking CKD's progression.

Keywords NHHR, NHANES, CKD, Cross-sectional study, Obesity, Elderly

CKD is marked by a decline in the glomerular filtration rate, heightened urinary albumin excretion, or a combination of these factors[1]. Patients with CKD often exhibit no obvious clinical symptoms in the early stages, but as the condition progresses, they may experience a range of symptoms, including edema, hypertension, increased risk of infections, and disturbances in lipid and electrolyte metabolism[2–4]. CKD, marked by diminished glomerular filtration rates and increased urinary albumin excretion, poses a significant public health issue, affecting around 10% of the worldwide population, notably among the elderly[5]. Thus, early and precise identification, intervention, and management of CKD are crucial to alleviate the healthcare burden on both patients and society. The causes of CKD are multifaceted and remain incompletely defined; however, risk factors such as inflammation, obesity, diabetes, hypertension, and cardiovascular disease (CVD) have been recognized[6,7].

The relationship between lipid metabolism and CKD is complex, with various studies having delved into the same. In the renal parenchyma, lipid deposits may induce inflammation and fibrosis. Renal tubulointerstitial fibrosis, a major histopathological manifestation, is closely associated with CKD advancement and eventual renal failure[8]. Commonly, CKD patients show raised levels of triglyceride-rich lipoprotein particles (TRLs), higher low-density lipoprotein cholesterol (LDL-C), and lower HDL-C. The NHHR, integrating the properties of both HDL-C and non-HDL-C, serves as a new composite index for evaluating atherosclerosis risk. Previous studies have confirmed that it is superior to traditional blood lipid indexes with respect to their assessment of atherosclerosis and metabolic syndrome risk[9,10]. Moreover, it has been reported that NHHR is related to type 2 diabetes, hypertension, and osteoporosis in previous research. So, this may be one of the reasons why physicians can consider the index of NHHR when evaluating disease risk in clinical practice[11–13]. Because of the superiority

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of NHHR in metabolic disease prediction, combining the relationship between CKD and lipid metabolism, the hypothesis was raised that NHHR might relate to CKD.

While NHHR has been studied in various aspects, the relationship between NHHR and elderly CKD patients has not been fully expounded. In this regard, the study leveraged data from NHANES from 2003 to 2016 to conduct the research on the potential link that may exist between NHHR and elderly CKD patients. It is anticipated to address the need and establish a foundation for monitoring and preventing CKD patients from the standpoint of lipid metabolism.

Methods

Survey description and study population

The NHANES is a recurring population-based database that is compiled in 2-year intervals by the National Center for Health Statistics (NCHS), which is a part of the Centers for Disease Control and Prevention (CDC) in the United States. The NHANES uses a complex, multistage, stratified, clustered probability design to create a dataset representative of noninstitutionalized U.S. residents[14]. All participants are asked to provide their informed permission once they have been fully explained the study's goals. The study utilized data from the NHANES, covering the years 2003 to 2016, starting with a base of 71,058 participants. As shown in Fig. 1 exclusion criteria were systematically applied to refine the sample: (1) exclusion of individuals under 60 years old, numbering 58,639; (2) removal of participants without complete NHHR data, totaling 1,378; (3) exclusion of subjects lacking comprehensive CKD data, amounting to 371; (4) patients with incomplete data on covariates such as poverty-to-income ratio (PIR), alcohol consumption, diabetes mellitus (DM), BMI, educational attainment, smoking status and hypertension ($n = 6,955$). Ultimately, 3,715 participants were deemed eligible for the study.

Definition of NHHR and CKD

All participants in this study had venous blood samples drawn in a fasting state. NHHR represents the quotient of non-HDL-C and HDL-C, with non-HDL-C calculated by deducting HDL-C from total cholesterol (TC)[15,16]. CKD was defined as an eGFR < 60 mL/min/1.73m^2 or the presence of albuminuria[14]. In order to determine eGFR, the CKD-Epidemiology Collaboration (CKD-EPI) formula is used[17]. The main sign of albuminuria is an albumin-to-creatinine ratio (UACR) of 30 mg/g or above[18].

Covariates

For this study, we investigated various factors that could influence the connection between NHHR and CKD. We took into account demographic information like gender, age, race, education level, marital status, and PIR. Laboratory and questionnaire data included triglycerides (TG), TC, HDL-C, glomerular filtration rate, urea, BMI, diabetes, smoking habits, alcohol intake, blood pressure status, and CVD. The levels of PIR were classified as low (PIR ≤ 1), middle (1 < PIR < 4), and high (PIR ≥ 4). The smoking status was classified as never smoked, past smoker, or current smoker. The levels of alcohol intake were likewise classified as none, light, moderate, or heavy. Detailed definitions of these variables are available in supplementary table **S1**, with complete data accessible on the NHANES website.

Statistical analysis

Considering the intricacies of the NHANES sampling process, this research adhered to CDC guidelines to select appropriate sampling weights for statistical analysis. Specific sub-weight for TC and HDL cholesterol (WTSAF2YR) were utilized. Continuous variables had their means and standard errors computed, whereas categorical variables had their percentages computed. In order to compare groups based on categorical data, we used weighted chi-square tests, and for continuous variables, we used weighted Student's t-tests. To increase the validity of the findings, confounders that might affect the relationship between NHHR and CKD were controlled for. Three weighted logistic regression models were used to further analyze the connection between NHHR and CKD. Basic demographic factors in Model 2 included: age, gender, race, education level, and marital status; Model 3 corrected for all study variables comprehensively; and Model 1 was left unadjusted. Moreover, NHHR levels were divided into quartiles to conduct a more nuanced analysis.

The individuals were categorized according to their gender, race, education level, marital status, BMI, PIR, smoking status, hypertension, and DM. Our objective was to analyze the correlation between NHHR and CKD across various clinical and demographic subgroups. To examine how this association varied among the subgroups, interaction tests were used. Employing techniques such as threshold effect analysis, smoothed curve fitting, the study investigated the correlation between NHHR and CKD. In the case of missing data, we opted to perform deletion of the missing values. Statistical analyses were executed using R (version 4.2.0) and Empower software, applying two-tailed tests with a significance threshold set at $P < 0.05$.

Results

Baseline characteristics

Table 1 details the baseline characteristics of the study's participants. The cohort comprised 3,715 individuals, with 49.48% male and 50.52% female. Non-Hispanic whites formed the largest racial group, representing 58.59% of the sample. CKD was prevalent in 35.99% of the participants, with an average NHHR of 2.70 ± 1.13. As detailed in Table 1, differences in covariates such as sex, age, race, PIR, alcohol consumption and BMI were significant across NHHR quartiles ($P < 0.05$). Conversely, no significant disparities were found in smoking, chronic diseases like hypertension, cardiovascular disease and diabetes.

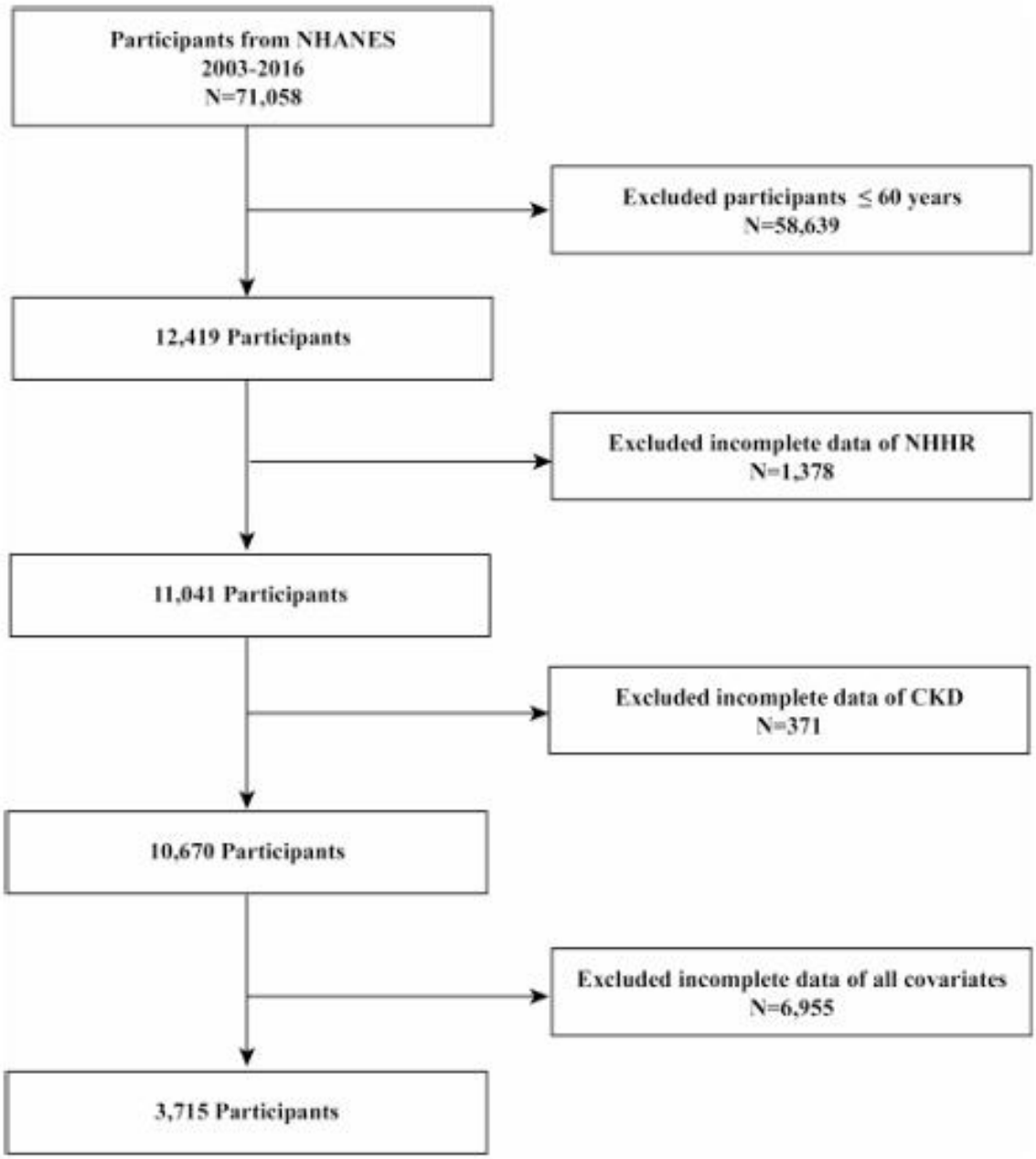

Fig. 1. Flow diagram of study cohort selection.

The association between NHHR and CKD

Table 2 displays the outcomes of a weighted multifactor logistic regression analysis that examined the correlation between NHHR and CKD. In total, three models were used for the analysis: one that was unadjusted, one that was adjusted for demographic characteristics such as age, sex, race, education level, and marital status, and one that was fully adjusted for all covariates. Model 2 showed a positive correlation with odds ratios (ORs) of 1.14 (95% CI: 1.04, 1.25) and Model 3 showed an odds ratio of 1.18 (95% CI: 1.07, 1.31), respectively, when NHHR was considered as a continuous variable. Further analysis dividing NHHR into quartiles showed a 41% increase in CKD likelihood in the highest quartile compared to the lowest in Model 2 (OR = 1.41; 95% CI: 1.08,1.86) and a 50% increase in Model 3 (OR = 1.50; 95% CI: 1.08,2.09), with both models exhibiting statistically

Characteristics	Quartiles of NHHR					
	Overall	Q1(< 1.877)	Q2 (1.879–2.497)	Q3 (2.497–3.345)	Q4(> 3.345)	
	N = 3,715	*N* = 929	*N* = 925	*N* = 932	*N* = 929	*P*-value
Age (years)	70.96 ± 6.83	72.04 ± 6.97	70.96 ± 6.76	70.84 ± 6.77	70.01 ± 6.65	< 0.001
Sex						< 0.001
Male	1,838 (49.48%)	365 (39.29%)	434 (46.92%)	490 (52.58%)	549 (59.10%)	
Female	1,877 (50.52%)	564 (60.71%)	491 (53.08%)	442 (47.42%)	380 (40.90%)	
Race						< 0.001
Non-hispanic White	2,190 (58.95%)	558 (60.06%)	535 (57.62%)	537 (57.62%)	562 (60.50%)	
Non-hispanic Black	600 (16.15%)	194 (20.88%)	162 (17.51%)	141 (15.13%)	103 (11.09%)	
Mexican American	480 (12.92%)	83 (8.93%)	114 (12.32%)	131 (14.06%)	152 (16.36%)	
Other race	445 (11.98%)	94 (10.12%)	116 (12.54%)	123 (13.20%)	112 (12.06%)	
Educational attainment						< 0.001
High school or less	2,020 (54.37%)	451 (48.55%)	512 (55.35%)	512 (54.94%)	545 (58.67%)	
More than high school	1,695 (45.63%)	478 (51.45%)	413 (44.65%)	420 (45.06%)	384 (41.33%)	
PIR						< 0.001
Low	553 (14.89%)	105 (11.30%)	143 (15.46%)	145 (15.56%)	160 (17.22%)	
Middle	2,253 (60.65%)	557 (59.96%)	550 (59.46%)	557 (59.76%)	589 (63.40%)	
High	909 (24.47%)	267 (28.74%)	232 (25.08%)	230 (24.68%)	180 (19.38%)	
BMI (kg/m^2)	29.05 ± 5.95	27.48 ± 6.13	28.90 ± 5.80	29.74 ± 5.92	30.07 ± 5.61	< 0.0001
Smoking status						0.073
Never	1,782 (47.97%)	481 (51.78%)	450 (48.65%)	429 (46.03%)	422 (45.43%)	
Now	394 (10.61%)	86 (9.26%)	99 (10.70%)	96 (10.30%)	113 (12.16%)	
Former	1,539 (41.43%)	362 (38.97%)	376 (40.65%)	407 (43.67%)	394 (42.41%)	
Drinking status						0.007
Never	630 (16.96%)	153 (16.47%)	171 (18.49%)	152 (16.31%)	154 (16.58%)	
Mild	1,422 (38.28%)	373 (40.15%)	364 (39.35%)	360 (38.63%)	325 (34.98%)	
Moderate	319 (8.59%)	100 (10.76%)	75 (8.11%)	68 (7.30%)	76 (8.18%)	
Heavy	250 (6.73%)	60 (6.46%)	70 (7.57%)	58 (6.22%)	62 (6.67%)	
Former	1,094 (29.45%)	243 (26.16%)	245 (26.49%)	294 (31.55%)	312 (33.58%)	
Hypertension						0.750
No	1,073 (28.88%)	280 (30.14%)	269 (29.08%)	262 (28.11%)	262 (28.20%)	
Yes	2,642 (71.12%)	649 (69.86%)	656 (70.92%)	670 (71.89%)	667 (71.80%)	
CVD						0.512
No	2,754 (74.13%)	675 (72.66%)	682 (73.73%)	705 (75.64%)	692 (74.49%)	
Yes	961 (25.87%)	254 (27.34%)	243 (26.27%)	227 (24.36%)	237 (25.51%)	
DM						0.067
No	2,402 (64.66%)	614 (66.09%)	609 (65.84%)	612 (65.67%)	567 (61.03%)	
Yes	1,313 (35.34%)	315 (33.91%)	316 (34.16%)	320 (34.33%)	362 (38.97%)	
	Overall	Q1(< 1.877)	Q2 (1.879–2.497)	Q3 (2.497–3.345)	Q4(> 3.345)	P-value
CKD						0.020
No	2,378 (64.01%)	583 (62.76%)	617 (66.70%)	615 (65.99%)	563 (60.60%)	
Yes	1,337 (35.99%)	346 (37.24%)	308 (33.30%)	317 (34.01%)	366 (39.40%)	

Table 1. Baseline characteristics of the study population. Continuous variables: values are expressed as mean ± standard deviation. Categorical variables: values are expressed as numbers (percentage). *NHHR* non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, *Q* quartile, *PIR* family poverty income ratio, *CVD* cardiovascular disease, *DM* diabetes mellitus, *CKD* chronic kidney disease, *BMI* body mass index.

significant trends (p for trend 0.015 and 0.019, respectively). Conversely, Model 1 did not exhibit any significant associations.

Smoothed curve fitting indicated a nonlinear relationship between NHHR and CKD (Fig. 2), manifesting as a J-shaped relationship. Threshold effect analysis revealed a statistically significant difference between linear and segmented linear regression models ($P = 0.002$). Table 3 identifies an inflection point of 1.8, with OR as 0.65 (95% CI: 0.44, 0.96) when the OR was below this inflection point, suggesting a negative correlation between NHHR and CKD. Conversely, a significant positive correlation existed between NHHR and CKD with an OR of 1.27 (95% CI: 1.16 ,1.39) above this inflection point, indicating a rise of 27% in CKD prevalence for every unit increase in NHHR.

Characteristic	Model 1 OR (95%CI), *P* value	Model 2 OR (95%CI), *P* value	Model 3 OR (95%CI), *P* value
NHHR (continuous)	1.05 (0.98,1.13), 0.169	1.14 (1.04,1.25), 0.004	1.18 (1.07,1.31), 0.002
NHHR (categorical)			
Q1 (< 1.877)	Reference	Reference	Reference
Q2 (1.879–2.497)	0.83 (0.66,1.05), 0.131	0.88 (0.70,1.10), 0.252	0.87 (0.69,1.10), 0.241
Q3 (2.497–3.345)	0.86 (0.67,1.11), 0.250	0.97 (0.74,1.27), 0.812	0.96 (0.74,1.26), 0.778
Q4 (> 3.345)	1.13 (0.88,1.46), 0.344	1.41 (1.08,1.86), 0.015	1.50 (1.08,2.09), 0.017
P for trend	0.367	0.015	0.019

Table 2. Weighted multivariate logistic regression analysis of NHHR and CKD. *NHHR* non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, *Q* quartile, *PIR* family poverty income ratio, *CVD* cardiovascular disease, *DM* diabetes mellitus, *CKD* chronic kidney disease, *BMI* body mass index; Model 1: unadjusted. Model 2: adjusted for age, sex, race, educational attainment, and marital status. Model 3: adjusted for age, sex, race, education attainment, marital status, BMI, PIR, smoking status, drinking status, hypertension, DM, CVD, dietary cholesterol intake and total cholesterol.

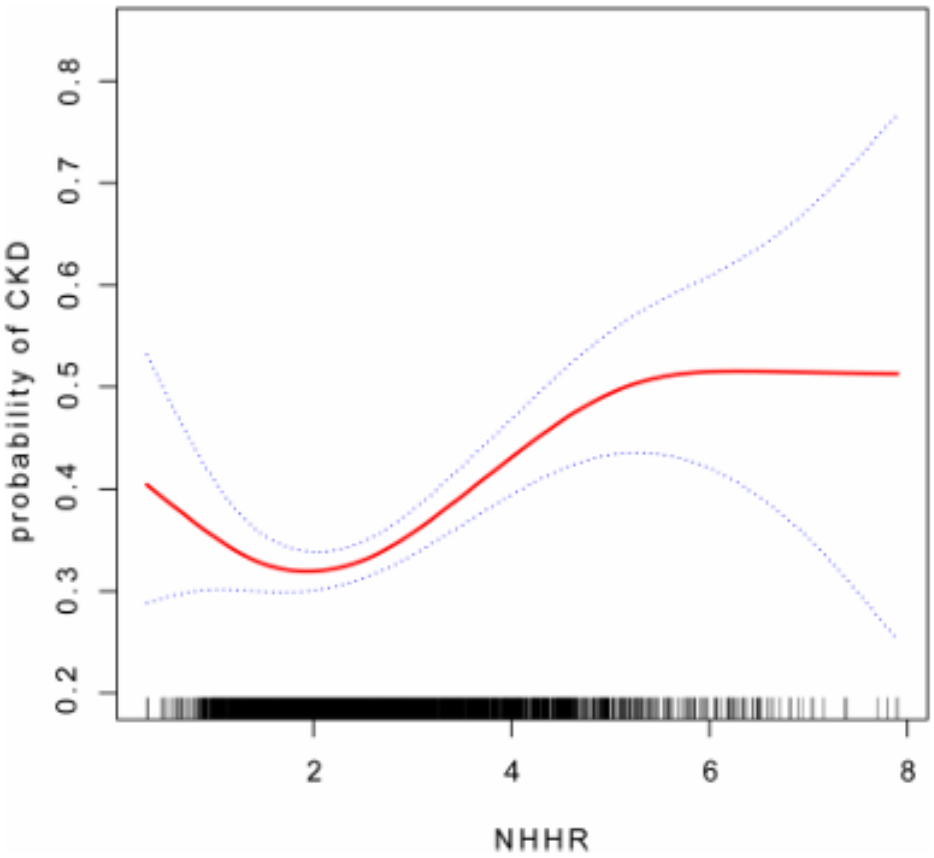

Fig. 2. Smooth curve fitting for NHHR and CKD. Subjects who did and did not develop CKD are identified as 1 and 0 on the y-axis, respectively. NHHR was a continuous variable. The solid red line represents the smooth curve fit between variables. Blue dotted lines represent the 95% CI from the fit. Adjustment factors included age, sex, race, education attainment, marital status, BMI, PIR, smoking status, drinking status, hypertension, DM, CVD, dietary cholesterol intake and total cholesterol.

NHHR	Adjust OR (95% CI), *P* value
Fitting by linear regression model	1.19 (1.10,1.28), <0.0001
Fitting by two-piecewise linear regression model	
inflection point	1.8
< 1.8	0.65 (0.44,0.96), 0.0298
≥ 1.8	1.27 (1.16,1.39), < 0.0001
Log-likelihood ratio test	0.002

Table 3. Threshold effect analysis of the association of NHHR with CKD. *NHHR* non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, *PIR* family poverty income ratio, *CVD* cardiovascular disease, *DM* diabetes mellitus, *CKD* chronic kidney disease, *BMI* body mass index The threshold effect analysis was adjusted for age, sex, race, education attainment, marital status, BMI, PIR, smoking status, drinking status, hypertension, DM, CVD, dietary cholesterol intake and total cholesterol.

Subgroup	OR (95%CI)	*P*-value	*P* for interaction
Sex			0.7425
Male	1.10 (1.01, 1.21)	0.0371	
Female	1.13 (1.02, 1.24)	0.0142	
Race			0.5063
Non-Hispanic white	1.13 (1.04, 1.24)	0.0049	
Non-Hispanic black	1.22 (1.02, 1.46)	0.0337	
Mexican American	1.02 (0.85, 1.23)	0.8208	
Other race	1.04 (0.84, 1.29)	0.7370	
Educational attainment			0.6035
High school or less	1.14 (1.04, 1.24)	0.0045	
More than high school	1.10 (0.99, 1.21)	0.0721	
PIR			0.3713
Low	1.02 (0.87, 1.21)	0.7685	
Middle	1.16 (1.07, 1.26)	0.0004	
High	1.09 (0.92, 1.29)	0.3205	
BMI			0.0203
<30	1.06 (0.97, 1.15)	0.2196	
≥ 30	1.24 (1.11, 1.38)	<0.0001	
Hypertension			0.1264
No	1.02 (0.89, 1.17)	0.7858	
Yes	1.15 (1.07, 1.24)	0.0003	
DM			0.4712
No	1.15 (1.05, 1.25)	0.0033	
Yes	1.09 (0.99, 1.20)	0.0776	
Smoking status			0.8528
Never	1.10 (1.00, 1.22)	0.0589	
Now	1.17 (0.97, 1.40)	0.0957	
Former	1.13 (1.02, 1.25)	0.0224	

Table 4. Subgroup analysis of the association between NHHR and CKD. *NHHR* non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, *CKD* chronic kidney disease, *BMI* body mass index, *DM* diabetes mellitus. Adjusted for age, sex, race, education attainment, marital status, BMI, PIR, smoking status, drinking status, hypertension, DM, CVD except the subgroup variable.

Subgroup analysis

Subgroup analysis and interaction tests assessed whether the correlation between NHHR and CKD varied across different subgroups. Table 4 demonstrates that the correlation remained consistent across subgroups stratified by sex, race, educational attainment, smoking status, PIR, BMI, hypertension, and DM (P values for all interactions > 0.05, except for BMI). Within the subgroup of individuals with BMI ≥ 30, there was a noTable 24% increase in the prevalence of CKD for every unit increase in NHHR. There was a clear difference observed in the BMI subgroup as shown in Fig. 3, figure S1 and figure S2, which is consistent with previous research.

2.1.2 ESTUDIO 2

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REVIEW Open Access

Understanding the heterogeneity and dysfunction of HDL in chronic kidney disease: insights from recent reviews

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Abstract

Chronic kidney disease (CKD) is a complex disease that affects the global population's health, with dyslipidemia being one of its major complications. High density lipoprotein (HDL) is regarded as the "hero" in the bloodstream due to its role in reverse cholesterol transport, which lowers cholesterol levels in the blood and prevents atherosclerosis. However, in the complex internal environment of CKD, even this "hero" may struggle to perform its beneficial functions and could potentially become harmful. This article reviews HDL heterogeneity, HDL subclasses, functional changes in HDL during the progression of CKD, and the application of HDL in CKD treatment. This review aims to deepen understanding of lipid metabolism abnormalities in CKD patients and provide a basis for new therapeutic strategies.

Keywords Chronic kidney disease, High density lipoproteins, Dyslipidemia, Subclasses

Introduction

Chronic kidney disease (CKD) poses a significant global health burden and is characterized by either an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 or the presence of other indicators of kidney damage, such as albuminuria [1]. According to a study conducted by the Global Burden of Disease group in 2020, CKD was ranked among the top 10 leading contributors to adverse outcomes on a global scale [2]. The morbidity of CKD is continuously rising, with contributing factors including demographic shifts (aging of the population), an increase in type 2 diabetes and hypertension cases, as well as low early detection rates for CKD [3–5].

In recent years, numerous studies have indicated that individuals with CKD exhibit a significantly increased mortality rate from cardiovascular diseases (CVD). The factors leading to this outcome can be broadly categorized into two types: traditional risk factors and specific risk factors (Fig. 1). Traditional factors include dyslipidemia, hypertension, hyperglycemia, smoking, and old age, all of which not only promote atherosclerosis but also damage the renal vasculature [6–9]. Specific risk factors include inflammation, endothelial dysfunction, vascular calcification, genetic factors, and proteinuria [10–13]. Both types of factors significantly increase the cardiovascular burden.

Among these risk factors, dyslipidemia is particularly noteworthy. One common manifestation of dyslipidemia in patients with CKD is a reduction in high-density lipoprotein cholesterol (HDL-C) levels [14]. In both CKD and end-stage renal disease (ESRD) patients, the serum HDL is not only quantitatively altered but also qualitatively compromised, further impairing its functionality.

HDL is a complex lipoprotein that exhibits significant heterogeneity in the bloodstream. This heterogeneity

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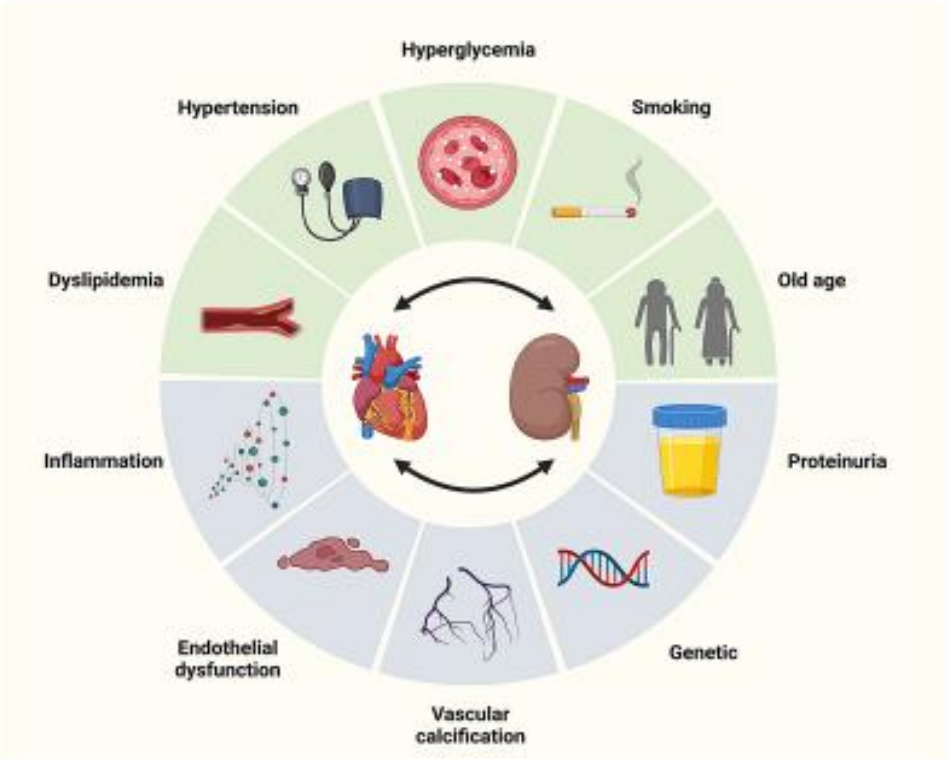

Fig. 1 Traditional and specific risk factors for cardiovascular disease in patients with chronic kidney disease. (Adapted from "Risk factors for sarcopenia", by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates)

arises from HDL's structural characteristics and its involvement in complex metabolic and interconversion processes within the body. HDL is synthesized in the liver and intestines and performs several critical functions in the blood, including reverse cholesterol transport and antioxidant activities [15]. The morphology and size of HDL vary according to its function and are influenced by cholesterol content, lipid components, and protein composition [16]. Additionally, HDL is modulated by various factors such as lifestyle, genetic factors, and medications, all of which contribute to changes in HDL heterogeneity [17].

In this review, we will examine four key aspects: (1) the structure and composition of HDL; (2) the primary functions of HDL; (3) metabolic alterations of HDL in chronic kidney disease (CKD); and (4) the application of HDL in the treatment of CKD.

Structure and composition of HDL

As early as 1955, Havel et al. succeeded in isolating and characterizing lipoproteins with densities ranging from 1.063 to 1.21 g/mL using ultracentrifugation [18]. Based on their findings, this lipoprotein was subsequently defined as HDL. HDL is a complex of lipids and proteins, exhibiting a sophisticated discoidal or spherical structure. The hydrophilic envelope on the surface of HDL particles consists mainly of phospholipids (PL), free cholesterol (FC), and apolipoproteins, whereas the hydrophobic core consists primarily of cholesteryl esters (CE) and triglycerides (TG) [19]. Compared to other lipoproteins, HDL contains a higher proportion of proteins and relatively lower levels of lipids, which is why it has the highest density.

Heterogeneity of HDL structure

Discoidal HDL

In 1971, Trudy Forte and her colleagues made the first observation of HDL particles using electron microscopy, marking a significant milestone in the understanding of HDL structure [20]. In normal individuals, HDL particles typically have a diameter ranging from 70 to 100 Å and a thickness of 35 to 50 Å, with a spherical shape [20]. As illustrated in Fig. 2A, these normal HDL particles are uniformly sized and aggregate into a monolayer

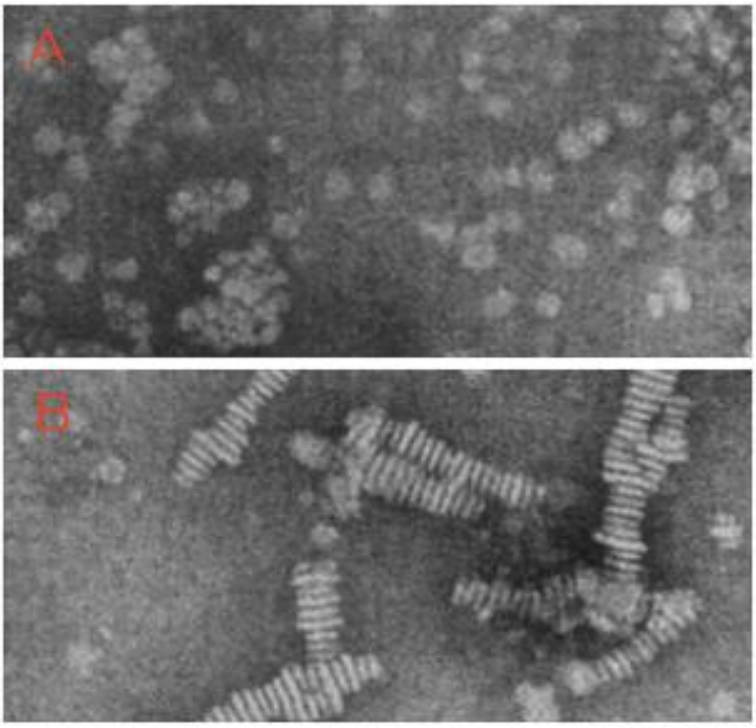

Fig. 2 Electron microscopy image showing the morphology of HDL. **A**: HDL particles in normal individuals are uniform in size, spherical, and aggregate into a single-layer structure. **B**: HDL particles in patients with LCAT gene deficiency are disc-like and arranged in a stacked formation. (These two images are extracted from the study by Trudy Forte et al. [20])

structure. However, in patients with lecithin-cholesterol acyltransferase (LCAT) gene defects, HDL exhibits notable heterogeneity, forming disc-like shapes that stack with a repeating spacing of approximately 50 to 55 Å, as depicted in Fig. 2B [20].

Interestingly, this disc-like structure of HDL can also be observed in the plasma of healthy individuals. In 1975, Alan R. Tall reported that incubating isolated apoproteins and phospholipids from healthy HDL in vitro leads to the formation of disc-like particles similar to those depicted in Fig. 2B, which do not stack [21]. In 1977, Jere Segrest proposed that apolipoprotein A-I (ApoA-I) stabilizes the disc-like structure of HDL by encircling its edges, akin to a "bicycle tire" [22, 23]. Subsequently, John Kane's laboratory identified a subclass in human plasma that migrates more slowly than the major HDL class in agarose gel electrophoresis, positioning itself between HDL and low-density lipoprotein (LDL) [24]. This subclass was therefore named pre-β HDL, also known as nascent HDL or discoidal HDL. Other research teams further confirmed the presence of discoidal HDL, suggesting that free cholesterol initially tends to associate with discoidal HDL [25, 26]. During the 1990s, multiple studies delved into the mechanism of discoidal HDL formation, proposing that lipid-free ApoA-I interacts with macrophage membranes via ATP-binding cassette transporter A1 (ABCA1), binding phospholipids and free cholesterol to form discoidal HDL [27–30]. Subsequent studies gradually confirmed this formation process [31, 32].

Spherical HDL

The free cholesterol within discoidal HDL is converted into cholesterol esters under the action of LCAT. Cholesterol esters are highly hydrophobic, and once formed, they aggregate into the core of the HDL particle. This process drives the transformation of discoidal HDL particles into spherical HDL particles [33–35]. Consequently, the levels of discoidal HDL in the plasma of healthy individuals are relatively low. Spherical HDL particles exhibit considerable heterogeneity in diameter, ranging from 7 nanometers (nm) to 14 nm [36]. This heterogeneity is also evident in the significant differences among particles in lipid proportions, protein ratios, and types of apolipoproteins they carry.

The structure of spherical HDL particles can be described using the "droplet" model, where lipids and apolipoproteins are primarily held together by non-covalent forces. The widely accepted model of human HDL

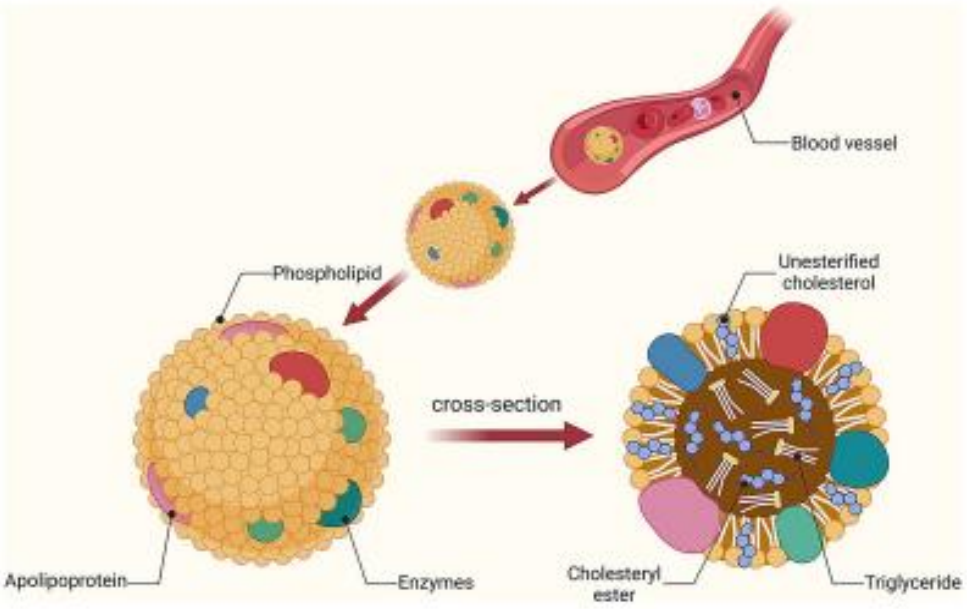

Fig. 3 Schematic diagram of the HDL structure. (Adapted from "Icon Pack - Metabolism", by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates)

Table 1 The protein components of HDL [40]

Apolipoproteins	Enzymes	Lipid transfer proteins	Acute-phase proteins	Complement components
ApoA-I, ApoA-II, ApoA-III, ApoC-I, ApoC-II, ApoC-III, ApoC-IV, ApoD, ApoE, ApoF, ApoJ, ApoL-I, ApoM	LCAT PON1 PAF-AH GSPx-3	CETP PLTP	SAA1 SAA4	C3

Abbreviations Apo: apolipoprotein, LCAT: lecithin-cholesterol acyltransferase, PON1: paraoxonase 1, PAF-AH: platelet-activating factor-acetylhydrolase, GSPx-3: glutathione peroxidase 3, CETP: cholesteryl ester transfer protein, PLTP: phospholipid transfer protein, SAA: serum amyloid A

particles depicts them as spherical entity with a diameter of approximately 10 nm, where the surface layer is composed of proteins and amphipathic lipid molecules surrounding a nonpolar core of CE and TG (Fig. 3). Many understandings of HDL structure stem from the preparation and study of reconstituted HDL (rHDL). rHDL is a self-assembled mixture of ApoA-I and dimyristoylphosphatidylcholine (DMPC) in aqueous solution, with diameters ranging from 9 to 20 nm, depending on the initial lipid-to-ApoA-I ratio [37, 38]. Research has revealed that discoidal HDL typically contains only two ApoA-I molecules, while spherical HDL contains three ApoA-I molecules. These three molecules are arranged in a "three-leaf clover model," with each helical domain providing mutual support [39]. Together with lipid molecules, they have formed the spherical structure of HDL particles.

Complexity of HDL composition

Protein components

Compared to other lipoproteins, HDL contains a richer proportion of protein components, including apolipoproteins, enzymes, and lipid transfer proteins, as shown in Table 1. Among these components, apolipoproteins and enzymes play pivotal roles in the metabolic functions of HDL.

Major apolipoproteins **ApoA-I** is the predominant protein in HDL particles, accounting for approximately 70% of the total HDL protein. Synthesized in the liver and small intestine, ApoA-I features eight α-helical domains, each containing 22 amino acids. These domains' amphipathic properties facilitate lipid binding [41]. Additionally, ApoA-I contains two repeated 11-amino-acid sequences, which enhance the molecule's stability and solubility [41]. ApoA-I plays a crucial role in maintaining the structural integrity of HDL particles and promotes reverse choles-

terol transport by activating LCAT, thus contributing significantly to the prevention of atherosclerosis [42].

Apolipoprotein A-II (ApoA-II), synthesized primarily in the liver, constitutes about 20% of the total HDL protein. ApoA-II exhibits strong lipophilicity, which enhances the structural stability of HDL particles and prevents the dissociation of lipid-free ApoA-I from HDL [43]. It is hypothesized that ApoA-II may influence the rate of HDL synthesis; however, its association with the reduced serum HDL levels observed in cardiovascular disease patients requires further investigation.

Apolipoprotein E (ApoE), although present in smaller amounts in HDL, plays a crucial functional role. In nascent discoidal HDL, ApoE adopts a "double belt" model, with two ApoE molecules arranged in a reverse parallel conformation around the nano-disk [44]. This conformation facilitates the binding of HDL to cell surface glycosaminoglycans, thereby modulating interactions between lipoprotein particles and cells [45–47].

Auxiliary proteins and enzymes CETP is a highly hydrophobic glycoprotein that primarily facilitates the transfer of CE and TG between HDL, LDL, and VLDL [48]. CETP's structure includes an N-terminal spherical domain and a long C-terminal region, which together enable CETP to transfer lipids between different lipoprotein types through a "tunneling mechanism." Specifically, the N-terminal domain of CETP binds to HDL and transfers cholesterol esters to LDL or VLDL via the C-terminal domain [49].

LCAT is the only enzyme capable of maintaining the balance of free cholesterol between peripheral tissues and HDL [50]. Mature LCAT is a glycoprotein composed of an α/β-hydrolase domain, a membrane-binding domain, and a cap domain [51–54]. LCAT catalyzes the conversion of free cholesterol in plasma to cholesteryl esters, thereby facilitating reverse cholesterol transport. Additionally, LCAT hydrolyzes the oxidized products of phosphatidylcholine and platelet-activating factor, thereby protecting platelet function and maintaining the antioxidant capacity of HDL [55–57].

Paraoxonase 1 (PON1) is an esterase and lactonase synthesized by the liver and primarily carried by HDL [58–60]. Structural studies reveal that PON1 is an interfacial activated enzyme, anchored to HDL by an N-terminal helix and another amphipathic helix at the active site [62, 63]. HDL particles carrying ApoA-I have a high affinity for PON1, forming a stable complex [62, 63]. However, the mechanisms of how PON1 integrates into HDL are still relatively limited and require further exploration. PON1 reduces lipid peroxides, thereby inhibiting the production of monocyte chemotactic protein 1 (MCP-1) and potentially delaying or reversing the progression of atherosclerosis [64–66]. Several animal and cohort studies have confirmed that PON1 stimulates HDL-mediated endothelial nitric oxide production and enhances macrophage cholesterol efflux [67–72].

Phospholipases, such as platelet-activating factor-acetylhydrolase (PAF-AH), hydrolyze short-chain pro-inflammatory oxidized phospholipids, helping to reduce inflammatory responses [73]. Additionally, glutathione peroxidase 3 (GSPx-3) exerts antioxidant effects on HDL, protecting biomolecules from oxidative damage [74].

Lipids composition

With the continuous advancement of mass spectrometry (MS) technology, the lipidomics of HDL is also evolving. Currently, over 200 lipid molecules can be analyzed and identified on HDL particles [75, 76]. The main lipid categories of HDL, as shown in Table 2, include phospholipids, sphingolipids, and neutral lipids.

Phospholipids are the most abundant lipids in HDL, constituting approximately 35–50% of the total lipid mass of HDL. Phosphatidylcholine (PC), an essential component of HDL and cell membranes, contains a high proportion of polyunsaturated fatty acid residues—a feature less common in other lipoproteins [77, 78]. The main molecular species of PC in HDL include 16:0/18:0, 18:0/18:2, 16:0/20:4, and 16:0/18:1 [79–81].

Table 2 The lipid components of HDL [40]

Phospholipids	Sphingolipids	Neutral lipids	Minor lipids
PC PC-plasmalogen LPC PE PE-plasmalogen PI Cardiolipin Phosphatidylserine Phosphatidylglycerol Phosphatidic acid	Sphingomyelin Ceramide Hexosyl Cer Lactosyl Cer S1P d18:1 S1P d18:0 SPC d18:1	Cholesteryl esters Free cholesterol Triacylglycerides Diacylglycerides	Free fatty acids Isoprostane-containing PC

Abbreviations PC: phosphatidylcholine, LPC: lysophosphatidylcholine, PE: phosphatidylethanolamine, PI: phosphatidylinositol, Cer: ceramide, S1P: sphingosine-1-phosphate, SPC: sphingomyelin-phosphocholine

Lysophosphatidylcholine (LPC), a product of LCAT-mediated hydrolysis of PC, accounts for 15% of the phospholipid mass [77, 79, 82]. Additionally, phosphatidylethanolamine (PE) and phosphatidylinositol (PI) are also significant phospholipids in HDL, with PE being notably important in plasma due to its antioxidant properties [77, 83–88]

Sphingolipids also play a significant role in HDL. Sphingomyelin (SM) is the most abundant sphingolipid in HDL, and its content affects lipid membrane properties and the surface pressure of lipoproteins, thereby regulating the activity of associated proteins [89–91]. Ceramide, although present in smaller amounts, also contributes to HDL structure, with 16:0 ceramide being particularly common [77, 79]. Sphingosine-1-phosphate (S1P) is another important sphingolipid in HDL, and its presence is crucial for maintaining the stability of HDL's biological functions by modulating cell proliferation, migration, and apoptosis [92–94]

Neutral lipids, such as cholesterol esters and triglycerides, also play a crucial role in HDL. Cholesterol esters account for 30–40% of the lipid content in HDL, with the majority existing as cholesteryl linoleate, which is vital for HDL's structural and functional roles [77, 89]. Triglycerides, derived from very low-density lipoprotein (VLDL) and LDL, exhibit similar strong hydrophobic properties as cholesterol esters. The principal types of triglycerides include oleic acid, palmitic acid, and linoleic acid, which play essential roles in lipid metabolism and transport [77]

Complexity of HDL subclasses and analytical methods

In 1954, Gofman and his colleagues first described the differences among HDL subclasses using ultracentrifugal analysis, revealing the diversity of HDL in lipid and protein composition [95]. This complexity of HDL is not only reflected in the classification of its subclasses but also in the identification and measurement of HDL by various analytical techniques

Traditional classification

Based on density, HDL is divided into HDL2 and HDL3: HDL2 has a density of 1.063–1.125 g/mL and is rich in lipids, while HDL3 has a density of 1.125–1.21 g/mL and is higher in protein content [95]. Using non-denaturing gradient gel electrophoresis (GGE), HDL2 and HDL3 can be further subdivided into multiple subclasses, including HDL2a, HDL2b, HDL3a, HDL3b, and HDL3c, with diameters of 8.8–9.7 nm, 9.7–12.0 nm, 8.2–8.8 nm, 7.8–8.2 nm, and 7.2–7.8 nm, respectively [96]

Electrophoresis-based classification

HDL carries surface charges and can be classified into α-HDL and pre-β HDL through agarose gel electrophoresis (AGE) [97, 98]. Most circulating HDL is α-HDL, while pre-β HDL is primarily discoidal. By combining agarose gel electrophoresis with GGE, two-dimensional electrophoresis can be performed, further subdividing HDL into α1, α2, α3, α4, preα1, preα2, preα3, preβ1, and preβ2 [19, 99]

Protein composition-based classification

HDL can also be classified according to the protein composition of its particles into HDL containing only ApoA-I and HDL containing both ApoA-I and ApoA-II [100]. HDL particles containing both ApoA-I and ApoA-II are generally more compact than those containing only ApoA-I [101]

Nuclear magnetic resonance (NMR)-based classification

NMR is a technique based on the physical phenomenon of atomic nuclei absorbing and emitting electromagnetic radiation in an external magnetic field. In the analysis of HDL, particles of different sizes exhibit distinct NMR signal characteristics, enabling the differentiation of various HDL subclasses based on these signals. By analyzing NMR spectra, the diameter range of HDL particles can be determined, classifying HDL into large, medium, and small subclasses [102]

Despite the increasing diversity of methods for studying HDL subclasses and the deepening understanding of HDL, significant challenges remain. Differences in the nomenclature, number, composition, and measurement parameters of HDL subclasses exist across various techniques. Some studies focus on measuring the concentration of HDL subclasses, while others emphasize the percentage of proteins or cholesterol. These discrepancies make it difficult to compare results across different studies. To promote consistency and comparability in HDL research, there is an urgent need to standardize the classification and measurement methods of HDL subclasses

HDL and reverse cholesterol transport (RCT)

HDL plays a crucial role in various physiological processes, with its most significant function being RCT. RCT is a mechanism that transports cholesterol from peripheral tissues back to the liver and is considered the primary anti-atherosclerotic function of HDL

ABCA1 and HDL formation

ABCA1 is an integral membrane protein that utilizes ATP as energy to transport lipids from the intracellular environment to the cell membrane [103]. ABCA1 is found in several cellular locations, including lysosomes, the Golgi apparatus, and the plasma membrane [104]. Under the influence of ABCA1, cholesterol is transported from lysosomes to the Golgi apparatus and then to the

plasma membrane. This process helps remove excess cholesterol from cells, influencing various cellular metabolic processes such as endogenous cholesterol synthesis, LDL receptor expression, and cholesterol ester transport [104]. ABCA1 transfers cholesterol and phospholipids from the inner leaflet of the plasma membrane to the outer leaflet, where they bind with lipid-free ApoA-I from the liver and intestine, forming discoidal HDL (Fig. 4) [105–107]. This process marks the initiation of RCT, with ABCA1 being pivotal in the formation of discoidal HDL.

HDL maturation and cholesterol esterification

After the formation of discoidal HDL, LCAT, activated by ApoA-I, esterifies the cholesterol [108]. The newly synthesized cholesterol esters are completely hydrophobic and gradually migrate to the core of the discoidal HDL, facilitating its transformation into mature spherical HDL. Meanwhile, membrane proteins such as ATP-binding cassette transporter G1 (ABCG1) and scavenger receptor class B type I (SR-BI) continue to transport intracellular cholesterol to HDL, further promoting HDL maturation (Fig. 4). ABCG1 is also an integral membrane protein with similar cellular localization to ABCA1, but it primarily targets mature HDL [109]

Cholesterol transport and clearance

Subsequently, HDL exchanges cholesterol esters and triglycerides with VLDL and LDL in an equimolar ratio [110]. The final step of RCT is mediated by SR-BI, a membrane protein of the CD36 family responsible for the selective uptake of cholesterol esters from HDL (Fig. 4) [111]. Through SR-BI, the liver absorbs cholesterol esters from HDL and hydrolyzes them into free cholesterol. The absorbed cholesterol can be converted into bile acids and stored in the gallbladder. During digestion, bile acids are released into the small intestine to aid in the digestion and absorption of fats. Additionally, the liver can utilize cholesterol for the synthesis of cell membranes and steroid hormones

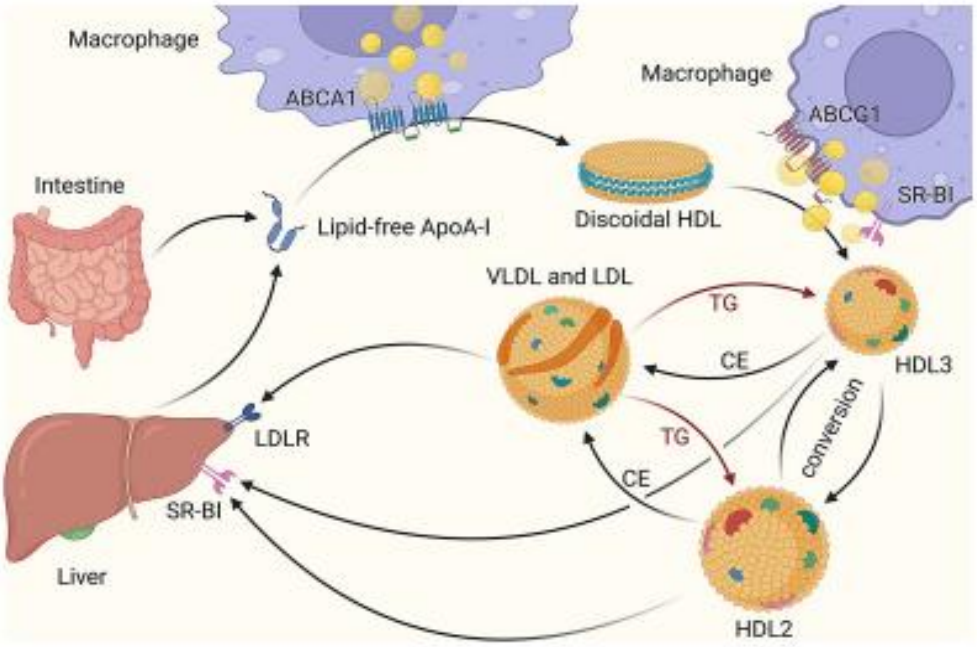

Fig. 4 The Process of HDL-Mediated Reverse Cholesterol Transport. The liver and intestines synthesize lipid-free ApoA-I, which initially acquires cholesterol and phospholipids from macrophages via ABCA1, forming nascent discoidal HDL. Subsequently, LCAT esterifies the cholesterol, rendering it fully hydrophobic and causing its migration to the core of the discoidal HDL, promoting its maturation into spherical HDL. Meanwhile, membrane proteins such as ABCG1 and SR-BI continue to transfer intracellular cholesterol to HDL, further aiding in HDL maturation. HDL2 and HDL3, the two subclasses of HDL, can interconvert. Next, HDL exchanges cholesteryl esters and triglycerides with VLDL and LDL in equimolar proportions. The final step of reverse cholesterol transport involves the selective uptake of cholesteryl esters from HDL particles by the hepatic SR-BI or the clearance of cholesteryl esters from VLDL and LDL via the LDL receptor (LDLR). (Adapted from "Icon Pack - Lipid", by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates)

How does CKD affect HDL metabolism?

In the previous sections, we have thoroughly discussed the physiological functions of HDL and its critical role in RCT. However, HDL metabolism is not always stable; its function and structure can undergo significant changes, particularly in certain disease states. CKD is one such pathological condition that can markedly impact HDL metabolism. In the following discussion, we will explore how CKD interferes with HDL metabolic processes through various mechanisms, thereby altering its protective role against atherosclerosis.

Structural interference

In HDL metabolism research, traditional perspectives have primarily focused on the liver, as it is the central site for HDL catabolism. However, recent studies suggest that the kidneys also play a significant role in HDL metabolism—a role that is not yet fully understood. Specifically, research has shown that the kidneys do not directly participate in the clearance of intact HDL particles but instead selectively remove specific HDL components, such as ApoA-I and ApoE [112]. This finding implies that the reduced plasma HDL levels observed in CKD patients may be related to this selective clearance mechanism of the kidneys. In patients with CKD, impairment of the glomerular filtration barrier allows apolipoproteins to be lost in the urine, which results in proteinuria. Therefore, the presence of proteinuria is considered a key indicator of apolipoprotein loss [113–115]. Additionally, CKD significantly affects the activity of enzymes involved in HDL metabolism, with changes in enzyme activity influencing the maturation and remodeling of HDL particles, ultimately altering HDL composition and function [116–118]. Therefore, the role of the kidneys in HDL metabolism extends beyond filtration, involving selective component removal and regulation of enzyme activity. This discovery offers a new perspective for understanding dysregulated plasma lipid metabolism in CKD patients.

During the progression of CKD, patients often experience complex changes in lipoprotein metabolism, profoundly affecting overall lipid metabolism. Notably, the lipid composition of HDL particles undergoes significant alterations, impacting not only their structure but also their function and metabolic pathways. The most prominent changes include an increase in TG content and a decrease in PL content within HDL particles. These alterations are closely associated with reduced hepatic lipase (HL) activity and increased phospholipid transfer protein (PLTP) activity [116, 119]. HL is a 65-kDa glycoprotein primarily synthesized and secreted by hepatocytes [120]. As a member of the triglyceride lipase family, HL acts as an important negative regulator of HDL levels by reducing the triglyceride and phospholipid content of HDL [121, 122]. Its decreased activity may hinder TG metabolism within HDL particles, leading to the accumulation of TG. PLTP is a member of the lipid transfer protein family. The N-terminal and C-terminal domains of PLTP are structurally connected, forming a hydrophobic channel that facilitates lipid molecule transport [123, 124]. PLTP is predominantly released by the liver, adipose tissue, and macrophages in plasma, playing a crucial role in mediating the exchange of phospholipids between lipoproteins [125, 126]. Simultaneously, upregulation of PLTP activity may promote the transfer of PL from HDL particles, resulting in reduced PL content, which negatively affects HDL functionality and stability. Furthermore, the protein composition of HDL particles also undergoes significant changes. Levels of ApoA-I, ApoA-II, and ApoM tend to decrease, while levels of serum amyloid A (SAA), ApoC-II, ApoC-III, and ApoA-IV increase markedly [127]. These changes not only reflect substantial adjustments in the composition of HDL particles but may also have far-reaching effects on HDL's physiological functions, including its antioxidant, anti-inflammatory, and anti-atherosclerotic properties.

Impact of HDL subclasses

The changes in HDL subclasses in patients with kidney disease represent a complex and nuanced area of research. In a study by Alabakovska et al., it was observed that the level of the HDL2b subclass decreased in ESRD patients, while the level of the HDL3c subclass increased [128]. This finding suggests that kidney disease affects HDL subclasses not only in terms of quantity but also potentially through the selective regulation of specific subclasses. In addition, multiple studies have demonstrated a significant reduction in the levels of the HDL2 subclass in ESRD patients, highlighting the adverse impact of ESRD on HDL subclass distribution [129, 130]. These effects include an increase in PL, unesterified cholesterol, and TG within HDL2, as well as a decrease in apolipoproteins in HDL3, along with reductions in both the concentration and activity of PON1 [129, 130].

However, research on patients with proteinuria shows different results compared to ESRD patients. Soto-Miranda et al. found that patients with proteinuria had a higher proportion of large HDL2b subclasses and a lower proportion of small HDL3c subclasses [131]. This trend differs from the one observed in ESRD patients, suggesting that different types or severities of kidney injury may have varying effects on HDL subclass distribution. However, the specific mechanisms by which kidney injury leads to these divergent changes remain unclear.

On the other hand, some studies also support the observation of a relative increase in large HDL subclasses in kidney disease patients [132–134]. This observation indicates that despite a decrease in total HDL levels, there may be compensatory mechanisms, particularly

involving large HDL subclasses, to maintain HDL functionality and integrity even in the face of lipid metabolism disorders associated with kidney disease.

Overall, understanding HDL subclass changes in kidney disease patients is still in its early stages. Future research needs to further explore the impact of different types of kidney lesions on HDL subclasses and elucidate the underlying biological mechanisms to better understand and manage lipid metabolism abnormalities in these patients.

Functional alterations

Several studies have demonstrated that the RCT capacity of HDL is significantly reduced in uremic patients undergoing dialysis [135–137]. This phenomenon not only reveals severe lipid metabolism abnormalities in these patients but also suggests a substantially increased risk of cardiovascular disease. The RCT capacity of HDL depends on the binding of cholesterol to HDL particles, a process closely associated with phospholipid levels, particularly the content of PC [138–142]. Research has shown that co-incubation of HDL with PC emulsions can significantly enhance HDL lipidation, thereby promoting cholesterol uptake from macrophages [138]. Furthermore, it has been reported that the infusion of PC emulsions containing ApoA-I into patients with severe atherosclerosis can improve angiographic parameters [143]. These findings suggest that alterations in phospholipid levels may have a critical impact on the cholesterol efflux capacity of HDL. However, clinical studies on phospholipid level changes in HDL among patients with kidney disease remain relatively scarce.

Impairment of HDL RCT capacity may be associated with decreased levels of specific apolipoproteins, such as ApoA-I, ApoC-III, and ApoD [144–146]. In ApoE-deficient mouse models, studies have shown a negative correlation between ApoE levels and HDL RCT capacity [144]. Additionally, elevated SAA levels may also be related to the reduced RCT capacity of HDL. Tsun et al. demonstrated that in patients with type 2 diabetes and early or severe kidney disease, increased SAA levels were associated with impaired cholesterol efflux capacity mediated by SR-BI [147]. Similarly, Beer et al. reported that SAA could adversely affect certain steps in the RCT pathway during acute inflammation [148]. In summary, these studies suggest that the decline in HDL RCT capacity in patients with kidney disease may be closely related to changes in phospholipid levels and the reduction of specific apolipoproteins. Further research in this area will help to better understand and manage cardiovascular risk in CKD patients.

Further research has revealed that patients with CKD exhibit significantly reduced expression levels of ABCA1, leading to a decrease in ABCA1-mediated cholesterol efflux capacity [149]. As a critical transport protein, the reduced expression of ABCA1 not only affects intracellular cholesterol efflux but may also have profound implications for overall cholesterol metabolism. Investigating the specific mechanisms underlying the reduced expression of ABCA1, scientists have discovered that this phenomenon may be associated with post-translational modifications induced by the binding of myeloperoxidase (MPO) to ApoA-I [150]. Specifically, MPO can generate cyanate (OCN^-), which is closely linked to protein carbamylation [151]. Additionally, OCN^- is a decomposition product of urea, which is particularly significant in kidney disease, as plasma levels of both urea and carbamylated proteins are significantly elevated in kidney disease patients [152]. Research indicates that the presence of just one carbamylated lysine residue on ApoA-I associated with HDL particles is sufficient to influence pathways related to ABCA1 and SR-BI, which induces cholesterol accumulation in macrophages [150]. This finding offers a new perspective on the lipid metabolism disorders observed in CKD patients.

HDL typically exerts protective effects on blood vessels, but this protection is significantly diminished in the context of CKD. Symmetric dimethylarginine (SDMA) has been identified in the HDL of CKD patients, and this compound can transform normal HDL into dysfunctional HDL [153]. As an endogenous inhibitor of endothelial nitric oxide synthase (eNOS), SDMA impairs the protective effects of HDL on the vascular endothelium by inhibiting nitric oxide production in endothelial cells [153]. Endothelial damage can be observed even in the early stages of CKD, and this damage progressively worsens as renal function declines [154]. Endothelial injury is a key precursor to atherosclerosis, and early endothelial dysfunction may lead to more severe cardiovascular disease.

Moreover, in CKD patients, HDL reduces nitric oxide availability in endothelial cells via Toll-like receptor 2 (TLR-2) [153]. This mechanism not only impairs the repair capacity of the endothelium but also increases the risk of pro-inflammatory activation and elevates arterial blood pressure. These physiological changes suggest that in CKD patients, HDL not only loses its protective effects but may even have detrimental impacts on vascular health. This phenomenon is particularly pronounced in patients undergoing dialysis, as the dialysis process may further impair HDL function, minimizing its protective effects on the vascular endothelium. Studies have also shown that the protective function of HDL on the vascular endothelium is weakest in dialysis patients but partially recovers after kidney transplantation [154]. Kidney transplantation significantly improves renal function, thereby partially restoring the normal function of HDL. This recovery may be related to the improvement

in post-transplant inflammatory status and changes in HDL composition. However, kidney transplantation does not fully restore HDL's protective function, indicating a continued need for research into therapeutic strategies targeting HDL dysfunction.

Oxidative stress is closely associated with the progression of CKD. Under normal physiological conditions, HDL reduces the formation of oxidized low-density lipoprotein (ox-LDL) through antioxidant enzymes such as PON1 and glutathione peroxidase, thereby decreasing oxidative stress and inflammatory responses [155–157]. These antioxidant enzymes enable HDL to effectively protect the vascular endothelium and inhibit atherosclerosis. However, in CKD patients, particularly those undergoing dialysis, the antioxidant activity of HDL is significantly reduced. For example, Moradi et al. found that the antioxidant capacity of HDL in dialysis patients is markedly lower compared to that in healthy controls [155].

Other studies have shown that the activity of PON1 in HDL2 and HDL3 in the plasma of CKD patients is significantly reduced, indicating a substantial decrease in their antioxidant protective capacity [129]. Additionally, it has been found that the decline in PON1 antioxidant activity is associated with the carbamylation of lysine 290 (K290) [158]. The reduction in antioxidant capacity not only signifies a diminished ability of HDL to clear ox-LDL but also suggests increased levels of free radicals and peroxides in these patients, further exacerbating oxidative stress and inflammatory responses. These changes highlight the severe dysregulation of lipid metabolism and antioxidant protection in CKD patients.

These findings underscore a critical point: under conditions of inflammation and oxidative stress in CKD patients, HDL does not always fulfill its atheroprotective role. Instead, the decline in HDL function may make CKD patients more susceptible to cardiovascular events such as heart disease and stroke. In this context, HDL not only loses its protective effects but may also have a detrimental impact on vascular health.

Application and challenges of HDL in the treatment of CKD

Changes in serum HDL levels and impaired HDL function are closely associated with CKD. This phenomenon suggests that pharmacological modulation or improvement of HDL metabolism could have potential benefits for the treatment of CKD.

ApoA-I mimetics

ApoA-I, as the primary protein component of HDL particles, has long been considered a promising therapeutic target. Research from the 1990s demonstrated that overexpression of ApoA-I and its infusion had protective effects in animal models, effectively preventing the formation of atherosclerotic lesions [159–161]. This finding was later applied to the renal field, where it was discovered that overexpression of ApoA-I significantly reduced serum creatinine levels in a lipopolysaccharide-induced renal injury mouse model [162]. Other studies have confirmed that infusion of ApoA-I mimetic peptides not only improved glomerular filtration rate but also reduced tubular damage and fibrosis [163, 164]. These results indicate that modulating ApoA-I levels can effectively alleviate renal injury.

Among ApoA-I mimetic peptides, D-4 F has been shown to reduce oxidized phospholipids and alleviate renal inflammation in atherosclerosis mouse models [165]. Peterson et al. found that D-4 F increases the activity of heme oxygenase-1 in the kidneys, thereby enhancing its antioxidant capacity [166]. Additionally, recent studies on ETC-642, a 22-amino acid ApoA-I mimetic peptide complexed with phospholipids, have demonstrated significant efficacy in sepsis treatment by markedly increasing serum HDL-C levels, reducing renal inflammation, and substantially improving renal function [167].

Enzyme therapy

In patients with CKD at different stages, the concentration or activity of LCAT is typically reduced [14]. Additionally, patients with familial LCAT deficiency (FLD) exhibit significantly lower serum HDL-C levels and often progress to renal failure in their forties [168]. Animal studies also indicate a close association between chronic renal failure and downregulation of the hepatic LCAT gene [169]. These observations suggest that a decline in LCAT activity may be closely related to the occurrence and progression of CKD.

Research by Baragetti et al. found that reduced serum LCAT levels can predict the early progression of CKD and confirmed that changes in HDL subtypes contribute to the worsening of renal damage [170]. Based on these findings, therapeutic targeting of LCAT is considered potentially beneficial for the kidneys. For example, recombinant human LCAT (rhLCAT) therapy has been shown to normalize lipid levels and significantly reduce proteinuria [171]. In vitro studies further confirmed that rhLCAT can reduce the formation of intracellular reactive oxygen species (ROS), thereby restoring the antioxidant capacity of HDL [170].

Additionally, clinical data suggest that decreased PON1 activity in circulation is associated with poor outcomes in CKD, indicating that PON1 may have potential renal protective effects [172–177]. However, the exact role of PON1 in CKD pathophysiology remains unclear. No specific drugs targeting PON1 have been reported

to date, highlighting the need for further research and development.

rHDL

Infusion of rHDL has shown therapeutic potential for atherosclerosis in CKD patients. CSL-111, an rHDL composed of human ApoA-I and soybean phosphatidylcholine, was demonstrated in 2007 by Tardif et al. through the "Effects of CSL-111 on Atherosclerosis: Safety and Efficacy" trial to improve plaque characteristics and coronary artery scores [178]. However, the trial also revealed that CSL-111 treatment induced liver dysfunction, leading to the termination of subsequent studies [179].

The second-generation recombinant HDL, CSL-112, shows promising prospects and does not induce hepatotoxicity [180]. Phase I clinical trials indicated that CSL-112 significantly increased pre-β HDL levels (by 36-fold) and cholesterol efflux (by 270%), without causing liver damage [180, 181]. In the CSL-112-2001 Phase II trial, CSL-112 also significantly elevated ApoA-I and cholesterol efflux levels in patients with acute myocardial infarction (AMI), including those with moderate CKD [182]. Additionally, a 6-gram dose of CSL-112 demonstrated good safety, but further research is needed to explore its renal protective capabilities [182].

Another rHDL, CER-001, was designed to mimic nascent pre-β HDL [179]. Recent studies have shown that CER-001 normalizes lipoprotein profiles and reduces lipoprotein X (LpX) in patients with rapidly progressive kidney disease and FLD [183, 184]. CER-001 appears to improve or at least slow the decline in renal function by reducing toxic LpX deposition in the kidneys and clearing LpX-induced lipid deposits [183, 184]. Research also indicates that CER-001 significantly improves conditions in patients with acute coronary syndrome (ACS) with extensive atherosclerotic lesions [185].

SGLT-2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) were initially developed as treatments for type 2 diabetes [186]. However, subsequent studies have revealed significant renal protective benefits of SGLT-2i [187, 188]. In two large prospective studies focused on renal outcomes—the "Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD)" and the "Canagliflozin and Renal Disease in Diabetes (CREDENCE)" trials—SGLT-2i treatment was associated with a 30–40% reduction in the risk of all renal endpoints. These endpoints include the occurrence and/or progression of albuminuria, decline in eGFR, end-stage renal disease (dialysis or transplantation), and renal death [187, 189].

Systematic reviews and meta-analyses have demonstrated that SGLT-2i provide substantial cardiovascular and renal outcome protection in CKD patients, supporting their continued use even with declining renal function [190]. Based on these findings, the Kidney Disease: Improving Global Outcomes (KDIGO) organization recommends SGLT-2i as the only drug class with Level 1 A evidence for diabetic CKD patients [191]. Despite the observed renal protective effects of SGLT-2i, their underlying mechanisms remain not fully understood.

A study by Li et al. explored the relationship between SGLT-2i, atrial fibrillation, and circulating metabolites, finding that SGLT-2i significantly impacts HDL subtype metabolism [192]. Specifically, SGLT-2i significantly increased HDL concentrations, particularly small HDL subtypes, while decreasing very large HDL levels [192]. Research by Fadini also supports this finding, showing an increase in small HDL subtype levels and a decrease in large HDL subtype levels after three months of dapagliflozin treatment [193]. Further studies have confirmed that SGLT-2i increases serum HDL-C concentrations [194–198]. These findings suggest that SGLT-2i have a regulatory effect on HDL, potentially providing new insights into the renal protective mechanisms of SGLT-2i for future research.

GLP-1 RAs

In the "2021 Standards of Medical Care in Diabetes," the American Diabetes Association (ADA) recommends considering glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in addition to SGLT2i for patients with high risk or established CKD [199]. GLP-1, an incretin hormone, improves glucose control through various mechanisms, including stimulating insulin secretion, enhancing pancreatic β-cell mass, inhibiting glucagon secretion, and slowing gastric emptying [200]. As GLP-1 mimetics, GLP-1 RAs have been shown to have significant effects on glycemic control, reduction of cardiovascular events, and renal protection [201–207].

Clinical trials have demonstrated the positive impact of GLP-1 RAs on renal health. For example, in a large randomized, double-blind, controlled trial conducted by Muskiet et al., liraglutide was found to help slow the increase in the urine albumin-to-creatinine ratio in patients with significant albuminuria [208]. Additionally, a prospective study in Japan revealed that liraglutide significantly improved eGFR, particularly in patients with eGFR ranging from 30 to 60 mL/min/1.73 m^2 [209]. Two other studies further confirmed the renal protective effects of liraglutide, showing significant reductions in proteinuria and 24-hour urinary protein excretion rate [210, 211]. These results indicate that liraglutide not only improves renal function but also effectively reduces markers of renal damage.

Despite the widespread recognition of the renal protective effects of GLP-1 RAs, research on their impact on

serum HDL-C levels remains limited. One study found that while GLP-1 RAs combined with metformin resulted in a slight increase in serum HDL-C levels, this change was not statistically significant [202]. This suggests that the potential effects of GLP-1 RAs on HDL-C are not yet fully understood. Therefore, further research is needed to explore the mechanisms by which GLP-1 RAs affect HDL-C and to evaluate their comprehensive role in the prevention and treatment of CKD, to better understand the overall benefits of these medications in CKD management.

Conclusions and outlook

This review explores the heterogeneity of HDL, the role of HDL in RCT, and the metabolic changes of HDL in CKD.

The kidneys affect HDL levels and its maturation and function by selectively removing HDL components and altering enzyme activity. These changes result in significant alterations in HDL structure and function, such as increased TG content, decreased PL content, and changes in HDL subtype distribution. These impacts not only weaken HDL's anti-atherosclerotic effects but may also increase cardiovascular risk in CKD patients.

Furthermore, HDL function in CKD patients significantly declines, leading to impaired cholesterol reverse transport capability, which is associated with reduced PL levels and decreased apolipoproteins (e.g., ApoA-I) in HDL. The loss of HDL's protective function for endothelial cells may exacerbate endothelial damage and oxidative stress, further increasing cardiovascular disease risk.

In terms of treatment, ApoA-I mimetics and rHDL have shown potential in improving HDL function and reducing renal inflammation, but their long-term safety and efficacy need further validation. SGLT-2i and GLP-1 RAs also show promise in improving cardiovascular and renal outcomes, but the specific mechanisms of their effects on HDL metabolism remain to be clarified.

Future research should focus on the mechanisms by which CKD affects HDL function and structural changes to better understand its role in CKD. Additionally, novel therapeutic approaches, such as targeted therapies for HDL function, should be explored, along with further investigation into the impact of SGLT-2i and GLP-1 RAs on HDL metabolism, to optimize treatment strategies. These studies hold the potential to provide more effective treatment options for CKD patients, improving their quality of life and prognosis.

Abbreviations

CKD	Chronic Kidney Disease
HDL	High Density Lipoprotein
eGFR	Estimated Glomerular Filtration Rate
CVD	Cardiovascular Diseases
HDL-C	High-Density Lipoprotein Cholesterol
ESRD	End-Stage Renal Disease
PL	Phospholipid
FC	Free Cholesterol
CE	Cholesteryl Ester
TG	Triglyceride
LCAT	Lecithin-Cholesterol Acyltransferase
Apo	Apolipoprotein
ApoA-I	Apolipoprotein A-I
LDL	Low-Density Lipoprotein
ABCA1	ATP-Binding Cassette Transporter A1
nm	Nanometer
rHDL	reconstituted HDL
DMPC	Dimyristoylphosphatidylcholine
PON1	Paraoxonase 1
MCP-1	Monocyte Chemotactic Protein 1
PAF-AH	Platelet-Activating Factor Acetylhydrolase
GSPx-3	Glutathione Peroxidase 3
CETP	Cholesteryl Ester Transfer Protein
PLTP	Phospholipid Transfer Protein
SAA	Serum Amyloid A
MS	Mass Spectrometry
PC	Phosphatidylcholine
LPC	Lysophosphatidylcholine
PE	Phosphatidylethanolamine
PI	Phosphatidylinositol
Cer	Ceramide
S1P	Sphingosine-1-Phosphate
SPC	Sphingomyelin-Phosphocholine
VLDL	Very Low-Density Lipoprotein
GGE	Gradient Gel Electrophoresis
AGE	Agarose Gel Electrophoresis
NMR	Nuclear Magnetic Resonance
RCT	Reverse Cholesterol Transport
ABCG1	ATP-Binding Cassette Transporter G1
SR-BI	Scavenger Receptor Class B type I
LDLR	LDL Receptor
MPO	Myeloperoxidase
SDMA	Symmetric Dimethylarginine
eNOS	endothelial Nitric Oxide Synthase
TLR-2	Toll-Like Receptor 2
ox-LDL	oxidized Low-Density Lipoprotein
K290	Lysine 290
FLD	Familial LCAT Deficiency
rhLCAT	recombinant human LCAT
ROS	Reactive Oxygen Species
AMI	Acute Myocardial Infarction
LpX	Lipoprotein X
ACS	Acute Coronary Syndrome
SGLT-2i	Sodium-Glucose Cotransporter 2 Inhibitors
GLP-1 RAs	Glucagon-Like Peptide-1 Receptor Agonists

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Author contributions

A. Zhen Xu conceived and wrote the manuscript. B. Shuo Yang and Liyan Cui reviewed and edited the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable. This manuscript does not involve experiments on humans or animals, and therefore does not require ethical approval or participant consent.

Consent for publication
All authors have read and approved the publication of this manuscript.

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The authors declare no competing interests.

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2.1.3 ESTUDIO 3

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A Study of Lipid Profile in Pre-Dialysis Chronic Kidney Disease Patients in Tertiary Care Hospital, South Gujarat

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Abstract: ***Objective*:** This hospital-based cross-sectional study aimed to estimate the prevalence and pattern of dyslipidaemia in pre-dialysis chronic kidney disease (CKD) patients and to evaluate its association with the stages of CKD. The study sought to determine the extent of lipid abnormalities and their correlation with disease progression. ***Methods*:** The study included 50 adult pre-dialysis CKD patients admitted to a tertiary care centre between May 2022 and January 2024. Patients were enrolled using purposive sampling. CKD staging was classified according to KDIGO guidelines. Lipid profiles were assessed, including total cholesterol, LDL, HDL, and triglycerides. Statistical analysis was performed using unpaired t-tests and chi-square tests, with significance at $p<0.05$. ***Results*:** Of the 50 pre-dialysis CKD patients (60% male), 48% had dyslipidaemia. It was more common in males (53%) than females (40%) and in those aged >50 years (64%) than in younger age groups ($p = 0.06$). Most patients (76%) were in Stage 5 CKD, where abnormal lipid levels were markedly higher. Significant associations were found between advanced CKD stage and elevated total cholesterol, LDL-C, and triglycerides ($p = 0.03$, 0.04, and 0.04, respectively), while low HDL-C was not statistically significant ($p = 0.21$). These findings suggest a worsening lipid profile with CKD progression. ***Conclusions*:** The study highlights the high prevalence of dyslipidaemia in pre-dialysis CKD patients, with lipid abnormalities worsening as CKD progresses. These findings emphasize the importance of early lipid monitoring and intervention to mitigate cardiovascular risk in this population.

Keywords: Dyslipidaemia, Chronic Kidney Disease (CKD), Pre-dialysis, Kidney Disease Improving Global Outcomes (KDIGO), Lipid Profile

INTRODUCTION

Chronic kidney disease (CKD) is one of today's leading public health problems, with increasing frequency and prevalence. According to the Kidney Disease: Improving Global Outcomes (KDIGO), CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m2 for 3 months or more, irrespective of cause [1].

According to the Global Burden of Disease study, CKD was ranked as the 12th leading cause of death globally in 2019, resulting in 1.2 million deaths. The prevalence of CKD is estimated to be around 9-13% worldwide, affecting over 700 million people [2]. While many patients with chronic kidney disease (CKD) may eventually have renal failure, the majority will surrender to cardiovascular disease before the need for dialysis since individuals with CKD face an elevated risk of acquiring cardiovascular disease due to several associated risk factors. These risk factors can be both traditional ones such as age, male gender, diabetes, obesity, hypertension, and dyslipidemia and non-traditional uremia-related risk factors such as anaemia, hyperhomocysteinemia, mineral bone disease-CKD with hyperparathyroidism, oxidative stress, hypoalbuminemia, and chronic inflammation [3]. However, a significant portion of the worldwide renal disease burden and its effects on the outcomes of other illnesses remains unquantified; hence, these figures are likely approximate.

CKD results in profound dysregulation of several key enzymes and metabolic pathways that eventually contribute to disordered high-density lipoprotein (HDL) cholesterol and triglyceride-rich lipoproteins [4]. Many epidemiologic studies have suggested the independent role of dyslipidemia on cardiovascular morbidity and mortality in the general population [5]. It contributes to accelerated atherosclerosis and a higher incidence of coronary artery disease due to elevated LDL-C and reduced HDL-C levels. Dyslipidemia often coexists with metabolic abnormalities like insulin resistance and diabetes, further compounding cardiovascular risk. It may also worsen renal function through mechanisms involving glomerular damage and inflammation. These impacts make dyslipidemia a key factor in shaping treatment strategies for individuals with CRF [6].

In India, CKD has emerged as a significant public health concern with an increasing prevalence and adverse outcomes. A population-based study conducted in 2019 estimated the prevalence of CKD in India to be approximately 17.2%. The study also highlighted the association of CKD with hypertension, diabetes, and rural-urban disparities in CKD prevalence [7].

The prevalence of CKD and its association with

cardiovascular complications pose a significant challenge for healthcare systems worldwide, including India. Understanding the current scenario and addressing CKD risk factors and management strategies are crucial for preventing disease progression, reducing morbidity and mortality, and improving the overall health outcomes for affected individuals.

MATERIALS AND METHODS

Study Design: This observational, cross-sectional study aims to estimate the prevalence and pattern of dyslipidaemia among pre-dialysis chronic kidney disease (CKD) patients.

Study Setting: The study was conducted from May 2022 to January 2024 at the Department of General Medicine, GMERS Medical College and Hospital, Valsad, Gujarat, India.

Study Participants: The study included 50 adult patients diagnosed with CKD stages 1–5, defined by the Kidney Disease Improving Global Outcomes (KDIGO) classification. All participants were enrolled during the study period. Adults aged 18 years or older with a confirmed diagnosis of chronic kidney disease (CKD) stages 1 to 5 and who had not yet initiated dialysis were included in the study. Exclusion criteria comprised pregnant women, individuals undergoing dialysis or those who had received a kidney transplant, patients receiving lipid-lowering medications, corticosteroids, or immunosuppressive therapy; participants following a lipid-lowering diet; and individuals who did not provide informed consent.

Exposures: The primary exposure variable in this study was the stage of chronic kidney disease (CKD), classified based on the kidney disease: Improving Global Outcomes (KDIGO) guidelines. CKD stages were defined as follows: Stage 1 with a glomerular filtration rate (GFR) ≥ 90 mL/min/1.73 m² accompanied by evidence of kidney damage; Stage 2 with GFR between 60–89 mL/min/1.73 m² and kidney damage; Stage 3 subdivided into 3a (GFR 45–59 mL/min/1.73 m²) and 3b (GFR 30–44 mL/min/1.73 m²); Stage 4 with GFR ranging from 15–29 mL/min/1.73 m²; and Stage 5 indicating kidney failure, with GFR < 15 mL/min/1.73 m².

Outcomes: The primary outcomes assessed in the study included the prevalence of dyslipidemia, which was defined as the presence of any abnormality in the lipid profile, specifically total cholesterol ≥ 200 mg/dL, LDL cholesterol ≥ 100 mg/dL, HDL cholesterol < 40 mg/dL, or triglycerides ≥ 150 mg/dL. In addition, comprehensive lipid profile measurements—including total cholesterol, LDL, HDL, and triglycerides—were obtained for all participants to evaluate lipid abnormalities.

Data Collection: Data were collected using a pre-structured case record form that captured socio-demographic information such as age, gender, occupation, and lifestyle factors; medical history including comorbidities like hypertension and diabetes mellitus; and findings from clinical examination including general physical assessment and vital parameters such as blood pressure, heart rate, and oxygen saturation. Blood samples were obtained following a 12-hour fasting period for lipid profiling, and serum levels of total cholesterol, LDL, HDL, and triglycerides were measured using standard laboratory protocols. Blood was drawn via venepuncture, and serum was separated and stored at -20°C until analysis. All biochemical assays were conducted using automated analysers in the hospital's central laboratory.

Statistical Analysis: The data were analyzed using Epi Info™ CDC version 7. Descriptive statistics were applied to summarise continuous and categorical variables, including mean, standard deviation, and frequency distributions. The association between chronic kidney disease (CKD) stages and lipid abnormalities was evaluated using independent t-tests for continuous variables such as lipid profile parameters, while Chi-square tests were employed for categorical variables, including the prevalence of dyslipidemia. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations: The Institutional Ethical Committee (IEC) of GMERS Medical College and Hospital, Valsad, approved the study. Written informed consent was obtained from all participants after providing a participant information sheet in their preferred language. Confidentiality of patient information was maintained throughout the study.

RESULTS:

This study involved a total of 50 CKD patients. There were 30 male and 20 female participants. Most of the participants, about 50% (n=25), were above 50 years of age, followed by 48% (n=24) in the 31–50 years age group and 2% (n=1) in the 18–30 years group. 56% (n=28) of the patients reported no significant comorbid conditions, whereas 18% (n=9) patients had diabetes mellitus, 16% (n=8) had hypertension, and 10% (n=5) patients had both diabetes and hypertension. On classifying the patients based on KDIGO staging, 24% (n=12) had Stage 4 CKD, and the other 76% (n=38) had Stage 5 CKD. (Table 1)

Table 2 shows the analysis of lipid parameters in pre-dialysis CKD patients. The mean total cholesterol level was 190.18 ± 53.44 mg/dL, with the mean LDL-cholesterol being 95.44 ± 12.68 mg/dL, while the mean HDL-cholesterol level was 41.84 ± 10.10 mg/dL. The mean serum triglyceride level among the study subjects was 113.16 ± 21.88 mg/dL. These findings show that patterns of dyslipidaemia were commonly associated with chronic kidney disease.

Table 1. Characteristics of the Study Subjects

Parameter	n (%)
Gender	
• Male	30 (60)
• Female	20 (40)
Age (years)	
• 18-30	1 (2)
• 31-50	24 (48)
• >50	25 (50)
Co-morbidities	
• Diabetes Mellitus	9 (18)
• Hypertension	8 (16)
• Diabetes with Hypertension	5 (10)
• No significant history	28 (56)
KDIGO Staging	
• Stage 4	12 (24)
• Stage 5	38 (76)

Table 2 Lipid Profile in Pre-Dialysis CKD Patients

Lipid Parameter	Mean ± SD
Total Cholesterol	190.18 ± 53.44
LDL- Cholesterol	95.44 ± 12.68
HDL- Cholesterol	41.84 ± 10.10
Triglycerides	113.16 ± 21.88

Assessing the association between KDIGO staging and lipid parameters among pre-dialysis CKD patients revealed that most patients in Stage 5 CKD had more abnormal lipid profiles than those in Stage 4. The presence of abnormal lipid parameters among patients in Stage 4 versus Stage 5 was elevated total cholesterol (10% vs 90%), elevated LDL-C (5.6% vs 94.4%), elevated triglycerides (9.5% vs. 90.5%) and reduced HDL-C (7.7% vs. 92.3%). The prevalence of abnormal LDL-C and triglyceride levels is significantly associated with advanced CKD stages (p = 0.02 and 0.04, respectively). In contrast, no significant association was observed between advanced CKD stage and abnormal levels of total cholesterol and HDL-C (p = 0.06 and 0.11, respectively). (Table 3)

Table 3: Relation of KDIGO Staging with Lipid Parameters

Parameter		Stage 4 (n=12)	Stage 5 (n=38)	Total (n=50)	p-value*
Total Cholesterol	Normal	10 (33.3%)	20 (66.7%)	30	0.06
	Abnormal	02 (10%)	18 (90%)	20	
LDL- Cholesterol	Normal	11 (34.4%)	21 (65.6%)	32	0.02
	Abnormal	01 (5.6%)	17 (94.4%)	18	
HDL- Cholesterol	Normal	11 (29.7%)	26 (70.3%)	37	0.11
	Abnormal	01 (7.7%)	12 (92.3%)	13	
Triglycerides	Normal	10 (34.5%)	19 (65.5%)	29	0.04
	Abnormal	02 (9.5%)	19 (90.5%)	21	

*p-value calculated using chi-square test

The mean values of Glomerular filtration rate (GFR) and serum creatinine according to stages of CKD are 25.65 ± 8.32 mL/min/1.73m² and 3.43 ± 1.73 mg/dL in Stage 4 and 7.05 ± 2.88 mL/min/1.73m² and 8.58 ± 3.11 mg/dL in Stage 5, respectively. Among the lipid parameters, the prevalence of elevated total cholesterol, elevated LDL-cholesterol and elevated TG was significant with advanced CKD stage (p-value= 0.03, 0.04, 0.04; respectively). Levels of HDL-cholesterol were lower in Stage 5 than Stage 4 but were not statistically significant (p= 0.21). These findings suggest a worsening of lipid profile parameters as CKD progresses.

Table 4 Mean RFT and Lipid Profile parameters with KDIGO Staging

Parameter	Stage-4 (n=12)	Stage 5 (n=38)	p-value*
Renal Function Tests			
GFR (mL/min/1.73m²)	25.65 ± 8.32	7.05 ± 2.88	< 0.001
Serum Creatinine (mg/dL)	3.43 ± 1.73	8.58 ± 3.11	< 0.001
Lipid Profile Parameters			

Total Cholesterol	171.25 ± 48.88	210.19 ± 55.56	0.03
LDL- Cholesterol	90.88 ± 8.59	98.92 ± 12.90	0.04
HDL- Cholesterol	44.63 ± 9.21	40.34 ± 10.62	0.21
Triglycerides	106.13 ± 16.00	119.84 ± 21.76	0.04

*p-value calculated using chi-square test

Of the 50 CKD subjects, 48% (n=24) had dyslipidaemia. The prevalence of dyslipidaemia was 40% (n=8) in female CKD patients and 53% (n=16) in male CKD patients, but the difference was not statistically significant (p=0.53). Dyslipidaemia was commoner in CKD patients who were of age more than 50 years (64%). There were 33% (n=8) patients in the age group 31-50 years with dyslipidaemia. The association between age group and dyslipidaemia showed statistical significance (p = 0.06), indicating a trend toward increased prevalence of dyslipidaemia with advancing age.

Table 5. Association between dyslipidaemia, gender and age among CKD subjects

Parameter	Dyslipidaemia Present, n(%)	Dyslipidaemia Absent, n(%)	p-value*
Gender			
Male (n=30)	16 (53%)	14 (47%)	0.53
Female (n=20)	8 (40%)	12 (60%)	
Age (in years)			
18-30 (n=1)	0	1 (100%)	0.06
31-50 (n=24)	8 (33%)	16 (67%)	
>50 (n=25)	16 (64%)	9 (9%)	

*p-value calculated using chi-square test.

DISCUSSION

The incidence of clinical coronary heart disease among CKD patients is 40%, with cardiovascular disease (CVD) mortality rates being 10 to 30 times higher than those of the general population across similar demographics [8]. CKD patients often present early signs of atherosclerosis, with dyslipidemia identified as a major risk factor for CVD. Significant deviations in lipoprotein metabolism are observed in these patients, potentially leading to severe dyslipidaemia in the disease's later stages. CKD, characterized by the gradual loss of kidney function due to underlying health issues, is a leading cause of death from cardiovascular causes among those with mild-to-moderate stages of the disease as well as end-stage renal disease (ESRD). Projections made by the global health burden of disease epidemiologists forecast that in 2040, CKD will be the 5th disease in rank responsible for death globally [9].

The present study aimed to determine the prevalence and pattern of dyslipidemia in pre-dialysis chronic kidney disease (CKD) patients, specifically those in Stages 4 and 5, in a tertiary care hospital in South Gujarat. The motivation behind this investigation lies in the well-established link between CKD and cardiovascular morbidity, with dyslipidemia recognized as a key contributor to this elevated risk.

The study used the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria[10] to define lipid abnormalities. Specific lipid abnormalities included elevated total cholesterol (TC) in 40%, elevated LDL-cholesterol (LDL-C) in 36%, elevated triglycerides (TG) in 42%, and low HDL-cholesterol (HDL-C) in 26% of participants. Notably, the severity and pattern of dyslipidemia showed a clear correlation with the CKD stage. Patients in Stage 5 had significantly higher mean total cholesterol, triglycerides, and LDL-C levels than those in Stage 4. Moreover, the prevalence of overall dyslipidemia, abnormal LDL-C, and elevated triglycerides was significantly greater in Stage 5, indicating a progressive worsening of lipid derangements with declining renal function. These findings support the premise that dyslipidemia intensifies with CKD progression, reinforcing the need for early and aggressive lipid monitoring and management in pre-dialysis patients to reduce cardiovascular complications.

Our study identified a 48% prevalence of dyslipidemia in pre-dialysis CKD patients, which is lower than that reported in various Indian and global studies. Choudhary et al. [11] indicated an 82.6% prevalence, whereas Khade et al. [12] discovered 73.1% among CKD patients. Similarly, Adejumo et al. reported a 60% prevalence in a Nigerian CKD group [13]. However, our findings are still significantly higher than those observed in non-CKD control groups, such as Adejumo's study, which found a 39% prevalence in the control group [13]. This demonstrates that dyslipidemia remains a considerable burden in pre-dialysis CKD, even if prevalence varies by geography. Variations in diagnostic criteria, CKD etiologies, population demographics, dietary trends, and genetic origins might all contribute to these disparities.

Participants in our study had a mean age of 50.02 ± 14.77 years, which indicates that our subject cohort was predominantly within the economically productive age group. This is similar to the average age reported by Rizwan et al. [14]. and slightly lower than that reported by Adejumo et al. [13]. (~47 years). The male predominance (60%) in our cohort is similar to that reported by Verma et al. [15]. (59%) but is less marked than in studies such as Rizwan et al. [14]. (66.9%), indicating some variability in gender distribution across CKD populations. Our population is characterised by significant renal impairment, with a mean GFR of 11.51 ml/min/1.73 m², and a majority of the study participants having Stage 5 CKD (76%). This implies that our results mainly reflect changes in lipid profile in the late stages of pre-dialysis CKD—conversely,

studies like those by Adejumo et al. [13]. Stage 3 also had the highest concentration of patients, which might also have affected the described lipid trends and overall prevalence of dyslipidemia.

Serum Total Cholesterol (TC)

In the present study, elevated total cholesterol (TC ≥200 mg/dL) was observed in 40% of participants, with a mean TC of 190.18 ± 53.44 mg/dL. A statistically significant increase was noted between CKD stages, rising from 171.25 mg/dL in Stage 4 to 210.19 mg/dL in Stage 5 ($p = 0.03$). This prevalence is comparable to Akpan et al. (44%)[16] but lower than the figures reported by Choudhary et al. [11]. (50.4%). The mean TC in our study aligns closely with the value reported by Bhushan et al. [17]. (195 mg/dL), yet exceeds that of Verma et al. [15]. (137 mg/dL). The moderate prevalence of hypercholesterolemia in our cohort may reflect competing influences such as malnutrition and inflammation, which are common in advanced CKD and can depress serum cholesterol. However, the significant upward trend from Stage 4 to 5 underscores the progressive dysregulation of lipid metabolism as renal function deteriorates.

Serum LDL-Cholesterol (LDL-C)

Elevated LDL-C (≥100 mg/dL) was identified in 36% of the cohort, with a mean LDL-C of 95.44 ± 12.68 mg/dL. A significant rise was observed from 90.88 mg/dL in Stage 4 to 98.92 mg/dL in Stage 5 ($p = 0.04$), and the prevalence of abnormal LDL-C was significantly higher in Stage 5 ($p = 0.02$). While this prevalence is lower than that reported by Khade et al. [12]. (59.6%) and Akpan et al. [16]. (48%), it still denotes a significant atherogenic trend. Our mean LDL-C is also lower than the values reported by Bhushan et al. (153 mg/dL). The relatively lower LDL-C levels in our predominantly Stage 5 population could reflect altered hepatic synthesis or increased catabolism due to chronic inflammation. Nonetheless, the statistically significant elevation between CKD stages supports the notion that LDL-C accumulation remains a significant metabolic derangement in end-stage renal disease.

Serum HDL-Cholesterol (HDL-C)

Low HDL-C (<40 mg/dL) was found in 26% of participants, with a mean level of 41.84 ± 10.10 mg/dL. No significant difference was observed in HDL-C between Stage 4 (44.63 mg/dL) and Stage 5 (40.34 mg/dL) ($p = 0.21$), nor in the prevalence of low HDL-C across stages ($p = 0.11$). This prevalence is substantially lower than those reported by Choudhary et al. (73.9%)[11] but is comparable to Khade et al. [12]. (34.6%). Our mean HDL-C is marginally higher than the values reported by Bhushan et al. [17]. (38 mg/dL) and similar to those observed by Rizwan et al. [14]. Several studies have noted markedly lower HDL-C levels in dialysis patients, indicating worsening HDL metabolism with advanced disease or dialysis initiation. Despite the relatively modest prevalence of low HDL-C in our cohort, this parameter remains clinically relevant due to its central role in reverse cholesterol transport. The lack of significant decline from Stage 4 to 5 may be due to a limited Stage 4 sample size or other confounding influences. However, qualitative dysfunction of HDL is likely present regardless of concentration, driven by reduced ApoA-I/A-II, impaired LCAT activity, and increased CETP-mediated exchange.

Serum Triglycerides (TG)

Elevated triglycerides (TG ≥150 mg/dL) were observed in 42% of patients, with a mean TG of 113.16 ± 21.88 mg/dL. Mean TG significantly increased from 106.13 mg/dL in Stage 4 to 119.84 mg/dL in Stage 5 ($p = 0.04$), with a considerably higher prevalence of hypertriglyceridemia in Stage 5 ($p = 0.04$). This prevalence is lower than reported by Choudhary et al. (67%) yet comparable to Khade et al. (36.5%)[12] and notably higher than Akpan et al. (26%)[16]. Our mean TG level is markedly lower than those reported by Bhushan et al. (206 mg/dL)[17] and Verma et al. (161 mg/dL)[15]. Our cohort's relatively modest TG levels could reflect regional dietary habits, genetic influences, or reduced hepatic production in some patients with malnutrition or chronic inflammation. Nonetheless, the significant increase in TG from Stage 4 to Stage 5 supports its role as a progressively worsening atherogenic marker in CKD. Prior studies, including Zhang et al. [19]., have identified TG as a key predictor of CKD risk and shown a negative correlation with eGFR, reinforcing the biological plausibility of our findings. Elevated TG in CKD is attributed mainly to reduced LPL activity and impaired catabolism of VLDL, particularly under the influence of uremic toxins and insulin resistance [6][18].

STRENGTHS AND LIMITATIONS

We provide this region-specific, globally unique data on the prevalence of dyslipidemia, comparing Stage 4 and Stage 5 CKD cases in South Gujarat advanced pre-dialysis CKD patients. KDIGO classification and laboratory techniques were conventional. However, there are significant limitations to recognize. The study's cross-sectional nature limits the determination of causation or the monitoring of lipid evolution over time. The total sample (N=50) is small, and the limited number of subjects in Stage 4 (n=12) restricts the power and generalizability of the stage comparison. Thus, the overwhelming dominance of Stage 5 patients (76%) in our cohort means our findings predominantly describe very advanced CKD and cannot be easily generalized to earlier stages or truly reflect the population prevalence of the overall CKD population. The fact that this is a single-centre study with purposive sampling also limits representativeness. We also did not measure advanced lipid markers such as ApoB, ApoA-I, or Lp(a), which may allow further risk stratification.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Our study emphasizes the need for early identification and control of dyslipidemia in CKD, even in the pre-dialysis phase. The debate about the utility of statins in end-stage renal disease endpoint continues. However, abundant data supports the beneficial effect of statin therapy on CKD as a whole, especially at earlier stages (i.e., Stages 3–4), particularly in the setting of additional CV risk factors. Our findings indicate that lipids should be routinely monitored and managed in patients with CKD, targeting specifically triglycerides and HDL-C rather than LDL-C alone. As shown, these abnormalities are atherogenic, so early interventions focused on lifestyle modification, glycemic

control, and pharmacologic therapy should be started.

CONCLUSION

In conclusion, this study reveals that dyslipidemia is highly prevalent (48%) among pre-dialysis CKD patients, predominantly in Stage 5, within a tertiary care hospital in South Gujarat. The lipid profile, particularly TC, LDL-C, and TG, significantly deteriorates as CKD progresses from Stage 4 to Stage 5. These findings highlight the substantial cardiovascular risk burden in advanced CKD and emphasize the necessity for diligent lipid profile monitoring and management to mitigate cardiovascular complications in this vulnerable population.

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2.1.4 ESTUDIO 4

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HDL and chronic kidney disease

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ABSTRACT

Low HDL-cholesterol (HDL-C) concentrations are a typical trait of the dyslipidemia associated with chronic kidney disease (CKD). In this condition, plasma HDLs are characterized by alterations in structure and function, and these particles can lose their atheroprotective functions, e.g., the ability to promote cholesterol efflux from peripheral cells, anti-oxidant and anti-inflammatory proprieties and they can even become dysfunctional, i.e., exactly damaging. The reduction in plasma HDL-C levels appears to be the only lipid alteration clearly linked to the progression of renal disease in CKD patients. The association between the HDL system and CKD development and progression is also supported by the presence of genetic kidney alterations linked to HDL metabolism, including mutations in the *APOA1*, *APOE*, *APOL* and *LCAT* genes. Among these, renal disease associated with LCAT deficiency is well characterized and lipid abnormalities detected in LCAT deficiency carriers mirror the ones observed in CKD patients, being present also in acquired LCAT deficiency. This review summarizes the major alterations in HDL structure and function in CKD and how genetic alterations in HDL metabolism can be linked to kidney dysfunction. Finally, the possibility of targeting the HDL system as possible strategy to slow CKD progression is reviewed.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in chronic kidney disease (CKD) patients and represents one of the major adverse outcomes in this clinical population [1]. Data from the US Renal Data System (USRDS) 2020 revealed that the prevalence of CVD increases with the progression of CKD, doubling in advanced CKD compared to patients without CKD [1]. A metanalysis of 21 general population cohorts (over 100,000 participants) demonstrated that lower estimated glomerular filtration rate (eGFR) and higher urine albumin creatinine ratio (UACR) were independently associated with higher CVD mortality, after adjusting for potential confounders such as diabetes and hypertension [2]. The spectrum of CVDs associated with CKD includes atherosclerotic CVD (ischemic heart disease, stroke and peripheral artery disease), ventricular hypertrophy, heart failure, as well as non-atherosclerotic CVD [3]. Increased CV risk in these patients is multifactorial, including both traditional (e.g., dyslipidemia and hypertension), and specific risk factors related to kidney function, such as endothelial dysfunction, increased activity of renin–angiotensin system and hyperphosphatemia [4]. Among the major pathophysiological mechanisms linking CKD to CVD, alterations in lipid profile are shared risk factors [5,6].

Reduced HDL-cholesterol (HDL-C) concentrations are a typical trait of CKD dyslipidemia [5]. Quantitative and qualitative alterations of plasma lipids and lipoproteins are detected in patients with renal disorders, in particular CKD and end stage renal disease (ESRD). Beyond the reduction in HDL-C levels, renal disease influences HDL composition affecting their functions.

HDLs are a highly heterogeneous class of lipoproteins, varying in size, shape and protein/lipid composition. This heterogeneity is consequent of the complexity of their metabolism and interconversion within the plasma compartment, where different HDL subclasses on the basis of their density, size, shape and protein/lipid composition may be identified [7]. Small discoidal HDLs, called preβ-HDLs, are mainly generated by the lipidation of the main protein component, apolipoprotein A-I (apoA-I), through the interaction with the ATP-binding cassette transporter A1 (ABCA1) [8]. These particles are good acceptors of additional cholesterol from ABCA1 and become substrates of lecithin:cholesterol acyltransferase (LCAT), responsible for cholesterol esterification in the plasma compartment, which lead to the maturation of nascent discoidal HDLs into spherical particles with a core of cholesteryl

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esters (CE) [9]. Subsequently, the cholesteryl ester transfer protein (CETP) promotes the interchange of CE and triglycerides (TG) between HDLs and apoB-containing lipoproteins, thus modifying the lipid core of HDLs and generating larger and less dense particles. Finally, the action of the endothelial lipase (EL) and the phospholipid transfer protein (PLTP) leads to the hydrolysis of TG and phospholipids (PL), generating again small lipid poor particles [10]. The major site of apoA-I and small HDL particle disposition is the kidney. Indeed, HDLs can be removed from the circulation by glomerular filtration, as their size allows crossing of the glomerular barrier [11]. In proximal tubules, apoA-I is entirely reabsorbed by the action of the cubilin – megalin complex. Specifically, cubilin, a multiligand receptor expressed in apical membranes of kidney tissue, binds apoA-I with high affinity and mediates endocytosis [12]. Lipid and apolipoprotein composition of HDLs affects their surface charge and apoA-I conformation, influencing their plasma clearance; in fact, small, discoidal and positively charged HDL particles are filtered more quickly than mature HDLs [13].

HDLs are involved in different atheroprotective mechanisms, including their central role in reverse cholesterol transport (RCT) in which they act as extracellular acceptors of cholesterol from cells, thus mediating cholesterol efflux capacity, the first step of this process. Cholesterol within HDL is then esterified by LCAT and migrates to the HDL core, thus maintaining the cholesterol gradient between HDL surface and cell membranes. Thereafter, CE can be routed to the liver by two different pathways for elimination through the bile. The first pathway is mediated by the interaction of HDL with hepatic SR-BI and the selective uptake of CE from HDL without particle internalization. The second one is an indirect pathway, with CE transferred from HDL to apoB-containing lipoproteins by the action of CETP; CE are then delivered to the liver by apoB-containing particles through the interaction with their receptors. It has been estimated that in humans, the indirect pathway mediated by CETP is responsible for the hepatic uptake of 70% CE, while the direct interaction of HDL with SR-BI for the remaining 30% [14]. Besides this major activity, HDLs contribute to atheroprotection by exerting antioxidant and anti-inflammatory actions and preventing and correcting several features of the endothelial dysfunction typical of the atherosclerotic process [15].

This review addresses the current knowledge on the three aspects: (i) how CKD affects HDL structure, composition, and functionality; (ii) how genetic and acquired HDL defects affect renal function; and (iii) how targeting the HDL system can benefit renal disease.

2. HDL structure and function in chronic kidney disease

The link between plasma HDLs and the kidney is bidirectional. On one side, CKD affects plasma HDL-C levels, HDL structure and subclass distribution, as well as HDL functionality; on the other end, inherited HDL disorders can lead to kidney dysfunction.

2.1. Structural changes

During CKD, both ABCA1 and LCAT are reduced, thus resulting in poor lipidation of apoA-I and in an impaired HDL maturation process. This leads to an alteration of HDL subclass distribution, with the accumulation of preβ-HDLs, as a consequence of reduced LCAT activity and selective reduction of particles containing both apoA-I and apoA-II (LpA-I:A-II). With the progression of the disease, a reduction of the particles containing only apoA-I (LpA-I) is also observed [5,16]. Besides alterations in HDL subclass distribution, HDL protein and lipid content are modified in CKD. HDLs become enriched in TG and depleted of PL, consistent with reduced activity of hepatic lipase and enhanced activity of PLTP [17,18]. Also the HDL proteome is markedly modified: apoA-I, apoA-II, apoM levels are reduced, whereas particles are enriched in serum amyloid A (SAA), apoC-II, apoC-III, apoA-IV, albumin, lipoprotein-associated phospholipase A2 (Lp-PLA2),surfactant protein B (SP—B), and a-1-microglobulin/bikunin precursor [19]. Furthermore, a significant reduction in HDL-associated antioxidant paroxonase (PON-1) activity is described in patients with stable mild to moderate CKD [20].

Several post-translational modifications occur in the HDL of CKD patients, among these carbamylation and glycation are implicated in alterations of HDL functionality. The reactive oxygen/nitrogen species increase myeloperoxidase (MPO) levels, resulting in increased apolipoprotein carbamylation induced by urea-derived cyanate, generally elevated in patients with CKD [21]. Hyperglycaemia in ESRD patients generates highly reactive α-oxoaldehydes that covalently modify plasma proteins, including apoA-I, resulting in alterations of the conformation of specific domains of apoA-I crucial for LCAT activation, consequently to the ability of glycated apoA-I to activate LCAT is reduced [22]. Moreover, the progressive decline in renal function increases reactive lipid peroxidation with a consequent raise of plasma levels of malondialdehyde (MDA) able to modify and cross-link specific residues in apoA-I [23]. Some of the structural modifications observed in HDLs are implicated in the impairment of fundamental HDL functions. The main structural and functional alterations of HDLs in CKD are summarized in Fig. 1.

2.2. Functional alterations

2.2.1. Cholesterol efflux capacity

CKD affects RCT at different levels including the HDL ability to promote cell cholesterol efflux and HDL maturation. Several studies have highlighted the impaired capacity of HDL from uremic patients, especially patients under dialytic treatments, to promote cell cholesterol efflux [24–27] and impairment is likely related to changes in lipid and protein composition. Changes in the PL and TG content of HDL are shown to correlate with impairment in cell cholesterol efflux, in particular the depletion of PL associated to the reduced content of apoA-I and apoA-II, due to increased content of SAA, is linked to impaired cholesterol efflux capability [24]. Also, post-translational modifications are implicated in this process. Indeed the myeloperoxidase binding to apoA-I inhibits the ABCA1-dependent cholesterol efflux activity of the modified lipoprotein [28]. Furthermore, a recent study has shown that monocytes from CKD patients display a lower expression of ABCA1 and, consequently, the ABCA1-mediated cholesterol efflux is impaired [29], confirming that ABCA1 and ABCG1 are down-regulated also in endothelial cells exposed to uremic plasma [30]. On the contrary, the impairment in efflux capacity is not observed in children with CKD and ESRD that show only a non-significant trend for reduced efflux [31].

2.2.2. Vasodilatory activity

The presence of CKD abolishes the vasoprotective properties of HDLs and drives the transformation of HDLs into harmful particles able to inhibit endothelial NO production [32]. Addressing the mechanism of the impaired vasoprotective properties of HDLs only in the presence of CKD is a complex task. However the direct effect of renal disease on HDL-mediated NO production was also evident in a study carried out in children with CKD, thus allowing the exclusion of confounding factors due to the presence of concomitant diseases in adults such as diabetes, coronary artery disease and smoking [33].HDL loses its endothelial protective properties even in early CKD, with a graded change with the degree of renal impairment, the most profound changes occurring in dialysis

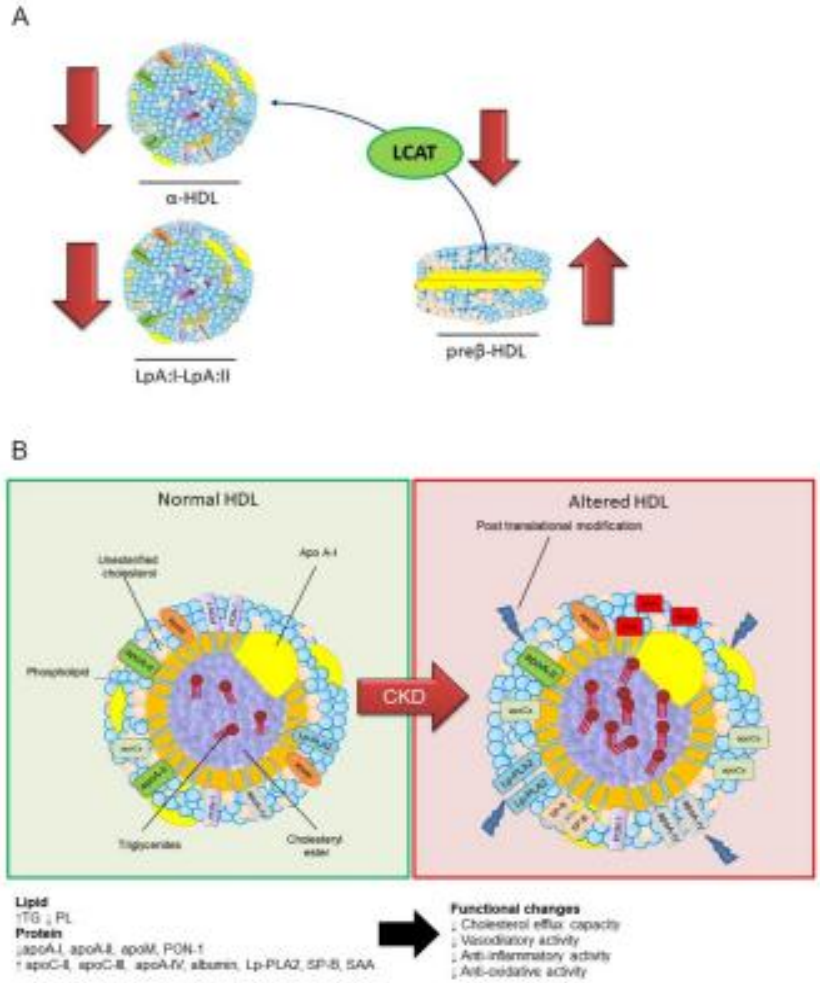

Fig. 1. Summary of the main changes in HDL subclasses (A) and structural and compositional changes (B) in chronic kidney disease.
ApoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II; apoM, apolipoprotein M; apoA-IV, apolipoprotein A-IV; apoC-II, apolipoprotein C-II; apoC-III, apolipoprotein C-III; LCAT, lecithin:cholesterol acyltransferase. Lp-PLA2, lipoprotein-associated phospholipase A2; PL, phospholipids; PON-1, paraoxonase-1; SAA, serum amyloid A; SP-B, surfactant protein B; TG, triglycerides.

patients, partly recovered after transplantation [33]. The structural alterations that change the HDL physiological ability to promote NO production can be multifaceted: HDLs from CKD patients are enriched in symmetric dimethylarginine (SDMA), an isomer of asymmetric dimethylarginine (ADMA), an endogenous endothelial nitric oxide synthase (eNOS) inhibitor [32]; moreover, in uremic patients the increased level of cyanate, promoting protein carbamylation, reduces the eNOS expression [34]. Furthermore, the depletion of LpA-I particles in patients under dialytic treatment [5] can contribute to the impaired activation of eNOS, since this specific HDL subclass is particularly efficient in promoting NO production [35].

2.2.3. *Anti-inflammatory activity*

HDLs from ESRD patients show impaired anti-inflammatory capacities, indeed the ability to inhibit the expression of interleukin-1 β (IL-1-β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) is significantly reduced in macrophage incubated with these particles compared to control HDL. It may thus enhance the recruitment of monocytes into the subendothelial space [25]. According with the studies carried out in adults, also HDLs from children with CKD and ESRD show an impaired ability to inhibit the macrophage expression of IL-1β, TNF-α and MCP-1 [31]. Moreover, HDLs from both adults and children with CKD and ESRD are not able to reduce MCP-1-induced chemotaxis [25,31].

Post-translational modifications have a primary role in altering the anti-inflammatory activity of HDL of CKD patients. MPO-modified HDLs increase the expression of the cell adhesion molecule VCAM-1 [36], and the enrichment in SDMA leads to the activation of endothelial TLR-2 via TLR-1- and TLR-6-coreceptor-independent alternative pathways impairing endothelial repair and enhancing endothelial pro-inflammatory activation [32]. Furthermore, evidence in rabbits show that glycated apoA-I is not able to prevent both endothelial adhesion molecule expression and infiltration of neutrophils into the inflamed carotid arteries [37]. Also, the proteome composition of HDLs from uremic patients can be

implicated in the impaired anti-inflammatory activity, mainly because of alterations in protein composition, such as the enrichment in SAA raising the production of IL-12, IL-10, TNF-a, and IL-6 from human monocytes [26].

2.2.4. Anti-oxidative activity

Oxidative stress is directly involved in the pathogenesis and progression of renal disease, and structural characteristics in CKD, loss of renal energy, and uremia result in an imbalance between free radical production and antioxidant defenses. In physiological conditions, HDL acts as an antioxidant defense and HDL-associated antioxidant enzymes such as PON-1 and glutathione peroxidase attenuate oxidative stress and inflammation by production of oxidized LDL and hydroperoxides. HDLs from CKD patients lose their ability to prevent LDL oxidation and show reduced levels of PON-1, LCAT, glutathione peroxidase and apoA-I [38–40]. Glycation, especially in patients with CKD and diabetes, may affect the HDL anti-oxidant activity [19]. In addition myeloperoxidase binding to apoA-I facilitates the selective targeting of apoA-I for site-specific chlorination and nitration by MPO-generated reactive oxidants [41]. Besides the reduction in PON-1 concentrations also PON arylesterase activity is decreased in CKD patients [20].

3. HDL and CKD progression in the general population

The alterations in the HDL system described above worsen the progression of CKD [42]. Reduction of HDL-C concentrations is the only lipid alteration associated with the progression of renal disease in hemodialysis patients [5] as well as in mild-to-moderate CKD patients, resulting in earlier entry into a dialysis program or in doubling of the plasma creatinine levels, independent of the classical risk factors such as diabetes and hypertension [43]. These findings are supported by the results of a large cohort of 2 million American veterans with a median follow-up of 9 years, in which individuals with HDL-C concentrations <30 mg/dL showed a 10%–20% higher risk for CKD and/or progression of CKD compared to subjects with HDL-C levels ≥40 mg/dL with a U-shaped relationship between HDL-C levels and incidence of CKD [44]. This and other studies noted a paradoxical association between elevated HDL-C levels and cardiovascular events or mortality in patients undergoing hemodialysis with chronic inflammation [45,46].The negative effects of high HDL-C levels on CKD progression can be partly explained by structural and functional alterations paradoxically exerting damaging effects, leading to adverse outcomes, including the deterioration of kidney function [47,48].

However, the relationship between HDL-C and CKD progression is not always observed; in the CRIC study carried out in 3939 CKD patients, HDL-C levels were not independently associated with the composite endpoint of ESRD or a 50% reduction in eGFR [49]. It is also important to underline that the epidemiologic studies on HDL-C levels and CKD progression cannot establish causality or consequentiality [50].

Overall, preclinical and clinical evidence support the association between HDL-C levels and CKD progression. However, this relationship leaves some open questions and controversial aspects that need to be further investigated.

4. HDL and CKD in the presence of genetic HDL defects

The association between altered lipid metabolism and CKD development and progression is supported by the presence of kidney alterations in genetic defects linked to HDL metabolism, such as in familial LCAT deficiency (FLD) [51].

Mutations in genes coding for key structural HDL proteins (i.e., *APOA1, APOE and APOL*) or HDL-related enzymes (i.e., *LCAT*) can cause diseases characterized by renal disorders.

The major HDL protein component is represented by apoA-I. More than 60 variants of the ***APOA1*** gene have been reported, but only half of them associate with low HDL-C [52], and more than 20 have been associated with an hereditary form of amyloidosis (OMIM #105200) [53]. The amyloidogenic effect is caused by single amino acid substitutions that increase the propensity of the apoA-I protein to form insoluble fibrils, mainly constituted by N-terminal polypeptide fragments [54]. These fibrils deposit in different organs, including the kidney as the primary target [55].Kidney apoA-I fibril deposition can lead to tubulointerstitial nephritis initially associated with mild renal dysfunction, and slowly progressing to end-stage renal disease [55].

APOA2 gene mutations leading to similar hereditary amyloidosis have been also reported, although less frequently [56].

ApoE is a structural regulatory protein constituent of chylomicrons, VLDL, LDL and HDL and mutations in the *APOE* gene have been associated with glomerulopathy (apoE2 homozygote glomerulopathy and lipoprotein glomerulopathy, LPG, OMIM#611771) [57]. ApoE2 homozygote glomerulopathy is characterized by glomerulosclerosis with foam cells infiltration and found in homozygous carriers of the apoE2 isoform [58]. LPG is characterized by dilation of capillaries in the glomerulus in presence of lamellated lipoprotein thrombi, due to abnormal lipoproteins composed of instable and aggregation-prone apoE mutants [59]. The first identified mutations in the *APOE* gene responsible for LPG were Arg25→Cys ($apoE_{Kyoto}$) and Arg145→Pro ($apoE_{Sendai}$) [60,61]. LPG-related proteinuria is sometimes mild but progresses to nephrotic syndrome in most cases [62].

Common *APOE* polymorphisms can affect renal function in several ways. For instance, a higher frequency of the ε2 allele and a reduced frequency of the ε4 is found in patients with end-stage renal disease [63] and other studies confirmed this observation also in the general population [64] and in type 2 diabetics [65,66]. Lastly, *APOE* expression may be dysregulated at the glomerular level in focal and segmental glomerulosclerosis, independent of the *APOE* genotype [67].

Apolipoprotein L-I (**apoL-I**) is a key component of the trypanolytic factor of human serum associated with HDLs [68], involved in the defense against pathogens, specifically in the adaptation to parasitic diseases. Two common risk alleles (G1 and G2) in the *APOL1* gene have been identified in individuals with sub-Saharan African ancestry and found to be associated with an increased risk of non-diabetic kidney disease, particularly focal segmental glomerulosclerosis (OMIM #612551) and HIV-associated nephropathy [69–71]. These variants presumably resulting from genetic protection against sleeping sickness, being absent in non-African populations, likely explain the higher prevalence of CKD in African Americans [71,72]. A focal and segmental glomerulosclerosis phenotype is associated to the above cited variants and linked to increased *APOL1* expression in glomeruli [73]. In the Atherosclerosis Risk in Communities (ARIC) study, black participants carrying the *APOL1* high-risk genotype had a significantly higher incidence of kidney failure and a more rapid eGFR decline compared to those carrying the low-risk allele [74].Since the role of apoL-I in kidney development or function is not known, it is not clear how it may be involved in CKD pathogenesis. Several mechanisms have been proposed. One of the hypotheses is that *APOL1* risk variants may create pores in membranes of kidney cells, acting as in trypanosomal organelles [75]. Expression of G1 or G2 is associated with endolysosomal and mitochondrial dysfunction [76], altered ion channel activity [77], induction of stress-activated protein kinase p38 MAPK and JNK [78] and autophagy [79,80], all contributing to renal damage.

LCAT is the enzyme responsible of cholesterol esterification in

plasma, primarily in HDLs (α-activity) but also in apoB-containing particles (β-activity). Loss-of-function mutations in the *LCAT* gene are responsible for two syndromes: familial LCAT deficiency (FLD, OMIM#245900) and fish-eye disease (FED, OMIM#136120), two rare autosomal recessive disorders, characterized by extremely low HDL-C levels and the presence of corneal opacity, i.e., the hallmark of the diseases. FLD-causing mutations lead to complete LCAT deficiency, since LCAT lacks bothα and β activity, whereas FED-causing mutations lead to partial LCAT deficiency, in which LCAT retains its capacity to esterify cholesterol on apoB-containing lipoproteins [81]. While FED mutations lead to a relatively more benign phenotype [82], FLD carriers can develop proteinuria as early as in the second decade of life [83] usually progressing to CKD by the fourth decade of life [84]. Lipid and lipoprotein abnormalities are present in FLD patients. Consistent with the lack of esterification, plasma unesterified cholesterol is raised and the unesterified to total cholesterol ratio is above 75%. Plasma HDLs do not only shown reduced cholesterol content, but also altered size and shape, with a preponderance of small discoidal pre-β HDL particles, indicative of incomplete HDL maturation [35].

In addition, due to the excessive amount of unesterified cholesterol an abnormal lipoprotein, called lipoprotein X (LpX), may be present [82]. LpX is composed by more than a 60%of phospholipids and 30% unesterified cholesterol [85]. LpX appears as a multilamellar vesicle with bi or multilayer phospholipids by electron microscopy size ranging from 30 to 70 nm in diameter [85]. Renal disease is the main cause of mortality and morbidity in FLD patients. Development and progression of renal damage in FLD patients is unpredictable and variable, also within the same family members, suggesting a role of genetics and environment on kidney decline [86]. Kidney biopsies of FLD show peculiar histopathologic changes, including mesangial expansion, irregular thickening of the glomerular capillary walls and increased mesangial cellularity [87]. In addition, unesterified cholesterol and phospholipids can deposit in the glomeruli, inducing vacuolization of the basement membrane and conferring a "foamy" appearance [87]. Alterations of podocyte structure with fused endothelial processes can be observed on electron microscopy [88], while immunofluorescence microscopy reveals the presence of IgM deposit and C3 in the capillary loops, mesangium and arteriolar walls [89,90].

Although the exact pathogenesis of renal disease in FLD is not fully elucidated, a direct role of LpX has been demonstrated in a mouse study. After intravenous administration of synthetic LpX, *Lcat*$^{-/-}$mice develop proteinuria and FLD renal histological hallmarks [91].

In humans, LpX is found in the capillary loops of the glomerulus, where it induces vascular and endothelial damage [90]. Some years ago, in an observational study, it has been shown that plasma unesterified cholesterol levels at diagnosis were able to predict the rate of progression of any renal events (i.e., dialysis, kidney transplantation or death for renal complications) in the larger cohort of FLD carriers described so far [84]. Moreover, unesterified cholesterol levels above the median were associated with lower event-free survival [84]. Excess unesterified cholesterol in these patients accumulates in LpX.

Lipoprotein remodeling with consequent reduction of plasma LpX, operated by HDL mimetic administration, can lead to partial amelioration of renal disease, and decreased lipid deposition in the kidneys [92]. In addition, the absence of renal disease in FED suggests that the residual LCAT activity is sufficient to prevent the formation of a sufficient amount of LpX to induce renal damage [81].

No cure is available so far for FLD patients. Available pharmacological approaches are meant to correct dyslipidemia and to delay renal failure. Renal transplantation represents an option in case of end-stage renal disease; however, it does not correct the enzymatic defect and renal disease can reoccur [92].

Recombinant human LCAT is currently in clinical development [93,94]. Small molecule LCAT activators have been tested *in vitro* and able to activate some mutant LCAT, but no further update is available [95,96]. Very recently, the HDL mimetic CER-001 proved its efficacy in reducing albuminuria and increasing podocyte in a mouse model of FLD [97]. Pharmacological approaches will be discussed further below.

5. Targeting HDL system to benefit renal disease

The presence of reduced plasma levels of HDL-C and impaired HDL functionality in CKD suggest the potential efficacy of pharmacological strategies acting on HDL metabolism to prevent and revert CKD, both in primary and secondary renal diseases.

5.1. Preclinical studies

Animal studies demonstrate that targeting apoA-I/HDL can ameliorate kidney injury; mice overexpressing apoA-I show indeed lower serum creatinine following lipopolysaccharide-induced kidney damage compared to control wild-type mice [98]. As a supporting evidence, infusion of an apoA-I mimetic peptide improved glomerular filtration rate, decreased tubular injury and tubulointerstitial fibrosis [99,100].Additionally, studies have shown that supplementation with an apoA-I mimetic peptide reduced proteinuria, glomerular, and tubulointerstitial injury in proteinuric apoE$^{-/-}$ mice [101].

In a mouse model of renal disease due to genetic LCAT deficiency, treatment with the synthetic HDL, CER-001, limited albuminuria and podocyte dysfunction [90]. In the same mouse model, treatment with recombinant human LCAT (rhLCAT) led to a normalization of the lipid profile, including maturation of HDL, elimination of LpX in plasma and kidneys, and markedly reduced proteinuria [102]. In vitro studies support the evidence that supplementation with rhLCAT restore HDL-antioxidant activity by reducing the formation of ROS in cultured renal cells [103].

Targeting the HDL system by administration of fenofibrate, a drug increasing plasma levels of HDL-C, showed cardiorenal protective effects. In a rat model of cardiac hypertrophy and nephropathy treatment with fenofibrate can indeed attenuate cardiac hypertrophy, and protect the kidneys, preventing morphological alterations [104].

Taken together this data support the clinical development of treatments targeting the HDL system to slow CKD progression.

5.2. Clinical studies

Most clinical studies on HDL-related drugs in CKD aimed to reduce the atherosclerotic burden observed in CKD have not shown any effect on renal disease progression. Approaches are in clinical development for genetically-determine CKD and in the future can be potentially apply to other renal disease.

CSL-112, a human plasma-derived apoA-I, was tested in post-acute myocardial infarction (AMI) patients with the aim of increasing cholesterol efflux capacity, which is substantially impaired following AMI [105]. The phase 2 trial CSL112_2001 enrolled AMI patients with moderate chronic kidney disease (eGFR <60 mL/min/1.73 m^2) to evaluate the safety of infusions in this subgroup [106]. Whether CSL112 protects from kidney injury in this cohort deserves further study.

Hung and colleagues demonstrate in a post-hoc analysis that IL-1 inhibition (canakinumab) improves HDL functionality in patients with stage 3–5 CKD, including those in maintenance hemodialysis,

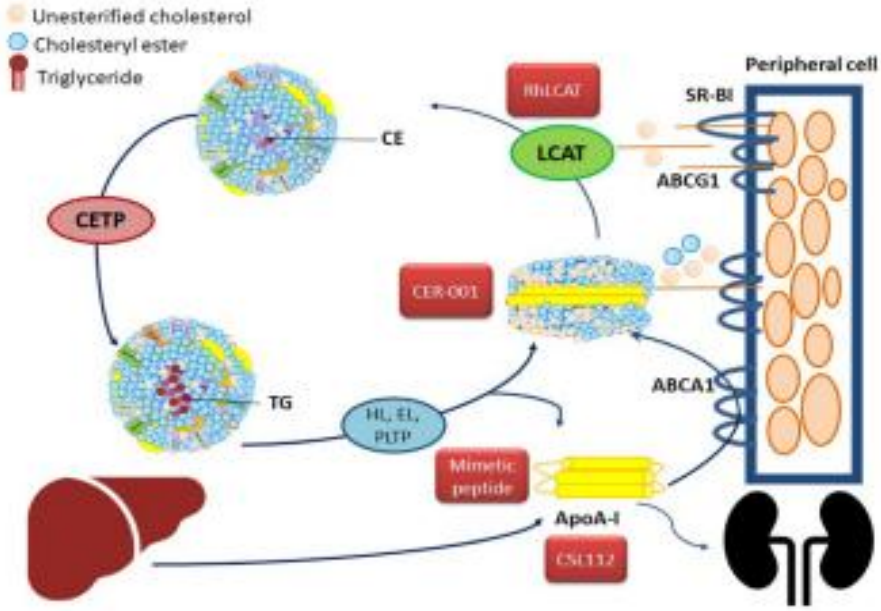

Fig. 2. Potential therapeutic approaches for CKD targeting HDL metabolism. ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; apoA-I, apolipoprotein A-I; CE, cholesteryl esters; CETP, cholesteryl ester transfer protein; LCAT, lecithin:cholesterol acyltransferase; SR-BI, scavenger receptor BI; TG, triglycerides.

however whether these changes produced a delay in CKD progression is not proven [107].

A safe profile of a single infusion of **rhLCAT** was assessed by Shamburek et al. in patients with stable coronary heart disease and low HDL-C [94]. RhLCAT was next tested in a single FLD patient where it corrected lipid abnormalities by esterifying the excess of unesterified cholesterol, thus preventing LpX formation. Consequently, renal function shows modest improvement during treatment, despite the presence of an advanced disease. Interestingly, anemia is also improved [93].

Recently, the HDL mimetic **CER-001** has been tested through a compassionate program in two FLD patients with a very progressive renal disease [92,108]. CER-001 is a novel engineered negatively charged HDL mimetic previously tested for atherosclerosis regression by virtue of its capacity to mobilize cholesterol from peripheral cells [109]. CER-001 normalizes the lipoprotein profile, decreasing LpX in favour of normal-sized LDL [92] and ameliorates or at least slows renal function decline by the reduction of nephrotoxic LpX deposition in the kidney and by removing LpX-induced lipid deposit [92,108]. CER-001 has the potential to be tested in more common kidney diseases characterized by kidney lipid deposits.

The potential targets in HDL metabolism and pharmacological approaches in clinical development are summarized in Fig. 2.

6. Conclusion

During CKD the reduction of HDL-C levels are followed through significant alterations in HDL structure and function, which worsen with the progression of renal impairment. The link between HDL system and kidney is clearly emerged in general population as well in genetic disorder of HDL system, which are characterized by impairment in renal function. In familial LCAT deficiency, leading to dramatic HDL defects and serious kidney disease, the LCAT enzyme, crucial player in HDL metabolism, is reduced and plasma concentrations are associated with CKD progression. Targeting the HDL system, including LCAT enzyme, can be a possible therapeutic strategy to restore plasma HDL-C levels and functionality of HDL particles, potentially slowing CKD progression.

Author contributions

All authors wrote the first draft and revised version of the manuscript. All authors have contributed to the content and have approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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2.1.5 ESTUDIO 5

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RESEARCH ARTICLE Open Access

Elevated triglycerides and reduced high-density lipoprotein cholesterol are independently associated with the onset of advanced chronic kidney disease: a cohort study of 911,360 individuals from the United Kingdom

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Abstract

Background: Increased total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) concentrations, are established risk factors for cardiovascular morbidity and mortality; but their impact on the risk of advanced chronic kidney disease (CKD) is unclear. This study evaluates the association between the different lipid profiles and the onset of advanced CKD using a general population sample.

Methods: This observational study used records of 911,360 individuals from the English Clinical Practice Research Datalink (from 2000 to 2014), linked to coded hospital discharges and mortality registrations. Cox models were used to examine the independent association between the equal quarters of TC, TG, LDL-C, and HDL-C and the risk of advanced CKD, after adjustment for sex and age, and potential effect mediators.

Results: During a median follow-up of 7.5 years, 11,825 individuals developed CKD stages 4–5. After adjustment for sex and age, the hazard ratios (HRs) and confidence intervals (CIs) for CKD stages 4–5 comparing the 4th vs. 1st quarters of TG and 1st vs. 4th quarters of HDL-C were 2.69 (95% CI, 2.49–2.90) and 2.61 (95% CI, 2.42–2.80), respectively. Additional adjustment for potential effect mediators reduced the HRs to 1.28 (95% CI, 1.15–1.43), and 1.27 (95% CI, 1.14–1.41), respectively. There was no evidence of fully adjusted associations with CKD stages 4–5 for levels of either TC or LDL-C.

Conclusions: Elevated TG and reduced HDL-C levels are independently associated with the onset of advanced CKD. Future studies, such as in basic science and randomized trials, are needed to understand whether associations between TG and HDL-C and the development of CKD are causal.

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Keywords: Dyslipidaemia, Cholesterol, Triglycerides, Estimated glomerular filtration rate (eGFR), Chronic kidney disease

Background

Chronic kidney disease (CKD) is an emerging major global public health problem, due to its increasing prevalence, poor outcomes, and substantial cost of renal replacement therapy [1]. CKD has multiple risk factors. Some risk factors for CKD, especially hypertension and diabetes, are well established; others are emerging, and yet others are unknown [2]. Thus, identification and treatment of modifiable risk factors remain the best strategy to prevent and delay CKD development.

Dyslipidaemia, including increased total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) are risk factors for cardiovascular disease (CVD) [3–9]. Data from several clinical trials have confirmed that treatment with a statin, which lowers LDL-C, substantially reduces the incidence of CVD [10, 11]. However, the association of these different lipids with the development of renal dysfunction remains controversial. Some observational studies have demonstrated a significant association between TC [12], TG [13], LDL-C [12], and HDL-C [14] and the development of CKD, whereas an opposite result was observed in other studies [15, 16]. These inconsistent findings may be attributed to reverse causality, different study populations, different adjustments, different definitions of CKD, and concurrent lipid-lowering therapy.

Given the clinical uncertainty, we sought to determine whether TC, TG, LDL-C, and HDL-C are independently associated with the onset of CKD stages 4–5 using large-scale, prospectively collected data from a general population. Also, we aimed to assess how much of the observed lipid-CKD associations are explained by the established risk factors for CKD.

Methods

Study design

The English Clinical Practice Research Datalink (CPRD) provides anonymous data from electronic health records of ≈ 674 primary care practices, covering ≈ 4.4 million active individuals, who represent approximately 8 % of the United Kingdom (UK) population. The CPRD population has been validated to be representative of the UK general population *vis-à-vis* sex, age, and ethnicity [17]. Linkage to area-based social deprivation, Hospitalisation Episode Statistics (HES), and mortality data was available for approximately 75% of all UK CPRD practices. HES database includes admission and discharge dates and diagnostic data (coded with the ICD-10) for several clinical conditions. Scientific approval for our study (15_029R) was given by the Independent Scientific Advisory Committee (ISAC), who govern research using CPRD data.

Study population

The data used here was formerly used to evaluate the association between body-mass index (BMI) and advanced CKD and end-stage renal disease (ESRD) [18]. It included 1,405,016 individuals from the CPRD database with a valid BMI measurement at any time between January 2000 and March 2014 [18, 19]. Details of the initial inclusion and exclusion criteria is described previously [18, 19]. In brief, eligible individuals had to be aged between 20 to 79 years, had BMI between 15 to 60 kg/m^2, and had a minimum of 2 years of data prior to their baseline date [19]. Of 1,405,016 individuals, we selected a secondary population of 1,006,629 (71.6%) with baseline data on TC. The first measurement of TC was the index date, and individuals were censored at the earliest date of - death, transfer out of practice, the last collection of quality data for their practice, or the end of the study in March 2014. To minimize reverse causality, we excluded 95,269 (9.5%) who had less than 2 years of follow-up data, leaving 911,360 individuals for analysis.

Definition of covariates

Covariates were defined at the individual's baseline or, when not present at that date, the most recent when they were recorded in the previous 2 years. For ease, all are labeled "baseline characteristics". We characterized smoking status as current or not. The index of multiple deprivation (IMD), a measure of area-based social deprivation, was characterized into equal tenths, where the first implied the least deprived 10%, and the tenth the most deprived 10%, of the English population. We characterised BMI into five groups: <20, $\geq 20-<25$, $\geq 25-<30$, $\geq 30-<35$, ≥ 35 kg/m^2. Comorbidities included prior diabetes mellitus (defined using diabetes diagnosis or treatment-related codes, a prescription of anti-diabetic medication or hemoglobin $A_{1c} \geq 6.5\%$ [≥ 48 mmol/mol]) and prior CVD (defined using 12 validated cardiovascular outcomes, and includes heart failure, coronary artery, cerebrovascular and peripheral arterial diseases) [18, 20]. Medications included the use of insulin, antihypertensives (renin-angiotensin-aldosterone system inhibitors, thiazides, and any other anti-hypertensive medication),

and statin (simvastatin, atorvastatin, and any other statin).

Definition of predictors and outcomes

Predictors - TC, TG, LDL-C, and HDL-C were determined from laboratory results and were grouped into equal quarters. The outcome of this study was the first record of CKD stages 4–5, derived from internationally recognised clinical definitions and a set of rules integrating mortality records, inpatient procedural or diagnostic codes, and laboratory test/diagnostic results [18, 19]. Where laboratory results were recorded, we calculated estimated glomerular filtration rate (eGFR) from creatinine results using CKD Epidemiology Collaboration (CKD-EPI) formula [21]. CKD stages 4–5 were defined if there were a minimum of two eGFR measurements <30 mL/min/1.73m^2, separated by no less than 3 months, with no eGFR result ≥ 30 mL/min/1.73m^2 in the intervening period [18, 19].

Statistical analyses

Baseline characteristics of the secondary population were stratified by the quarters of lipids and presented as means and standard deviations (SDs) for normally distributed variables, but for asymmetric distributions medians and interquartile ranges (25th–75th percentile) were reported. Number and percentage were reported for categorical variables. The associations between the quarters of lipids and the risk of advanced CKD were quantified using complete case Cox proportional hazards analyses. We constructed two models: Model 1 was adjusted for sex and age; Model 2 was adjusted for sex, age, and potential mediators of the effect, comprising smoking status, IMD tenth, systolic blood pressure (SBP), BMI, eGFR, prior diabetes mellitus, prior CVD, antihypertensive medication, insulin, and statin use, at baseline. Pre-specified subgroup analyses by baseline age, sex, BMI, eGFR, diabetes mellitus, CVD, and statin use were performed to evaluate potential effect modification in the adjusted models. The overall and sex-stratified correlations among the different lipids were assessed using Pearson's correlation coefficients. Furthermore, lipids were analyzed as continuous variables using a restricted spline model adjusted for all the variables in Model 2. The reference values were fixed at the median value of the first quarters - 166, 66.4, and 88.9 mg/dL for TC, TG, and LDL-C, respectively, while for HDL-C, the reference value was fixed at the median value of the fourth quarter, 73.5 mg/dL. All reported p values were two-tailed, and p values less than 0.05 were considered statistically significant. All statistical analyses used R v3.2.2 (www.R-project.org).

Results

Baseline characteristics

Of the 911,360 individuals who had baseline total cholesterol recorded, 53% were women, the mean age of the study population was 54.6 (SD 12.9) years, the mean eGFR was 79.6 (SD 17.7) mL/min/1.73 m^2 and 12% took statins (Table 1). Baseline characteristics of the individuals, stratified by the quarters of baseline TC, TG, LDL-C, and HDL-C are presented in Table 1 and Supplemental Table S1-S3. Age, SBP, TG, and LDL-C increased with higher TC. The frequency of females and overweight (BMI ≥ 25 and <30 kg/m^2) also increased, whereas eGFR levels and frequencies of prior diabetes mellitus, prior CVD, antihypertensive, insulin, and statin use decreased with higher TC levels (Table 1).

Association between quarters of baseline lipids and advanced CKD

During a median follow-up of 7.5 (25th–75th percentile, 4.9–10.1) years, 11,825 individuals developed advanced CKD. The hazard ratios (HRs) and confidence interval (CIs) of the association between the quarters of baseline lipid levels and advanced CKD are shown in Table 2. After accounting for sex and age, the HRs and CIs comparing the 4th vs. 1st quarters of TC, TG, and LDL-C and advanced CKD were 0.62 (95% CI, 0.59–0.65), 2.69 (95% CI, 2.49–2.90), and 0.61 (95% CI, 0.57–0.66), respectively. For HDL-C the HR comparing the 1st vs. 4th quarters and advanced CKD was 2.61 (95% CI 2.42–2.80) (Table 2, Model 1). Adjustment for sex, age, and potential effect mediators reduced all lipid-advanced CKD associations, but the HRs remained significant for TG (HR 4th vs. 1st, 1.28, 95% CI, 1.15–1.43) and HDL-C (HR 1st vs. 4th, 1.27, 95% CI, 1.14–1.41) (Table 2, Model 2).

To further evaluate the association between the lipids and advanced CKD, we fitted the lipids as a continuous variable using a restricted spline model adjusting for sex, age, smoking status, IMD tenth, SBP, BMI, eGFR, prior diabetes mellitus, prior CVD, antihypertensive medication, insulin, and statin use. We found an increasing log-linear relationship between TG and advanced CKD, whereas a decreasing association was observed with HDL-C (Fig. 1). In contrast, there were no associations between TC and LDL-C levels and advanced CKD.

The associations between the quarters of both TG and HDL-C with advanced CKD were consistent across subgroups of the baseline characteristics (Fig. 2). Yet, there was evidence of heterogeneity (p value for interaction <0.05) by sex. Visual inspection of the forest plot indicates a stronger association between quarters of TG (4th vs. 1st) and HDL-C (1st vs. 4th) with advanced CKD in females than males. The sex-stratified correlation

Table 1 Baseline characteristics of the main study population across the quarters of baseline total cholesterol

Variables	Total ($n = 911,360$)	Q1 ($n = 227,711$)	Q2 ($n = 222,006$)	Q3 ($n = 230,520$)	Q4 ($n = 231,123$)
TC, mg/dL, median [25th–75th %]	213 [182–243]	166 [151–174]	197 [189–205]	224 [217–232]	263 [251–286]
Age, years, mean (SD)	54.6 (12.9)	52.0 (14.6)	53.7 (12.9)	55.5 (12.0)	57.2 (11.3)
Female sex, n (%)	479,498 (52.6)	109,838 (48.2)	113,745 (51.2)	121,932 (52.9)	133,983 (58.0)
Current smoker, n (%)	189,234 (20.8)	47,246 (20.7)	44,875 (20.2)	47,006 (20.4)	50,107 (21.7)
IMD tenth > 5, n (%)	381,892 (41.9)	100,777 (44.3)	92,536 (41.7)	93,717 (40.7)	94,862 (41.0)
BMI, kg/m^2, mean (SD)	28.5 (5.8)	28.4 (6.2)	28.5 (5.9)	28.7 (5.7)	28.6 (5.3)
BMI category, kg/m^2, n (%)					
< 20	17,862 (3.2)	6940 (4.5)	4484 (3.2)	3694 (2.7)	2744 (2.1)
≥20, < 25	141,377 (25.0)	42,219 (27.4)	36,159 (25.8)	33,175 (23.8)	29,824 (22.6)
≥25, < 30	214,076 (37.8)	53,723 (34.8)	51,854 (37.0)	54,326 (39.0)	54,173 (41.0)
≥30, < 35	120,029 (21.2)	30,535 (19.8)	29,134 (20.8)	30,366 (21.8)	29,994 (22.7)
≥35	72,311 (12.8)	20,779 (13.5)	18,508 (13.2)	17,686 (12.7)	15,338 (11.6)
SBP, mmHg, mean (SD)	139 (20.9)	134 (19.9)	138 (20.5)	141 (20.7)	144 (21.2)
TG mg/dL, median [25th–75th %]	124 [85.0–177]	97.4 [70.9–136]	112 [79.7–159]	126 [88.6–181]	159 [112–230]
LDL-C, mg/dL, median [25th–75th %]	128 [104–155]	88.9 [77.3–103]	120 [108–128]	143 [131–151]	174 [160–193]
HDL-C, mg/dL, median [25th–75th %]	53.8 [42.9–65.0]	49.5 [40.2–58.0]	53.4 [42.9–64.2]	54.1 [45.6–65.7]	55.7 [46.4–68.1]
eGFR, mL/min/1.73 m^2, mean (SD)	79.6 (17.7)	82.6 (19.0)	80.7 (17.4)	78.7 (16.8)	76.2 (16.7)
Prior diabetes mellitus, yes, n (%)	93,097 (10.2)	36,985 (16.2)	22,607 (10.2)	18,255 (7.9)	15,250 (6.6)
Prior CVD, yes, n (%)	129,643 (14.2)	49,824 (21.9)	30,272 (13.6)	25,451 (11.0)	24,096 (10.4)
Antihypertensive med., yes, n (%)	317,501 (34.8)	88,945 (39.1)	74,634 (33.6)	76,040 (33.0)	77,882 (33.7)
Insulin, yes, n (%)	19,458 (2.1)	9281 (4.1)	4716 (2.1)	3262 (1.4)	2199 (1.0)
Statin category, n (%)					
Simvastatin	60,696 (6.7)	33,010 (14.5)	13,603 (6.1)	8143 (3.5)	5940 (2.6)
Atorvastatin	34,237 (3.8)	18,448 (8.1)	7690 (3.5)	4327 (1.9)	3772 (1.6)
Other statins	12,345 (1.4)	4462 (2.0)	3249 (1.5)	2562 (1.1)	2072 (0.90

Continuous values shown as mean (standard deviation) or median [interquartile range]; categorical values shown as number (percentage)

Abbreviations: *Q* Quarters, *IMD tenth* Index of Multiple Deprivation tenth (First = least deprived, Tenth = most deprived), *BMI* body-mass index, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglycerides, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *CVD* cardiovascular disease, *med* medication, *Other statins* Cerivastatin, Fluvastatin, Pravastatin, or Rosuvastatin

analyses showed that TG levels are negatively correlated with HDL-C levels in both females ($r = -0.36$) and males ($r = -0.35$) (Supplemental Table S4).

Discussion

In this large cohort, nearing a million individuals, with more than 7 years median follow-up we found an independent and graded association between quarters of baseline TG and HDL-C and onset of CKD stages 4–5. The hazard ratio for the highest versus lowest quarters was 1.28 (95% CI, 1.15–1.43) for TG and the lowest versus the highest quarters was 1.27 (95% CI, 1.14–1.41) for HDL-C, after adjustment for sex, age, smoking status, IMD tenth, BMI, SBP, eGFR, prior diabetes mellitus, prior CVD, antihypertensive medication, insulin, and statin use, at baseline. Also, the pattern of the associations between the quarters of TG and HDL-C with CKD stages 4–5 appears to be consistent by pre-defined baseline subgroups, except that there was evidence of a greater effect in women than men. In addition, there was a stronger association between TG and advanced CKD in individuals with eGFR ≥60 mL/min/1.73 m^2 than eGFR <60 mL/min/1.73 m^2. These findings suggest that therapeutic approaches such as fibrates that reduce TG levels and raise HDL-C levels, which were correlated in this study population, may thus reduce the risk of advanced CKD. Conversely, there was no evidence of an association between quarters of TC and LDL-C with risk of CKD stages 4–5, suggesting that lowering TC and LDL-C levels might not have an effect on the prevention of advanced CKD.

Several small studies have found that TG and/or HDL-C levels are associated with the development and/or progression of CKD [13, 22–25]. A systematic review and meta-analysis of longitudinal studies

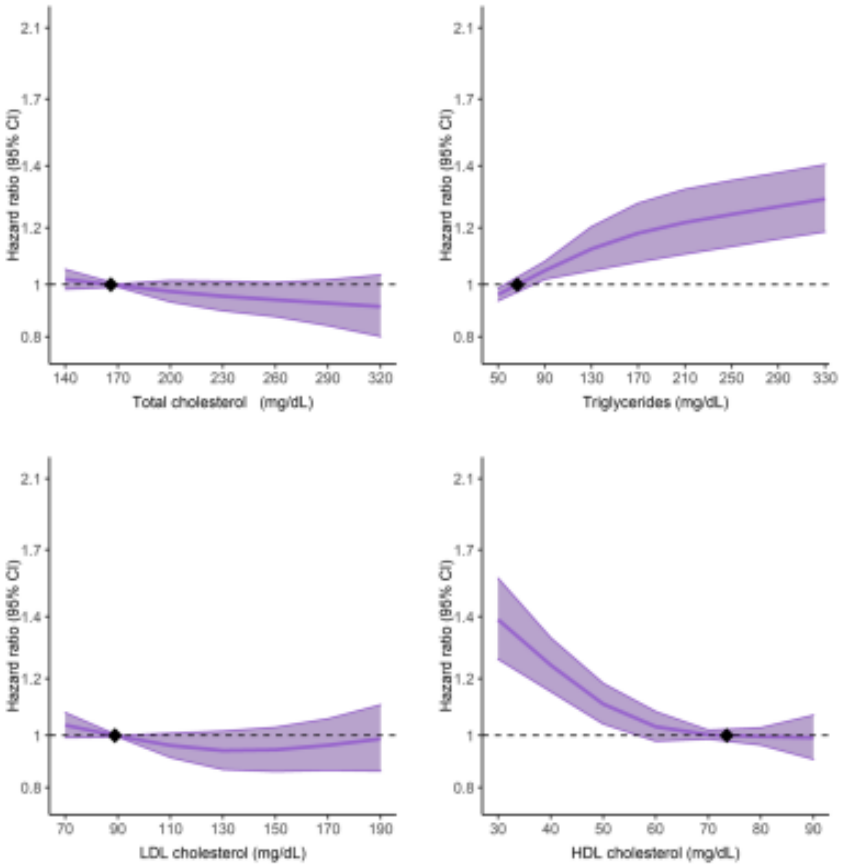

Fig. 1 Hazard ratios (95% confidence intervals) for CKD stages 4–5 by baseline lipid levels. The restricted cubic spline of lipids was fitted in a multivariate model adjusting for sex, age, smoking status, IMD tenth, SBP, BMI, eGFR, prior diabetes mellitus, prior CVD, antihypertensive medication, insulin, and statin use

the case. Second, the completeness of data was another limitation. In our study, 27.5% of individuals had missing TG measurements, 44.5% individuals had missing LDL-C measurements, and 28.6% individuals had missing HDL-C measurements. The decisions to perform cholesterol tests may have been related to confounding by indication if laboratory tests were ordered when individuals presented with illness. Accordingly, individuals with non-measured cholesterol values might differ from those with values recorded. Third, although major risk factors and the issue of reverse causality have been considered, as with any epidemiological study, there are possibilities that residual confounding and selection bias might still exist. Finally, the inclusion of proteinuria would have been helpful as extra confirmation of renal dysfunction, however, it was only available in a small proportion of individuals, so, unfortunately, it was not included in our CKD definition.

Conclusions

Our study found that elevated TG and reduced HDL-C levels are independently associated with a higher risk of CKD stages 4–5. This suggests that TG and HDL-C

(See figure on next page.)

Fig. 2 Association between quarters of baseline TG and HDL-C with the hazard of CKD stages 4–5 by pre-defined subgroups of baseline characteristics. The multivariate model was adjusted for sex, age, smoking status, IMD tenth, SBP, BMI, eGFR, prior diabetes mellitus, prior CVD, antihypertensive medication, insulin, and statin use. Q indicates lipid quarters, and the reference value is Q1 and Q4 for TG and HDL-C, respectively. *P* value < 0.05 indicates the presence of significant interaction by baseline sub-groups

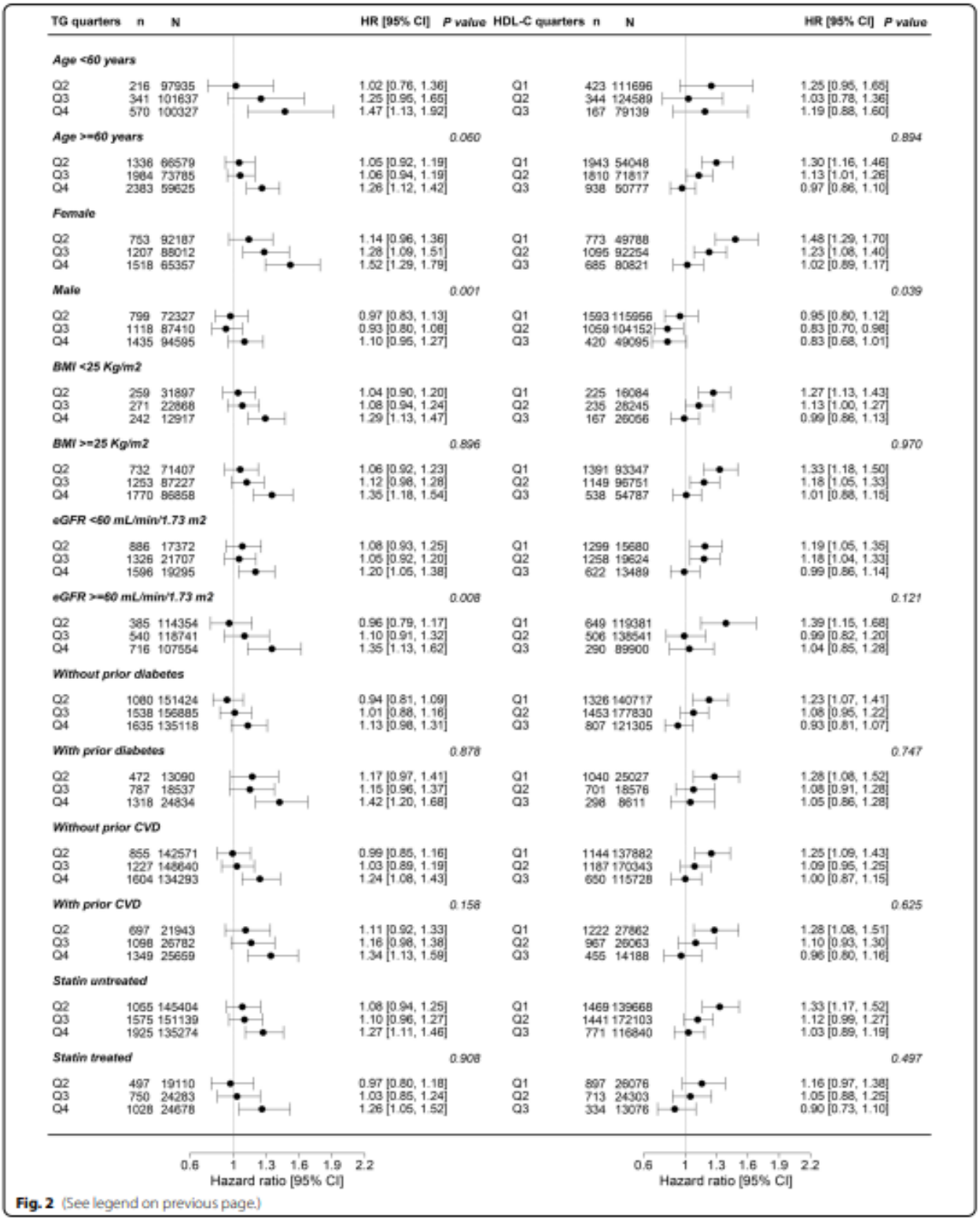

Fig. 2 (See legend on previous page.)

levels might be useful for risk stratification as well as for a potential target to reduce the risk of development of CKD. Future studies are needed to understand the potential causal relationship between TG and HDL-C levels and CKD.

Abbreviations

CKD: Chronic kidney disease; ESRD: End-stage renal disease; TC: Total cholesterol; TG: Triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; IMD: Index of Multiple Deprivation; BMI: Body-mass index; SBP: Systolic blood pressure; eGFR: Estimated glomerular filtration rate; CVD: Cardiovascular disease; CPRD: Clinical Practice Research Datalink; HES: Hospitalisation Episode Statistics; ISAC: Independent Scientific Advisory Committee; HRs: Hazard ratios; CIs: Confidence intervals; SDs: Standard deviations; CSPPT: China Stroke Primary Prevention Trial; ARIC: Atherosclerosis Risk in Communities;; ADVANCE: Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-022-02932-2.

Additional file 1.

Acknowledgments

Not applicable.

Authors' contributions

Both authors have read and approved the manuscript. MW1 wrote the first drafts and perfromed all the data analyses. MW1 and MW2 designed the study and rewrote the original drafts.

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Availability of data and materials

The anonymized patient-level data analyzed in this study cannot be shared for reasons of information governance. However, data can be accessed by application to Clinical Practice Research Datalink (CPRD), https://www.cprd.com/home/.

Declarations

Ethics approval and consent to participate

Ethical and scientific approval for use of CPRD data was obtained from the Independent Scientific Advisory Committee of CPRD (protocol no. 15_029R). Informed consent was waived because data is anonymized for research purposes.

Consent for publication

Not applicable.

Competing interests

MW2 is a consultant to Amgen and Kirin, and has funding from the Australian National Health and Medical Research Council. Other authors declare no competing interests.

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2.1.6 ESTUDIO 6

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Association Between Renal Dysfunction and Low HDL Cholesterol Among the Elderly in China

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Objective: Chronic kidney disease (CKD) and cardiovascular disease (CVD) have a high morbidity and mortality among the elderly. Low levels of high-density lipoprotein cholesterol (HDL-C), a traditional risk marker for CVD, are common in CKD patients. Little is known about the association of low HDL-C with renal dysfunction in the community dwelling population.

Methods: This was a population-based cross-sectional study included 4,753 participants enrolled in a prospective study, the Shanghai Elderly Cardiovascular Health (SHECH) study. Estimated glomerular filtration rate (eGFR), calculated by the Chinese Modification of Diet in Renal Disease (C-MDRD equation), was used to assess renal dysfunction. Associations between renal dysfunction and low HDL-C were evaluated using multiple logistic regression models and restricted cubic splines.

Results: Of 4,649 individuals who met inclusion criteria, 620 (13.34%) had low HDL-C at <40 mg/dl. In the fully adjusted model, lower eGFR of <60 ml/min/1.73 m^2 (OR, 2.03; 95% CI, 1.21–3.43) and marginal eGFR of 60 to 90 ml/min/1.73 m^2 (OR, 1.26; 95% CI, 1.01–1.58) were significantly associated with low HDL-C, compared with normal eGFR of ≥90 ml/min/1.73 m^2. Moreover, consistent findings were obtained in subsidiary analyses using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Fully adjusted cubic spline models indicated a significant dose-response relationship between eGFR and low HDL-C (*P* for non-linearity, 0.356).

Conclusion: In this general elderly population, renal dysfunction was independently and significantly associated with low HDL-C, and the prevalence of low HDL-C increased with decreasing eGFR, such that even slight changes in renal function may be associated with altered lipid levels.

Keywords: renal dysfunction, dyslipidemia, estimated glomerular filtration rate, high-density lipoprotein cholesterol, cardiovascular prevention

INTRODUCTION

China has gained remarkable achievements in controlling the burden of cardiovascular disease (CVD) over the past two decades, and the standardized mortality rate has shown a significant decrease (1). However, the disease burden due to CVD remains severe in patients with chronic kidney disease (CKD) (2). The China Kidney Disease Network (CK-NET) annual report shows that the prevalence of CVD in CKD patients in China is as high as 50.8% (3). CVD is the leading cause of death in CKD patients at different stages of CKD (4), especially in patients with end-stage renal disease (ESRD), the CVD mortality rate is 10–20 times higher than that of the general population (5). On the other hand, population aging is increasing with socioeconomic development. It is estimated that by 2025, there will be 300 million people aged 60 and above in China (6). Studies show that the disease burden in CKD patients increases with age (7, 8), and nearly one-half of CKD patients were aged 60 years or older (3). Therefore, it is imperative to prevent CVD events in the elderly population, especially those with CKD.

High-density lipoprotein cholesterol (HDL-C) is a traditional protective factor for CVD (9), which was thought to achieve its protective effect by mediating the reverse cholesterol transport pathway (10, 11), but it is known to decrease significantly in CKD patients (12, 13). The Framingham Heart Study showed that for every 1 mg/dl (0.026 mmol/L) increase in HDL-C, CVD risk was significantly reduced by 2–3% (14). Since then, more and more epidemiological studies have expanded and validated the findings (15). Previous studies have observed that HDL-C may be related to renal function in adults (16–19). However, the association of low HDL-C with renal dysfunction has not been well-defined, especially in elderly subjects living in the community in China. Since HDL-C changes might also be related to age, gender, body weight, physical activity, medication, disease, etc. (20), the independent association between HDL-C and renal dysfunction in the community elderly population should be estimated after adjusting for these potential confounders.

METHODS

Study Population

The Shanghai Elderly Cardiovascular Health (SHECH) study is a multistage cluster sampling survey of community non-institutionalized residents aged 60 years and older conducted since 2013. Its design details have been described previously (21). Briefly, 4,753 participants aged 60 to 104 years were recruited in the community during 2017 and underwent a comprehensive health screening at Shanghai East Hospital. Participants underwent blood tests after fasting for at least 10 h overnight, and blood samples were sent to the Blood Laboratory of Tongji Medical School affiliated Shanghai East Hospital for measurement within 2 h. In the current analysis, 104 participants were excluded due to missing both HDL-C and serum creatinine (SCr) measurements, so 4,649 participants were included (**Figure 1**).

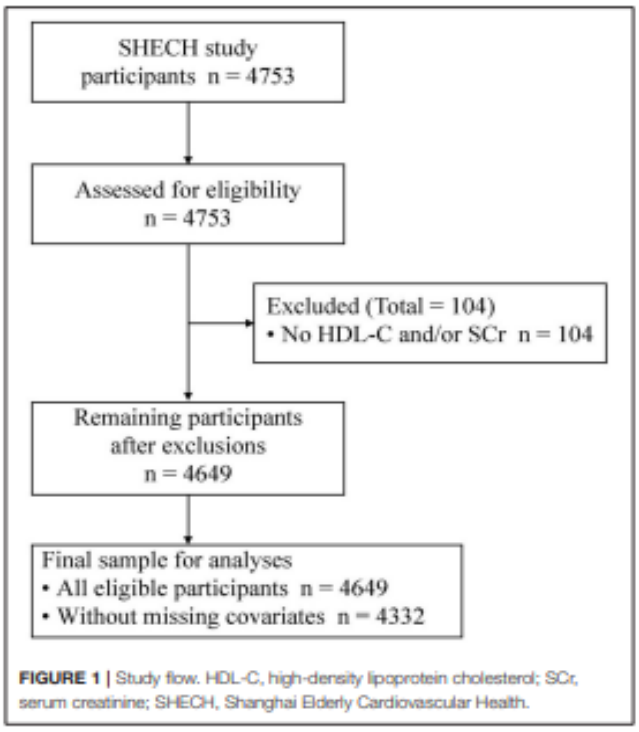

FIGURE 1 | Study flow. HDL-C, high-density lipoprotein cholesterol; SCr, serum creatinine; SHECH, Shanghai Elderly Cardiovascular Health.

Data Collection

Participant information was collected through standardized questionnaires, including demographics, lifestyles, medication and disease history, etc. It was recoded if postmenopausal females were taking hormone replacement therapy as estrogen and/or progestin.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Abdominal obesity was defined as a waist circumference of >90 cm in males and >80 cm in females (22). Creatinine clearance (CCr) was determined by the Cockcroft-Gault equation (23). Current smoking was defined as smoking more than 100 cigarettes in a lifetime and still smoking. Current drinking as drinking 1 or more alcoholic beverages each week during the previous year. Physical activity was considered active if at least 4 days of exercise or recreational activities were performed per week and more than 30 min/day.

Hypertension was defined as an average of two measurements of systolic blood pressure of ≥140 mmHg, or diastolic blood pressure of ≥90 mmHg, or normal blood with concomitant use of antihypertensive agents (24). Diabetes was defined as fasting plasma glucose of ≥7.0 mmol/L or current use of insulin or oral antidiabetic agents. Atherosclerotic cardiovascular disease (ASCVD) was defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or atherosclerotic peripheral artery disease (25). Liver dysfunction was defined as aspartate aminotransferase of >40 U/L, alanine aminotransferase of >50

U/L, or a history of liver disease. All disease histories were confirmed by reviewing the outpatient medical records of primary care in the community health centers.

Two seated blood pressure measurements using a mercury sphygmomanometer after at least 5 min of quiet rest were obtained by trained and certified staff who followed a standard protocol, with the average of two measurements used for the analysis. Hemoglobin AIc was measured using high-performance liquid chromatography (Tosoh Corporation, Tokyo, Japan). SCr, uric acid (UA), urea nitrogen (UN), lipids, and glucose were measured using a biochemical autoanalyzer (Cobas 8000, Roche Diagnostics, Mannheim, Germany).

TABLE 1 | Baseline characteristics of participants according to low HDL-C status.

Characteristics	All (n = 4,649)	Low HDL-C		P-value
		Yes (n = 620)	No (n = 4,029)	
Age (years)	72 (6)	72 (6)	72 (6)	0.560
Male	2,090 (44.96)	371 (59.84)	1,719 (42.67)	<0.001
BMI (kg/m^2)	24.68 (3.46)	25.68 (3.03)	24.52 (3.50)	<0.001
WC (cm)	87.84 (12.22)	90.94 (10.71)	87.37 (12.37)	<0.001
Abdominal obesity	2,527 (54.36)	369 (59.52)	2,158 (53.56)	0.001
Current smoking	971 (20.89)	174 (28.06)	797 (19.78)	<0.001
Current drinking	747 (16.07)	115 (18.55)	632 (15.69)	0.071
Physical activity	3,902 (83.93)	519 (83.71)	3,383 (83.97)	0.871
Statin	377 (8.11)	57 (9.19)	320 (7.94)	0.335
β-Blocker	281 (6.04)	47 (7.58)	234 (5.81)	0.105
Hormones	21 (0.45)	4 (0.65)	17 (0.42)	0.653
ASCVD	728 (15.66)	117 (18.87)	611 (15.17)	0.018
Diabetes	1,640 (35.28)	277 (44.68)	1,363 (33.83)	<0.001
Hypertension	3,454 (74.30)	496 (80.00)	2,958 (73.42)	<0.001
Liver dysfunction	224 (4.82)	43 (6.94)	181 (4.49)	0.008
Homocysteine (μmol/L)	14.90 (12.60–18.00)	16.30 (13.70–19.78)	14.60 (12.50–17.70)	<0.001
SBP (mmHg)	141.98 (20.72)	142.77 (19.65)	141.85 (20.88)	0.298
DBP (mmHg)	80.45 (10.75)	80.63 (10.65)	80.44 (10.70)	0.685
HbAlc (%)	6.00 (5.80–6.50)	6.20 (5.80–6.80)	6.00 (5.80–6.40)	<0.001
FPG (mmol/L)	5.38 (4.94–6.24)	5.65 (5.07–6.96)	5.36 (4.93–6.14)	<0.001
TC (mg/dl)	192 (48)	171 (35)	195 (49)	<0.001
TG (mg/dl)	124 (91–172)	195 (141–274)	118 (88–159)	<0.001
LDL-C (mg/dl)	127 (37)	112 (32)	129 (37)	<0.001
ALT (U/L)	16 (12–21)	18 (13–24)	15 (12–21)	<0.001
AST (U/L)	20 (18–24)	20 (17–24)	20 (18–24)	0.049
UN (mg/dl)	15.78 (4.41)	15.78 (4.81)	15.78 (4.35)	0.977
UA (mg/dl)	5.63 (1.46)	6.17 (1.55)	5.54 (1.43)	<0.001
SCr (mg/dl)	0.87 (0.25)	0.93 (0.29)	0.86 (0.24)	<0.001
CCr (ml/min)	66.47 (18.76)	68.70 (18.12)	66.13 (18.84)	0.002
eGFR (C-MDRD) (ml/min/1.73 m^2)				0.001
60<	126 (2.71)	25 (4.03)	101 (2.51)	
60–90	1,198 (25.77)	189 (30.48)	1,009 (25.04)	
≥90	3,273 (70.40)	400 (64.52)	2,873 (71.31)	
eGFR (CKD-EPI) (ml/min/1.73 m^2)				<0.001
60<	570 (12.26)	105 (16.94)	465 (11.54)	
60–90	3,087 (66.40)	401 (64.68)	2,686 (66.67)	
≥90	940 (20.22)	108 (17.42)	832 (20.65)	

Data are mean (standard deviation), median (interquartile range), or frequency (percentage). Hormones refers to hormone replacement therapy for postmenopausal females as estrogen and/or progestin.

HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; ASCVD, atherosclerotic cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbAlc, hemoglobin Alc; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UN, urea nitrogen; UA, uric acid; SCr, serum creatinine; CCr, creatinine clearance; eGFR, estimated glomerular filtration rate; C-MDRD, Chinese Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Outcome Ascertainment

In this study, estimated glomerular filtration rate (eGFR) was used to assess renal dysfunction. eGFR was calculated using the Chinese Modification of Diet in Renal Disease (C-MDRD) equation where eGFR (ml/min/1.73 m^2) = 186 ∗ SCr (mg/dl)$^{-1.154}$ ∗ age (years)$^{-0.203}$ ∗ 0.742 (if female) ∗ 1.233 (if Chinese) (26) [with subsidiary analyses using eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (27)].

Statistical Analyses

The study outcome was low HDL-C, which was defined as <40 mg/dl according to Chinese guidelines (28). Baseline characteristics of participants were summarized as mean [standard deviation (SD)] or median [interquartile range (IQR)] for continuous variables, and frequency (percentage) for categorical variables.

Statistical significance was tested using Student's *t* test, Welch's *t* test, and Mann–Whitney *U* test for normally or skewed distributed continuous variables and Chi-square test for categorical variables. Pearson's correlation coefficients were calculated to initially assess the correlation between HDL-C and renal function.

Multiple logistic regression models were performed to evaluate the relationship between eGFR and low HDL-C. Three models were fitted: Model I: unadjusted; Model II: adjusted for age, gender, and BMI; and Model III: as for Model II plus smoking, drinking, physical activity, β-blocker, statin, diabetes, liver dysfunction, ASCVD and triglycerides. Restricted cubic splines with three knots at the 25th, 50th, and 75th percentiles were used to simulate the association of eGFR with low HDL-C.

All *P*-values were two sided, and statistical significance was defined as $P < 0.05$. Analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics

Among 4,649 participants, 2,090 (44.96%) were males, 1,640 (35.28 %) had diabetes, and 224 (4.82%) had liver dysfunction. The mean (SD) age was 72 (6) years; the mean (SD) eGFR was 101.77 (22.56) and 77.27 (14.35) ml/min/1.73 m^2 for the C-MDRD and CKD-EPI equations, respectively; the mean (SD) HDL-C was 55 (16) mg/dl. Low HDL-C was observed in 620 participants (13.34%). Compared with those with non-low HDL-C, participants with low HDL-C were more likely to be males, obese, current smokers, hypertensive, diabetic, and ASCVD patients (**Table 1**).

HDL-C and Renal Function

The preliminary exploration of HDL-C and renal function is presented in **Table 2**. HDL-C was positively correlated with UN, UN/SCr, and eGFR, while negatively correlated with UA, SCr, and CCr ($P \leq 0.010$). Although there were significant correlations between HDL-C and renal function, all were relatively weak. Therefore, further analysis was performed.

TABLE 2 | Pearson's correlation coefficients between HDL-C and renal function.

	HDL-C		
	r	95% CI	*P*-value
UA	−0.261	−0.289 ~ −0.236	<0.001
UN	0.038	0.010 ~ 0.069	0.010
SCr	−0.140	−0.167 ~ −0.114	<0.001
UN/SCr	0.173	0.143 ~ 0.203	<0.001
CCr	−0.153	−0.181 ~ −0.122	<0.001
eGFR, C-MDRD	0.047	0.017 ~ 0.080	0.002
eGFR, CKD-EPI	0.048	0.017 ~ 0.079	0.001

UN, urea nitrogen; UA, uric acid; SCr, serum creatinine; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; CCr, creatinine clearance; eGFR, estimated glomerular filtration rate; C-MDRD, Chinese Modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CI, confidence interval.

eGFR and Low HDL-C

Decreased eGFR (C-MDRD) showed a significant independent association with low HDL-C. Compared with normal eGFR, the unadjusted odds ratios (OR) for lower and marginal eGFR were 1.78 (95% CI, 1.13–2.79) and 1.35 (95% CI, 1.12–1.62), respectively (Model I). The association was further strengthened, and the ORs were 1.81 (95% CI, 1.13–2.90) and 1.33 (95% CI, 1.10–1.62), respectively, after adjustment for age, gender, and BMI only (Model II). The association with low HDL-C was significantly higher in lower (OR, 2.03; 95% CI, 1.21–3.43) and marginal eGFR (OR, 1.26; 95% CI, 1.01–1.58) after further adjustment for lifestyles, medication and disease history, and triglycerides (Model III). eGFR, as a continuous variable, was significantly associated with low HDL-C (unadjusted OR (95% CI) per SD decrease: in Model I: 1.15 (1.05, 1.25), $P = 0.002$; multivariable-adjusted OR (95% CI): in Model II: 1.16 (1.06, 1.27), $P = 0.001$; in Model III: 1.17 (1.06, 1.30), $P = 0.002$) (**Table 3** and **Figure 2**). To further evaluate whether the relationship between eGFR and low HDL-C was linear, a restricted cubic spline model was fitted, and no evidence of non-linearity was found (*P* for non-linearity, 0.356, **Figure 3A**).

Subsidiary Analyses

To further confirm the findings, the CKD-EPI equation was used instead of the C-MDRD equation to calculate eGFR for verification (27). The results revealed that the association of low HDL-C with lower eGFR was significantly increased compared with normal eGFR in any of the models, and the ORs were increased with adjustment for lipid metabolism confounders (OR (95% CI): in Model I: 1.74 (1.30, 2.33), $P < 0.001$; in Model II: 2.05 (1.46, 2.88), $P < 0.001$; in Model III: 2.05 (1.44, 2.92), $P < 0.001$) (**Table 4**). However, the association of low HDL-C with marginal eGFR was not statistically significant compared with normal eGFR in any of the models (all $P > 0.1$, **Table 4**). Notably, the strength of association and non-linear relationship between eGFR, as a continuous variable, and low HDL-C remained generally consistent [fully adjusted OR (95% CI), 1.17 (1.06, 1.29), **Table 4**; *P* for non-linearity, 0.602, **Figure 3B**].

TABLE 3 | Odds ratios (95% CI) for eGFR, calculated by C-MDRD equation, in relation with low HDL-C.

eGFR (ml/min/1.73 m², median)	Model I		Model II		Model III	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Per SD decrease*	1.15 (1.05–1.25)	0.002	1.16 (1.06–1.27)	0.001	1.17 (1.06–1.30)	0.002
60< (53.16)	1.78 (1.13–2.79)	0.012	1.81 (1.13–2.90)	0.013	2.03 (1.21–3.43)	0.008
60–90 (80.75)	1.35 (1.12–1.62)	0.002	1.33 (1.10–1.62)	0.004	1.26 (1.01–1.58)	0.039
≥90 (108.49)	1.00 [ref.]		1.00 [ref.]		1.00 [ref.]	
Trend	$P < 0.001$		$P < 0.001$		$P = 0.002$	

Model I: unadjusted. Model II: adjusted for age, gender, and BMI. Model III: as for Model II plus smoking, drinking, physical activity, β-blocker, statin, diabetes, liver dysfunction, ASCVD, and triglycerides.

SD, standard deviation; CI, confidence interval; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; C-MDRD, Chinese Modification of Diet in Renal Disease.

**One SD is equal to 22.6.*

DISCUSSION

This study found that eGFR was significantly associated with low HDL-C in community dwelling elderly, and this relationship was independent of identified HDL-C confounders, including age, gender, BMI, smoking, drinking, physical activity, β-blocker, statin, diabetes, liver dysfunction, ASCVD, and triglycerides. The findings also confirm some of the associations previously found in population studies: HDL-C levels were lower in males than females (29, 30), decreased with increasing BMI and triglycerides (31, 32), and were higher in individuals drinking alcohol (33, 34).

The decrease in eGFR is thought to lead to low HDL-C, which may be related to the significant changes in proteomics and lipidomics. Vaziri et al. found ApoA-I levels in ESRD patients were significantly decreased, due to both impaired synthesis and enhanced catabolism of ApoA-I in CKD patients. ApoA-I is an essential component of HDL particles, and its concentration decreases in CKD leading to a decrease in HDL-C (35). Meanwhile, the lack of hepatic triacylglycerol lipase in CKD patients leads to a decrease in cholesterol in HDL particles and an increase in triacylglycerol (36). On the other hand, oxidative stress and inflammatory reactions, uremic toxins, etc. in CKD patients cause denaturation, oxidation, and carbamylation of ApoA-I and other protein components of HDL particles, which affects the binding of HDL to cell surface cholesterol transporters, resulting in a decrease in HDL's ability to promote cholesterol efflux (37, 38). This in turn impairs the reverse cholesterol transport, and consequently promotes foam cell formation, accelerated atherosclerosis, endothelial dysfunction, oxidative stress, systemic inflammation, and glomerulosclerosis, which would exacerbate the occurrence and development of CVD or ESRD (12). Thus, it might be predicted that low HDL-C would be associated with decreased eGFR.

Conversely, previous studies have shown that low HDL-C can predict a deterioration in renal function (16–19). Low HDL-C could independently predict an increase in renal dysfunction in 840 patients with different kidney diseases, from the MDRD study (16), which was consistent with the result of the Atherosclerosis Risk in Communities (ARIC) cohort study (17). Bowe et al. used the U.S. Veterans Administration (VA) databases to conduct a retrospective cohort study of nearly 2 million male veterans and found that low HDL-C was significantly associated with the risk of incident kidney disease and its progression (18). Meanwhile, it has been reported that low HDL-C may be a surrogate marker of poor overall metabolic health (18). From our findings, it could be suggested to some extent that even in the general population, decreased eGFR may contribute to poor overall metabolic health and thus indirectly enhance CVD. Lees et al. incorporated eGFR into the traditional CVD risk prediction model and found that eGFR significantly enhanced the risk prediction ability of the models (39), which somewhat reflected the results of the present study. Additionally, data from UK Biobank showed that just examining total cholesterol and HDL-C could predict the impact of blood lipids on CVD risk (40). Consequently, in the general population, especially those with renal dysfunction, more attention should be paid to HDL-C levels, which may help predict the development of CVD as early as possible.

The association of low HDL-C with marginal eGFR presented different results in the analysis using C-MDRD and CKD-EPI equations, which may be attributed to differences in the original populations used to develop the equations. The cohort used to develop the MDRD equation was CKD patients, and the relationship between GFR and SCr concentrations is different among healthy and CKD individuals (41). Consequently, it is not unexpected to observe that the MDRD equation systematically underestimates GFR at high GFR levels (>60 ml/min/1.73 m²). This systematic underestimation at the population level leads to overestimations of CKD stage III prevalence (eGFR <60 ml/min/1.73 m²) in the general population. However, the population used to develop the CKD-EPI equation was mostly individuals with GFR > 60 ml/min/1.73 m², which somewhat corrected the bias of the MDRD equation (27). Hence, the performance of the CKD-EPI equation was particularly improved for individuals with GFR >60 ml/min/1.73 m², which was also seen in the European elderly population (42). However, it is noteworthy that the CKD-EPI equation provided only marginal improvement in precision compared with the MDRD equation (43, 44). Murata et al. compared the accuracy of the MDRD

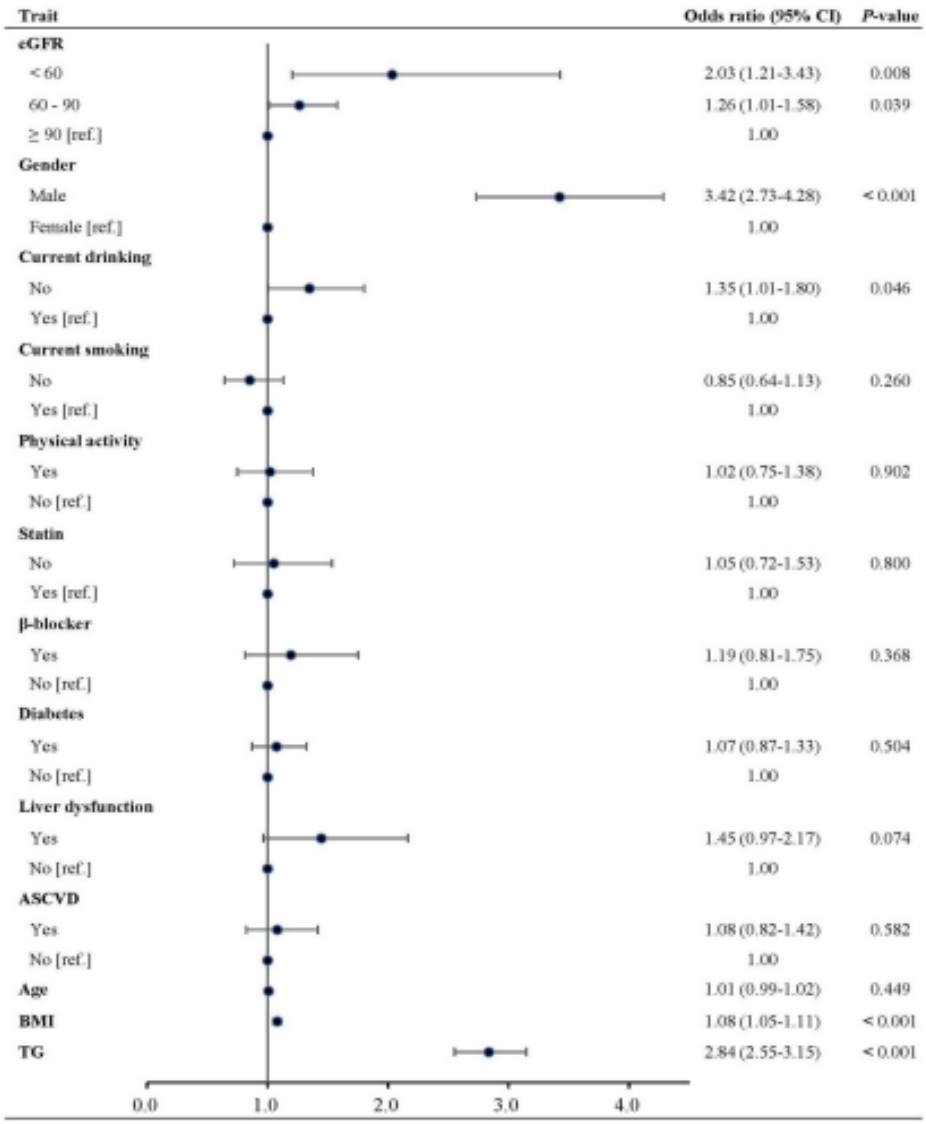

FIGURE 2 | Multivariable-adjusted odds ratios of low HDL-C in participant subgroups. HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; TG, triglycerides.

and CKD-EPI creatinine equations for estimating GFR in 5,238 patients and confirmed that the CKD-EPI creatinine equation underestimated GFR to a lesser extent than the MDRD equation in pre- and post-donation kidney donors. However, in patients with native CKD, renal transplant recipients and other organ recipients, the CKD-EPI equation did not perform better or was even slightly worse than the MDRD equation with a trend to overestimation (45). This overestimation in CKD patients could be the price of improved performance at higher GFR levels (44, 46). Furthermore, van den Brand et al. investigated 6,097 Caucasian participants and calculated eGFR using the MDRD and CKD-EPI equations and found that the CKD-EPI had higher estimates of GFR for subjects aged <70 years compared with the MDRD equation, but lower estimates for those aged 70 years and older (47). Hence, it might be considered that MDRD and CKD-EPI equations help to complement each other for validation in epidemiological studies.

This study had several strengths, including a large natural population of older participants, numerous confounders, medical record review to determine disease status and use of the China-specific eGFR definition. These all help in reducing bias.

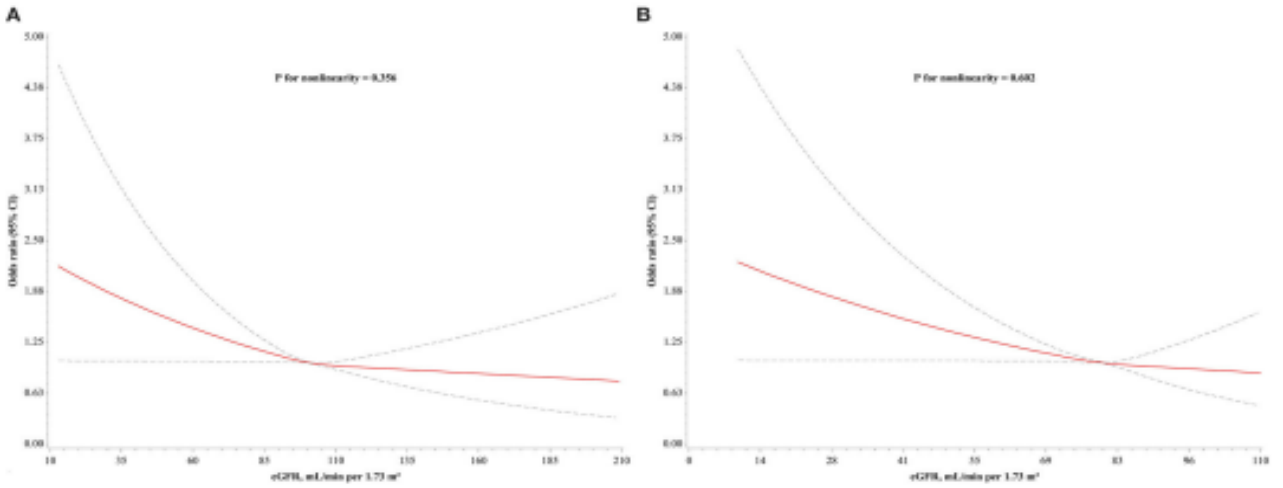

FIGURE 3 | Adjusted dose-response relationship between low HDL-C and eGFR. **(A)** eGFR calculated using C-MDRD equation; **(B)** eGFR calculated using CKD-EPI equation. Odds ratios (95% CI) were obtained from restricted cubic splines with knots placed at 25, 50, and 75th percentiles of eGFR distribution. Reference points were median values of eGFR (**A**: 101 ml/min/1.73 m^2; **B**: 80 ml/min/1.73 m^2). Models were adjusted for age, gender, BMI, smoking, drinking, physical activity, β-blocker, statin, diabetes, liver dysfunction, ASCVD, and triglycerides. Solid line represents odds ratios and dotted lines represent 95% CI. HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; C-MDRD, Chinese Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval.

TABLE 4 | Odds ratios (95% CI) for eGFR, calculated by CKD-EPI equation, in relation with low HDL-C.

eGFR (ml/min/1.73 m^2, median)	Model I		Model II		Model III	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Per SD decrease*	1.17 (1.08–1.27)	<0.001	1.21 (1.10–1.33)	<0.001	1.17 (1.06–1.29)	0.001
60< (51.97)	1.74 (1.30–2.33)	<0.001	2.05 (1.46–2.88)	<0.001	2.05 (1.44–2.92)	<0.001
60–90 (78.03)	1.15 (0.92–1.44)	0.226	1.19 (0.93–1.52)	0.159	1.23 (0.93–1.62)	0.141
≥90 (92.66)	1.00 [ref.]		1.00 [ref.]		1.00 [ref.]	
Trend	$P < 0.001$		$P < 0.001$		$P < 0.001$	

Model I: unadjusted. Model II: adjusted for age, gender, and BMI. Model III: as for Model II plus smoking, drinking, physical activity, β-blocker, statin, diabetes, liver dysfunction, ASCVD, and triglycerides.

SD, standard deviation; CI, confidence interval; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

**One SD is equal to 14.4.*

Limitations of the present study should be considered. Firstly, given the nature of cross-sectional studies, it remains unclear whether the association between eGFR and low HDL-C changes over time, and therefore the causality between the two cannot be determined. Secondly, although confounders affecting HDL-C levels have been considered as much as possible, residual unmeasured confounders may remain. Thirdly, all participants were older adults in the Chinese community, making it difficult to generalize to different ethnic populations. Furthermore, over 70% of subjects in this sample had normal renal function according to the C-MDRD equation, which was markedly higher than the elderly population in the Caucasian community (48). Though previous studies have illustrated that the prevalence of CKD was lower in Asians than in Caucasians after adjusting for sex and age (49), considering that GFR of individuals decreases with age, the possibility that this may be an artifact of the C-MDRD equation could not be ruled out. Lastly, given the nature of epidemiological studies, multiple assessments of renal functional status were not achievable. Though poor eGFR may represent an episode of acute kidney injury, this is less likely in community populations. There are limitations to the estimation of GFR in older adults regardless of equations applied, but importantly, these equations are all frequently used in the clinical setting so that understanding the association between eGFR and lipids remains relevant. It is also reassuring that, despite these limitations, similar strength of association and dose-response relationships existed between renal dysfunction and low HDL-C, irrespective of methods used to define renal dysfunction.

CONCLUSION

In this general elderly population, renal dysfunction was strongly associated with low HDL-C, independent of established HDL-C confounders. There was a dose-response relationship between low HDL-C and eGFR, with low HDL-C frequency increasing with decreasing eGFR. These findings raise the possibility that even slight changes in renal function may be associated with lipid levels in humans. Thus, it is speculated that there may be a reciprocal causality between renal dysfunction and lipid changes, which warrants further exploration in prospective studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Tongji University Affiliated Shanghai East Hospital (2017-010). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AY was responsible for conceptualization, formal analysis, and writing the manuscript. BT and YZ were responsible for revising the manuscript. LY was responsible for investigation and data collection. HF, ZL, YZ, and LZ were responsible for resources, supervision, and project administration. LZ was responsible for funding acquisition. All authors have read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.644208/full#supplementary-material

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2.1.7 ESTUDIO 7

biomedicines

MDPI

Review

New and Emerging Biomarkers in Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) represents a major and widespread global health challenge. It affects over 800 million people worldwide, which is approximately 13% of the world's population. Over the past 20 years, it has consistently ranked among the leading causes of death. As a result of its typically painless and asymptomatic presentation in the early stages of the disease, CKD is frequently diagnosed late, when the patient is already suffering from serious complications. In recent years, studies have identified novel biomarkers associated with the pathophysiology of CKD, including chronic inflammation, tubular injury, and CKD-related outcomes such as bone and mineral metabolism disorders, cardiovascular events, and all-cause mortality. Identifying and using these emerging biomarkers—like kidney injury molecule, N-acetyl–D-glucosaminidase, ficolins, the NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome, soluble suppression of tumorigenicity-2, galectin-3, growth differentiation factor-15, soluble urokinase-type plasminogen activator receptor, sclerostin, the Dick-kopf proteins, and indexes such as the systemic inflammation response index—may lead to a significant advancement in early diagnosis, risk stratification, and personalized treatment strategies for CKD patients. Despite their potential, the routine clinical use of these novel biomarkers remains limited due to challenges such as high costs and the lack of standardized testing methods. There is still considerable room for advancement in both the diagnosis and management of CKD. Hopefully, increasingly more new biomarkers will become usable in clinical practice, ultimately improving care quality and outcomes for patients with CKD.

Keywords: inflammation; kidney biomarkers; chronic kidney disease; cardiorenal syndrome risk; kidney physiopathology; kidney injury

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1. Introduction

Chronic kidney disease (CKD) is a widespread global health issue affecting approximately 13% of the world's population, which means that it afflicts over 800 million people [1]. It has remained one of the most prominent causes of death over the past two decades [2,3]. The rise in risk factors, particularly diabetes mellitus, hypertension, cardiovascular disease, and obesity, compounds the burden of CKD in the population [1]. CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health [4]. The pathophysiology of CKD is complex, but the main pathological hallmarks include fibrosis, tubular atrophy, and chronic inflammation. The progression of this process is primarily driven by proteinuria, hypoxia, and oxidative stress [5]. Early detection of CKD provides opportunities to effectively attenuate

the progression of renal dysfunction and prevent outcomes associated with CKD. However, primarily due to its typically painless and initially asymptomatic presentation, CKD is frequently diagnosed in the later stages. Currently, in clinical practice, the diagnosis and staging of CKD are made by estimating glomerular filtration rate (GFR) using creatinine and cystatin C or by albuminuria (ACR) [4]. These diagnostic criteria reflect renal function based on glomerular filtration. However, studies from recent decades identified novel biomarkers associated with the pathophysiology of CKD, including chronic inflammation, tubular injury, and CKD-related outcomes. These markers enable a more specific representation of overall kidney function and CKD complications.

2. Methodology

In this narrative review, we attempted to provide a comprehensive overview of recent advances in the identification of novel biomarkers for CKD. We conducted a comprehensive search of the relevant literature, mainly studies published in the last decade. Both clinical studies (observational studies, cohort studies, clinical trials) and preclinical research (animal models, mechanistic studies) were included to provide a broad understanding of biomarker relevance from basic science to clinical application. Studies not available in English, conference abstracts without full texts, and data still awaiting publication were excluded.

We strived to include a wide array of biomarkers and present an integrated view on both established and newly emerging biomarkers, with special attention to those that are rarely mentioned in previous reviews, such as ficolins or Dick-kopf proteins, and others that have only recently gained attention in CKD research, like inflammatory indices. Through a comprehensible pathophysiological framework and extending the understanding of biomarkers' functions beyond their primary roles, we tried to place a focal point on the translation of these into clinical practice.

A major limitation of this review is the fact that, given our focus on covering a broad spectrum of biomarkers, the depth of discussion for each individual marker was necessarily limited.

3. Biomarkers of Tubular Secretion

Creatinine, cystatin C, and estimated glomerular filtration rate (eGFR) are the primary parameters used for the definition and staging of chronic kidney disease (CKD). These markers reflect renal function based on glomerular filtration. However, their utility is limited, particularly in detecting the early stages of CKD [6]. Consequently, there is an urgent need to identify more sensitive biomarkers for the early detection of CKD that may more comprehensively represent overall kidney function. Considering tubular injury as a key mechanism in the progression of CKD [7], biomarkers of tubular secretion may prove useful for diagnosing this condition.

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein with undetectable expression in the normal kidney [8]. KIM-1 consists of an immunoglobulin-like domain and an extracellular mucin domain. Renal injury factors lead to the upregulation of KIM-1 expression by proximal tubule epithelial cells. The mucin domain is shed, resulting in elevated levels of KIM-1 in urine and plasma [9,10]. KIM-1 serves as a sensitive biomarker of proximal tubule injury in both acute kidney injury (AKI) and chronic kidney disease (CKD) [10–12]. In a cross-sectional study by Waikar et al. (2016), a strong positive correlation was demonstrated between urinary KIM-1 level and the albumin-to-creatinine ratio (ACR) in individuals with and at risk for CKD (95% CI: 0.15-0.17), suggesting its potential role in the diagnosis and prognosis of CKD [13]. Urinary KIM-1 levels increased progressively with declining eGFR, until eGFR fell below 15 mL/min/1.73 m², likely re-

flecting a reduction in tubular mass responsible for KIM-1 expression [13]. Waikar et al. also reported reduced urinary KIM-1 levels in users of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), which correlates with the nephroprotective properties of these classes of medications [13–15]. The upregulation of KIM-1 has also been observed in various glomerulopathies, including diabetic glomerulopathy and IgA nephropathy [16,17]. Chronic KIM-1 expression is a component of the pathogenesis of chronic kidney disease. It plays a significant role in the progression of inflammation and tubulointerstitial fibrosis in renal tissue, partly by promoting the secretion of monocyte chemoattractant protein-1 (MCP-1) [18]. In conclusion, KIM-1 is not only a sensitive biomarker for CKD but can also be a potential therapeutic target in kidney disease [18,19].

N-acetyl–D-glucosaminidase (NAG) represents another urinary biomarker of proximal tubular injury [20]. This lysosomal enzyme has been investigated as a potential predictor of diabetic nephropathy, highlighting the role of tubular injury in the early stages of diabetic kidney disease [21,22]. Urinary NAG excretion can be detected before the appearance of microalbuminuria and macroalbuminuria in diabetic kidney disease (DKD) [23]. NAG is not filtered through the glomerulus due to its relatively high molecular weight, but it may appear in the urine as a consequence of tubular injury, including exposure to high urinary glucose [24,25]. Urinary NAG levels are not only significantly higher in diabetic patients but also reflect renal impairment, indicating the promising utility of NAG in monitoring diabetic kidney disease (DKD) [26]. Furthermore, Kim et al. demonstrated that urinary NAG may reflect glycemic control in patients with type 2 diabetes mellitus due to its correlation with glucometabolic parameters [27]. More recently, the application of NAG in the real-time monitoring of kidney function in DKD was presented. Ten et al. fabricated a NAG-responsive NIR-II fluorescent nanoprobe that specifically interacts with NAG to produce NIR-II fluorescence signals, enabling the noninvasive detection of kidney dysfunction [28].

Uromodulin, also known as Tamm–Horsfall protein, is a renal-specific protein expressed exclusively by the thick ascending limb of the loop of Henle and the distal convoluted tubule [29]. It is a major protein present in the urine of healthy individuals [30,31]. Numerous studies demonstrated multiple physiological functions of uromodulin, including ion reabsorption in the thick ascending limb, blood pressure control, protection against kidney stone formation, and immunomodulation [32–37]. Additionally, uromodulin prevents bacterial urinary tract infections. It counteracts the adherence of Escherichia coli to the urothelial surface by binding specifically to type 1 fimbriated Escherichia coli [38,39].

Both urinary and serum uromodulin have been investigated in the context of CKD. Distal tubular damage leads to lessened urinary excretion of Tamm–Horsfall protein [40–42]. It is also modulated by common variants in the UMOD gene, which encodes uromodulin [43]. In a case–control study, Köttgen et al. identified an association between a single-nucleotide polymorphism in the UMOD region (rs4293393) and elevated uromodulin concentrations as a predictor of CKD onset [44]. Urinary uromodulin serves as a biomarker of kidney tubulointerstitial damage [45], a key pathological mechanism affecting CKD development [46]. Urinary uromodulin level has been shown to predict rapid progression to end-stage kidney disease (ESKD) in CKD patients within 1 year [47].

According to research, serum uromodulin may also serve as a biomarker for kidney function assessment [48–50]. In an observational study including 170 patients with CKD, Fedak et al. demonstrated a strongly positive correlation between serum uromodulin concentrations and eGFR [51]. Importantly, the relationship between serum uromodulin and eGFR was independent of age, sex, BMI, and body surface area, enhancing the potential diagnostic utility of this protein [51]. Serum uromodulin, as a marker of tubular secretion,

represents functional nephron mass and kidney function as a whole [49,52]. In this way, serum uromodulin can help identify the early stages of CKD, including the creatine-blind range of CKD [52,53]. Similarly to urinary uromodulin, serum uromodulin may be used to identify high-risk groups for the incidence of ESKD in CKD patients [54]. Its level is also associated with a common CKD outcome—cardiovascular disease [55].

What is more, uromodulin has been implicated in various health conditions associated with CKD. Low serum uromodulin levels may be correlated with kidney function and renal disease activity in lupus nephritis and ANCA-associated glomerulonephritis [56,57]. In the course of Fabry disease, uromodulin excretion is also disturbed, ranging from normal to markedly decreased or even absent. However, a study of 15 male Fabry disease patients has shown that enzyme replacement therapy leads to the normalization of urinary uromodulin excretion [58]. Mutations in the gene encoding uromodulin underlie medullary cystic kidney disease type 2 and familial juvenile hyperuricemic nephropathy [59]. In these kidney diseases, impaired uromodulin export dynamics lead to an intracellular accumulation of this protein in the tubular epithelium of the thick ascending limb of Henle's loop. Consistently, urinary uromodulin excretion is reduced [60].

In conclusion, uromodulin is a promising biomarker for CKD, including the early stage of CKD. Furthermore, given its important role in maintaining kidney function, this protein may serve as a predictor of CKD onset and progression and could represent a novel target for therapeutic intervention.

The Klotho protein, another potential biomarker for CKD, was first identified in 1997 as an anti-aging molecule [61]. Subsequent research has established the role of Klotho deficiency in the aging process and the pathogenesis of age-related diseases [62–65]. This protein is predominantly expressed in the kidney, specifically in both the proximal and distal tubules [66]. Additionally, it has also been detected in the epithelium of the choroid plexus in the brain, as well as in the heart, pituitary gland, parathyroid gland, and other tissues [67]. Klotho is a transmembrane protein that functions as a coreceptor for fibroblast growth factor (FGF) [68]. Its extracellular domain undergoes shedding, resulting in the release of a soluble form into the bloodstream and urine [69]. Many studies have investigated the correlation between circulating soluble Klotho levels and kidney function. The majority indicated a positive correlation between serum and urine Klotho levels and estimated glomerular filtration rate (eGFR) in CKD [70–72]. In contrast, Seiler et al. reported no link between plasma Klotho and kidney function [73]. These divergences are likely due to variability in assay methods and the heterogeneity of CKD populations. However, Klotho is a substantiated renoprotective molecule, and its deficiency plays an important role in CKD progression [74–76]. It may serve as a potential biomarker for the early stages of CKD and a therapeutic target, and it can also predict CKD complications, though there is a requirement for the standardization of measurement methods for its clinical application.

Proteins in the Dickkopf (DKK) family are antagonists and modulators of the Wnt/beta-catenin signaling pathway [77]. This family encompasses four key proteins: Dick-kopf-1, Dick-kopf-2, Dick-kopf-3, and Dick-kopf-4 [77]. Of these, Dick-kopf-1 and Dick-kopf-3 have recently emerged as potentially significant novel biomarkers in the course of not only the diagnosis and progression of CKD complications due to their direct mechanism of action, as well as their involvement in "cross-talk" with other body tissues, but also as a potential prognostic marker [78,79].

Dickkopf-3 (DKK-3) is a urinary glycoprotein secreted as a response to stress and is expressed in tubular cells after injury [80], serving as a marker for ongoing tubular stress with the potential of serving as a biomarker of CKD progression; currently, several studies have confirmed its potential as an ongoing biomarker of renal injury [81]. Urinary levels of DKK-3 (uDKK-3) have been associated with poor renal survival in CKD and estimated

eGFR decline [82]. High urinary levels of DKK-3 have demonstrated increased eGFR loss [83] in resistant hypertension CKD patients, where eGFR loss was higher even up to 24 months later [82]. This was especially the case when uDDK-3 was greater than or equal to 400 pg/mL, resulting in a statistically significant eGFR decline as well as the more frequent appearance of proteinuria [82]. uDDK-3 has also been correlated with an increased risk of CKD progression in patients diagnosed with chronic obstructive pulmonary disease (COPD) [83].

Dickkopf-1, as a protein involved in the regulation of bone metabolism, will be further discussed in subsequent sections of this review.

The biomarkers mentioned in the text are presented in Table 1.

Table 1. Biomarkers of tubular secretion.

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
KIM-1 (Kidney Injury Molecule-1)	Proximal tubule epithelial cells	Marker of proximal tubule injury	Elevated in AKI and CKD; correlates with ACR, associated with inflammation and fibrosis
NAG (N-acetyl-á-D-glucosaminidase)	Lysosomes of proximal tubule cells	Enzyme indicating tubular injury	Early marker of diabetic nephropathy (before albuminuria); reflects renal impairment and glycemic control
Uromodulin (Tamm–Horsfall Protein)	Thick ascending limb of Henle's loop and distal convoluted tubule	Involved in ion transport, immunity, and prevention of kidney stones	Urinary and serum levels predict CKD onset and progression; reflects tubular damage and nephron mass
Klotho	Proximal and distal renal tubules; other tissues	Anti-aging and renoprotective molecule	Positive correlation with eGFR; deficiency promotes CKD progression
Dickkopf-3 (DKK-3)	Tubular epithelial cells in kidneys (expressed in response to injury)	Urinary stress glycoprotein marker; reflects ongoing renal tubular stress and injury	Elevated urinary DKK-3 linked to eGFR decline and CKD progression; associated with proteinuria and poor renal outcomes; predictor of CKD progression in COPD and resistant hypertension

Abbreviations: AKI, acute kidney injury; ACR, albumin–creatinine ratio; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

4. Inflammatory Biomarkers

Impaired kidney function leads to the accumulation of uremic toxins and oxidative stress, activating pro-inflammatory pathways. Over the years, many inflammatory markers have been associated with chronic kidney disease. They are not only indicators of systemic inflammation but can also be used as predictors of cardiovascular disease, stroke, progression of kidney damage, and loss of renal function, as well as overall mortality [84–92]. Elevated levels of biomarkers such as C-reactive protein (CRP) [93–103], tumor necrosis factor alpha (TNF-a) [93,94,104–114], interleukin-6 (IL-6) [93,99,101,113,115–120], interleukin-1b (IL-1b) [102,103,113,121,122], interleukin-10 (IL-10) [93,123–125], fibrinogen [103,114,115,126,127], serum amyloid A (SAA) [128–131], and Transforming Growth Factor-Beta (TGF-β) [132,133] are well known to be correlated with CKD.

On the other hand, a high concentration of some inflammatory markers may seem to play a therapeutic role. For example, interleukin-10 (IL-10) may reduce fibrosis and inflammation [123,124].

In recent years, new inflammatory molecules and indexes have emerged as biomarkers for CKD. Below are some key findings regarding their potential role in CKD.

Ficolins are pattern recognition molecules. They play a role in pathogen recognition, complement activation, and inflammation regulation. There are three main types of ficolins: M-ficolin (ficolin-1), L-ficolin (ficolin-2) and H-ficolin (ficolin-3). Mainly, L-ficolin and

H-ficolin were studied in relation to CKD. The pattern recognition molecules within the complement system, such as H-ficolin and mannan-binding lectin (MBL), recognize specific molecular patterns on the surface of microorganisms and, by binding them, can activate the lectin pathway of the complement system. This, in turn, leads to inflammation. Hyperglycemia alters glycans enzymatically and non-enzymatically by the formation of advanced glycation end-products. These glycan alterations may be the cause of a harmful complement auto-attack initiated by pattern recognition molecules. Østergaard et al., in their article, suggested that higher levels of H-ficolin were associated with diabetic kidney disease progression. However, while the association with DKD progression was independent of other well-established risk factors, the effect disappeared after adjusting for triglyceride levels. Furthermore, in the studied cohort, high concentrations of H-ficolin predicted diabetes-related mortality but were not connected to all-cause mortality and cardiovascular events [134]. Elevated H-ficolin levels at the time of kidney transplantation were found to be an independent and significant risk factor for shorter graft survival [135]. What is more, L-ficolin gene polymorphism was shown to influence kidney allograft functions [136].

The NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome is a multiprotein complex and a component of the innate immune system. By triggering the release of pro-inflammatory cytokines such as IL-1B and IL-18, it plays a role in inflammation, fibrosis, and the progression of CKD. Research has shown that through damaged mitochondria and an elevated production of reactive oxygen species (ROS), the NLRP3 inflammasome is activated in uremic patients treated with dialysis [137]. Other authors have suggested that NLRP3 inflammasome inhibition may be a promising therapeutic target in hyperoxaluria and nephrocalcinosis [121], as well as reducing renal fibrosis [138].

Serum tumor necrosis factor receptor 1 and 2 (TNFR1 and TNFR2) levels are related to eGFR in healthy subjects, which highlights their potential as early biomarkers for CKD [139]. In a study by Oh et al., elevated concentrations of tumor necrosis factor receptors (TNFRs) were correlated with an increased risk of progression in immoglobulin A nephropathy (IgAN). Circulating TNRFs can be early biomarkers to predict the severity and clinical outcome of IgAN [140]. TNFRs can also be a prognostic biomarker for diabetic kidney disease [107]. Further studies focused on TNFRs evaluated Black individuals with hypertension-attributed CKD and older adults with type 2 diabetes and albuminuria, proving that increases in TNFR1 and TNFR2 were associated with worsening kidney function in those groups [141].

Calprotectin is circulation damage-associated molecular pattern protein, considered an acute-phase protein. It originates mainly from myeloid cells and is released during neutrophil degranulation. Higher levels of circulating calprotectin are linked to increased risk of new-onset CKD [142]. Plasma calprotectin was also identified as a contributor to vascular calcification, cardiovascular (CV) outcomes, and mortality in patients with CKD [143,144].

The systemic inflammation response index (SIRI) is a novel predictive biomarker derived from the ratio of peripheral neutrophil, monocyte, and lymphocyte counts, calculated as (neutrophil count × monocyte count/lymphocyte count). The SIRI, as well as other indexes like the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII), were found to be significantly increased in CKD stage 5 compared to other CKD stages [145,146]. A high SIRI is linked to a greater risk of CKD in patients with hypertension. As the SIRI increases, the risk of CKD in hypertensive patients also rises [147]. Furthermore, an elevated SIRI is linked to an increased risk of both all-cause and cardiovascular mortality in patients with CKD. Regular monitoring of the SIRI can aid in the early identification of high-risk patients, enabling

prompt and targeted interventions [148]. Some studies have shown that it can be especially significant in the early stages (I-III) of CKD [87].

An elevated NLR is linked to increased proteinuria, higher serum creatinine levels, reduced eGFR, and a greater prevalence of advanced CKD. Therefore, a high NLR indicates a more advanced stage of CKD and may serve as a biomarker for predicting its progression [149]. NLR can also be used as a complementary prognostic marker for cardiovascular risk evaluation in patients with moderate-to-severe chronic kidney disease [150] and a predictor of cardiovascular and all-cause mortality in hemodialysis patients [151].

Hypoalbuminemia, a well-known sign of protein-energy wasting (PEW) or malnutrition, is frequently seen in individuals with CKD and is linked to an increased risk of cardiovascular complications. Recently, the C-reactive protein to albumin ratio (CAR) has emerged as a novel marker for PEW, as this condition appears to stem not only from insufficient dietary intake but also from persistent systemic inflammation. Measurement of CAR may be useful in clinical practice because this newly introduced surrogate marker of the PEW is simple and can be easily obtained in routine practice. In their research, Takahashi et al. showed that the pre-procedural CRP/albumin ratio could predict both the risk of amputation and mortality after lower extremity revascularization and could stratify the risk in HD patients with PAD [152]. In other studies, a higher CAR was found to be an independent risk factor for diabetic nephropathy [153] and CKD in general [154]. CAR has the potential to become a key biomarker for offering new avenues for advancing early risk stratification, precision therapies, personalized management, and preventive strategies in CKD [155].

Although increased levels of inflammatory indices such as the SIRI or NLR correlate with the progression of CKD, as well as with worsening outcomes in CKD patients, it is important to note that this association does not always imply a direct causal relationship. Systemic inflammation may be a consequence of underlying conditions such as malignancies, infections, or autoimmune diseases, which also contribute to CKD progression. In those cases, the inflammation may not be primarily caused by CKD or be the main reason for CKD progression.

The biomarkers mentioned in the text are presented in Table 2.

Table 2. Inflammatory biomarkers.

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
Ficolins	Liver, immune cells	Pattern recognition molecules; activate lectin pathway of the complement system	Elevated levels are associated with diabetic kidney disease progression and diabetes-related mortality; affect post-transplant graft outcomes
NLRP3 inflammasome	Immune system (intracellular complex)	Activates IL-1B and IL-18; stimulated by ROS and mitochondrial damage	Promotes inflammation, fibrosis, and CKD progression; considered a therapeutic target in hyperoxaluria, nephrocalcinosis, and renal fibrosis
TNFR1 and TNFR2 (tumor necrosis factor receptor 1 and 2)	Circulating receptors of TNF-alpha	Mediate inflammatory signaling; correlate with renal function	Early CKD biomarkers; predict progression in IgA nephropathy and DKD; prognostic in hypertension-related CKD
Calprotectin	Myeloid cells (especially neutrophils)	Acute-phase protein; released during neutrophil degranulation	Associated with new-onset CKD, vascular calcification, and increased cardiovascular and all-cause mortality in CKD patients
SIRI (systemic inflammation response index)	Derived from blood cell counts	Systemic inflammation index (Neutrophil × Monocyte/Lymphocyte)	Elevated in hypertensive patients at risk of CKD; predicts cardiovascular and all-cause mortality—especially useful in early CKD stages (I–III)

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Soluble suppression of tumorigenicity-2 (sST-2) is a soluble isoform of ST2, an interleukin-1 receptor-like 1 and member of the interleukin-1 receptor family. Interaction between interleukin -33 (IL-33), the transmembrane ST2 receptor (ST2L), and sST-2 plays a significant role in the inflammatory response to cardiac stress, and sST-2 is strongly associated with myocardial fibrosis, remodeling, and heart failure progression [172,173]. Several studies have reported that elevated serum levels of sST-2 are correlated with progression and higher risk of mortality in CKD participants [169,174] and increased risk of cardiovascular mortality in dialysis patients. Furthermore, sST-2 levels are not correlated with eGFR in CKD patients, indicating that sST2 is the least impacted by declining kidney function. These findings suggest its potential as a reliable biomarker for patients with cardiovascular disease and coexisting chronic kidney disease [175].

Recent reports reveal that elevated concentrations of sST2 and Gal-3 are associated with an increased cardiothoracic ratio (CTR) in CKD patients. This relationship may enable better cardiovascular risk evaluation for CKD patients [176].

Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine elevated in conditions associated with inflammation and oxidative stress, as well as in different types of cardiovascular events like heart failure and atrial fibrillation. Recently, GDF-15 has been described as a promising biomarker of atherosclerosis [177]. In terms of kidney disease, available studies indicate that GDF-15 is involved in the pathophysiology of CKD, diabetic nephropathy, and kidney cancer [178]. Furthermore, elevated levels of GDF-15 are associated with adverse renal outcomes and may serve as a potential biomarker for predicting the progression of chronic kidney disease (CKD) and its cardiovascular complications [179,180].

Soluble urokinase-type plasminogen activator receptor (suPAR) is a soluble form of urokinase-type plasminogen activator receptor (uPAR) involved in systemic inflammation and immune activation [181]. suPAR is a membrane bound receptor that interacts with and activates integrins in diverse cell types, such as podocytes, tubular epithelial cells (TECs), and fibroblasts, leading to a loss of glomerular filtration barrier integrity and podocyte damage.

Elevated suPAR levels have been associated with an increased risk of cardiovascular disease and kidney function decline in CKD patients [182,183]. Recent studies suggest that higher suPAR levels correlate with greater mortality and cardiovascular events, making suPAR a significant predictor for improving risk stratification and early intervention in CKD populations.

The combination of NT-proBNP, cardiac troponins, galectin-3, sST-2, GDF-15, and suPAR represents a promising approach for a more comprehensive cardiovascular risk assessment and mortality prediction in CKD patients. These biomarkers also demonstrate the potential of predicting CKD progression and guiding future therapeutic strategies.

The biomarkers mentioned in the text are presented in Table 3.

Table 3. Cardiovascular biomarkers.

Biomarker	Origin/Source	Mechanism/Function	Clinical Relevance
Galectin-3	Macrophages, epithelial cells, fibroblasts	ß-galactoside-binding lectin; mediates inflammation, fibrosis, cardiac remodeling	Elevated in CKD and heart failure. Predicts renal fibrosis, rapid renal function decline, and CV mortality. Correlates with serum creatinine and proteinuria. Potential early biomarker of both renal and cardiac complications.
sST2 (soluble suppression of tumorigenicity-2)	Cardiomyocytes, endothelial cells	Soluble form of ST2 receptor; binds IL-33, modulating inflammatory responses to cardiac stress	Predicts CKD progression and cardiovascular mortality. Especially valuable in dialysis patients.

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Another significantly promising biomarker is sclerostin. Like FGF-23, it is also produced by osteocytes and has been associated with chronic kidney disease–mineral bone disorder (CKD-MBD) [204].

Sclerostin, a 22 kDa glycoprotein and a product of the SOST gene, is a soluble antagonist of the classical Wnt-beta signaling pathway [205] and regulates bone mass via Wnt-chain signaling. Like FGF-23, sclerostin has been found to be positively correlated with stages of CKD, beginning at CKD stage 2, and its levels increase with disease progression. Both FGF-23 and Sclerostin have been associated with bone turnover parameters [204]. However, unlike FGF-23, sclerostin's presence is greater in cortical bone than in cancellous bone.

Overall, sclerostin has been linked with fewer osteoblasts and osteoclasts, and its elevation results in a thinner trabecular bone and a lower osteoid surface because of its correlation with decreased bone building, demonstrated through a lower activation frequency and bone formation rate, which occurs at high sclerostin levels [204]. Ji et al. (2018) have shown that sclerostin is elevated in serum in CKD3-CKD5 and is positively correlated with serum creatinine, blood phosphate [206], PTH, vitamin D, alkaline phosphatase, and calcium–phosphate products [207]. Sclerostin has been shown to be related to the calcium and phosphate mechanism, but there is still a lack of specific research regarding the exact mechanism of the correlation between calcium and phosphate in CKD-MBD. On the other hand, it has been negatively correlated with eGFR and blood calcium [207].

Serum sclerostin has been predicted as a potential sensitive indicator of the occurrence of CKD-MBD, and due to its close relationship to the prognosis of CKD, there has been a proposed association of sclerostin's involvement in CKD pathogenesis [205]. Moreover, sclerostin has been shown to be related to metabolic disturbances, and a recent study demonstrated its relationship to hyperglycemia in non-dialysis CKD males specifically [206]. In pre-dialysis end-stage kidney failure (ESKD), serum sclerostin has been shown to have a positive correlation with pulmonary hypertension [208].

Dick-kopf-1 is a secreted antagonist of the Wnt pathway and inhibits the formation of the Wnt-Fzd-LRP5/6 trimeric complex [209]. It has an established role in embryonic development and bone formation in adults, where it is increasingly recognized as a major modulator of the metabolism of bone [210]. Elevated levels of DKK1 have also been observed in numerous human cancers.

However, more recently, it has emerged as a potential therapeutic target for CKD progression and the development of complications. DKK1 has been independently associated with low bone turnover, and in stages 3 and 4 of CKD, circulating levels of DKK1 and sclerostin have appeared to be predictive of bone disease [200]; however, further research is required to assess its efficacy as a potential biomarker in the diagnosis, treatment, and monitoring of renal osteodystrophy [209]. Serum levels of DKK1 were positively associated with faster progression to end-stage renal disease [209]. Several studies have reported lower levels of DKK1 in CKD as compared to controls, with levels dropping even early in the course of CKD [210], with the lowest being reported in CKD-4 [209]. Yet, Fang et al. (2014) demonstrated that increased renal production of DKK1 and circulating DKK1 levels were positively associated, and they hypothesized their relationship to CKD pathogenesis [211]. Further studies to gain a more precise insight into this mechanism and its relationship to CKD-MBD are required to validate it as a potential biomarker.

The biomarkers mentioned in the text are presented in Table 4.

Table 4. Bone and mineral metabolism biomarkers.

Biomarker	Origin / Source	Mechanism / Function	Clinical Relevance
Parathyroid Hormone (PTH)	Parathyroid glands	Regulates calcium homeostasis	Established marker of SHPT and bone mineral disorder (CKD-MBD). A predictor of CKD progression, cardiovascular events, and mortality.
Fibroblast Growth Factor 23 (FGF-23)	Osteocytes and mature osteoblasts	Regulates phosphate metabolism. Suppresses 1-á-hydroxylase activity, reducing calcitriol production. Acts on parathyroid glands to suppress PTH.	Elevated early in CKD, before changes in phosphate, calcium, or PTH. Predicts CKD progression, all-cause mortality, and CV events.
Sclerostin	Osteocytes (mainly in cortical bone)	Reduces osteoblast activity and bone formation rate. Affects calcium–phosphate homeostasis.	Negatively correlated with eGFR. Promising marker for CKD-MBD and disease progression. Linked with hyperglycemia and pulmonary hypertension in CKD patients.
Dickkopf-1 (DKK-1)	Various tissues including bone; secreted protein	Regulates bone metabolism and embryonic development. Proposed involvement in "cross-talk" between tissues.	Emerging marker for CKD-related bone disorders and CKD-MBD. Levels correlate with disease severity and lower levels reported in advanced CKD. Associated with low bone turnover. Predictive of progression to ESKD.

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral bone disorder; CV, cardiovascular; ESKD, end-stage kidney disease; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.

7. Conclusions

There is a multitude of biomarkers related to CKD, with new ones emerging every year. The identification and implementation of novel biomarkers in CKD in clinical practice can result in significant advancements in early diagnosis, risk stratification, and personalized treatment strategies. These arising biomarkers may offer superior sensitivity in the detection of early kidney dysfunction and provide deeper insights into disease progression, correlated comorbidities, and potential therapeutic targets. However, the widespread clinical integration of these biomarkers faces challenges, mainly related to high costs and the necessity for standardized assays. The growing relevance of biomarkers in assessing kidney disease progression has been increasingly emphasized in the recent literature. Several reviews have explored advances in biomarker research for CKD [212–215], underscoring their potential in the comprehensive management of the disease, while also addressing the substantial challenges associated with their clinical implementation. It is essential to note that, whilst specific biomarkers are linked to differing CKD mechanisms and comorbidities, it is vital to recognize that many of the aforementioned biomarkers exhibit associations with multiple complications of CKD. This intersection is a reflection of the inherent complexity and multi-morbid nature that is characteristic of CKD. Due to this, the proposed division of biomarkers cannot be regarded as either definitive or exclusive. Acknowledging this inter-related nature of CKD is crucial for the appropriate interpretation of current and new biomarker data and for the successful development of comprehensive management strategies. The extension and continuation of research is pivotal for advancements in the diagnosis and treatment of CKD, and hopefully, as a result, a wider array of biomarkers will become accessible for use in daily clinical practice, enhancing the quality of healthcare delivered and improving patient outcomes for CKD.

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2.2 Metabolismo lipídico

Las lipoproteínas son moléculas de gran magnitud que son las responsables de transportar lípidos a través del torrente sanguíneo facilitando su debida distribución, almacenamiento, y uso energético.

Estas macromoléculas son de carácter anfipático, dado a que mantienen una porción proteica y lipídica. Desde punto de vista biomolecular estas conforman una porción esférica que presenta un núcleo hidrófobo compuesto por triglicéridos y colesterol; y una monocapa de fosfolípidos, porciones de colesterol y estructuras proteicas especializadas, como las apolipoproteínas.

Carlos Carvajal (2014) describe los cuatro grupos de lipoproteínas basadas en su densidad.

- **Quilomicrones:** Son grandes moléculas de triglicéridos que se encargan de transportar los lípidos que fueron ingeridos en le dieta desde el intestino delgado, hasta los tejidos periféricos, junto a ello permiten la absorción de las proteínas liposolubles.
- **VLDL**: Esta es una lipoproteína de muy baja densidad, ya a partir a esta se le puede empezar a considerar como *colesterol malo* debido a la **baja densidad proteica**. Esta partícula tiene la principal función de llevar los triglicéridos del torrente sanguíneo hacia los tejidos circundante.
- **LDL:** Al igual que VLDL, esta lipoproteína de baja densidad se denomina colesterol malo. La gran diferencia es la densidad lipídica en comparación a el VLDL. También se debe considerar que el LDL tiene un poco más de porcentaje proteico en comparación a la VLDL.

- **HDL:** Esta es la lipoproteína alta densidad, coloquialmente conocida como *“colesterol bueno”*. Esta partícula posee la propiedad **antiaterogénica**. Esto significa que cuenta con la capacidad de eliminar el colesterol de los tejidos circundantes y devolverlo al hígado, a este proceso se le conoce como **transporte reverso de colesterol.** Sin embargo, en pacientes con alteraciones renales crónicas estas macromoléculas experimentan cambios a nivel bioquímico y estructural que limitan su capacidad ateroprotectora.

2.2.1 Estructura de las lipoproteínas de alta densidad

La estructura de la HDL es una de las arquitecturas biológicas más complejas y variantes en el cuerpo humano. Ya que, a diferencia de las demás lipoproteínas, esta depende de la dinámicas de sus apolipoproteínas. La HDL es un compendio de la apolipoproteína AI y la ApoE.

No solo actúa como componente estructural de las lipoproteínas, sino que cuenta con la característica de poder solubilizar las moléculas lipídicas por medio de las hélices α anfipáticas.

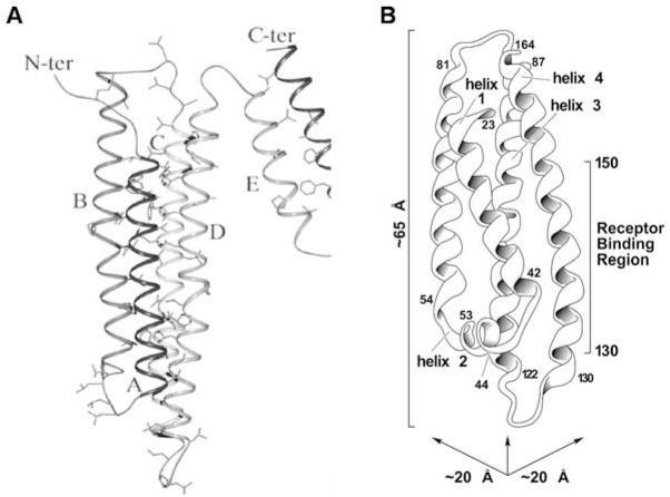


Figura 1. Estructuras de apolipoproteínas en estado libre de lípidos. Fuente: Lund-Katz, S., & Phillips, M. C. (2010). High density lipoprotein structure-function and role in reverse cholesterol transport. Sub-cellular biochemistry, 51, 183–227. https://doi.org/10.1007/978-90-481-8622-8_7

2.2.1.1 Apolipoproteína A-I

Es una proteína de 243 aminoácidos, formada en el hígado, que tiene como función clave el metabolismo de lípidos. Compone la HDL (colesterol bueno).

Su trabajo no es solo transportar, sino que también coordina procesos y la activación de la ABCA1 y la LCAT para estimular la salida de los fosfolípidos y el colesterol libre.

De acuerdo con **Stasi et al.** C (2022) y **Ducasa, GM, et al.** (2021) la acción del ABCA1 y la LCAT dependen directamente del estímulo por parte de la ApoA-I. Se evidenció que sin este estímulo el colesterol no saldría de las células facilitando procesos inflamatorios, perdiendo su capacidad a antiaterogénica. Y terminando en la muerte celular.

Desde el punto de vista sistémico, la ApoA-I se organiza estructuralmente en dos porciones.

La porción amino-terminal (N-terminal), está formada por cadenas de hélice de sentido antiparalelo, que están organizadas en sentido globulares que mantienen su estabilidad gracias a las capacidad de tener interacciones hidrofóbicas en su interior. En cambio, la porción carboxi-terminal (C-terminal) está conformada de manera irregular. Y desorganizada, Y mantiene su capacidad lipofílica.

2.2.2 Transporte reverso del colesterol

El exceso de colesterol en las células periféricas, junto a su incapacidad de llegar a catabolizarlo obliga al organismo a recurrir al transporte reverso de colesterol, para poder mantener su homeostasia de los lípidos.

El transporte reverso del colesterol constituye una serie de mecanismos que van desde la captación del colesterol celular en los tejidos periféricos, su metabolismo en el interior de la partícula y su paso al hígado, luego a su excreción.

Asimismo, se ha evidenciado que no todo el colesterol tiene como sitio final el hígado, y que estos pueden seguir una vía alternativa en donde los ésteres de colesterol son transferidos a lipoproteínas de bajas densidades (VLDL, LDL) por la mediación de la CETP. Pero esto representa un proceso con potencial tanto proaterogénico como antiaterogénico, ya que hasta cierto punto puede facilitar que las lipoproteínas de bajas densidades (VLDL, y LDL) sean eliminadas por el organismo, ya que una vez estas sean transferidas son captadas por los receptores de LDL (LDLr) o el receptor relacionado con LDL (LRP1), para contribuir con la excreción en la bilis, o la síntesis de ácidos biliares.

Sin embargo, este proceso puede no ser exitoso, ya que, si el hígado no capta de manera eficiente, estas moléculas pueden permanecer por un largo plazo en la circulación favoreciendo así la oxidación, y la posterior formación de células espumosas por el proceso de fagocitosis por parte de los macrófagos, favoreciendo así el origen o la formación de las placas de ateroma. **(Figura 2**).

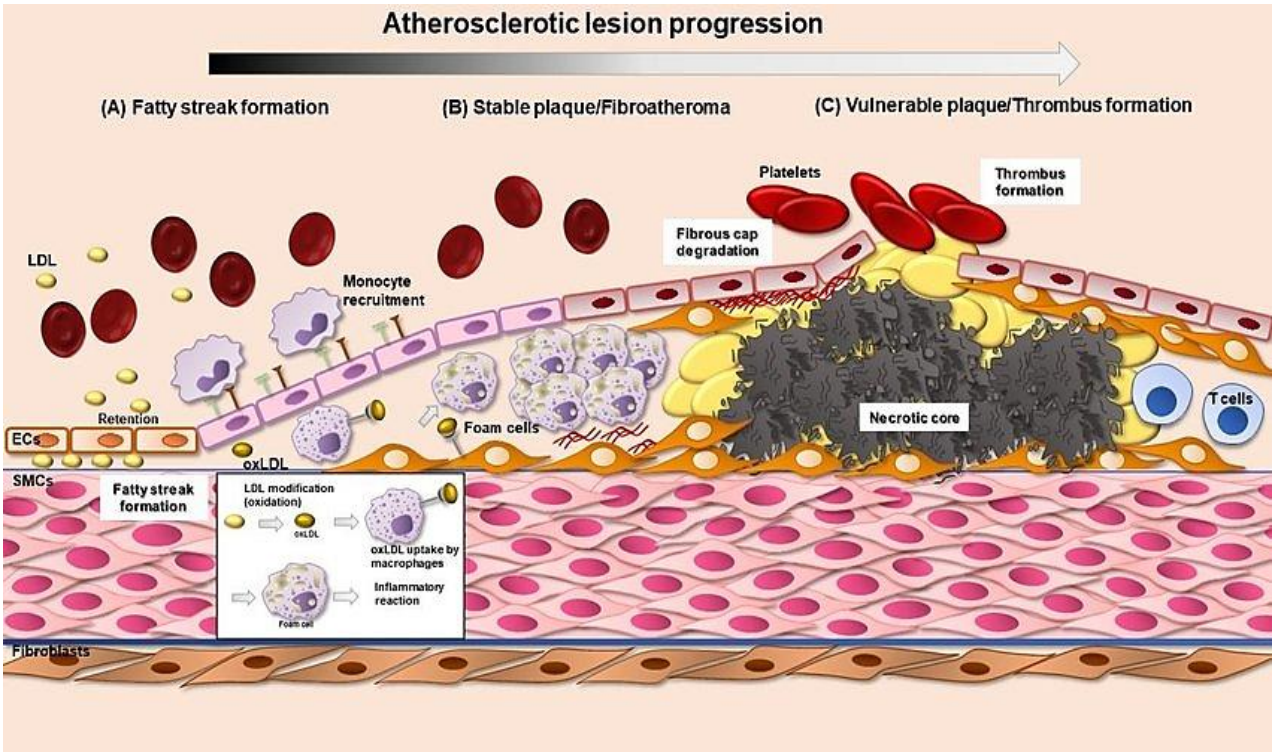


Figura 2. Formación de la placa aterosclerótica. La retención de lipoproteínas en la pared vascular y el flujo sanguíneo alterado activan la expresión de moléculas de adhesión endotelial (VCAM-1, ICAM-1), promoviendo el reclutamiento de monocitos al endotelio. Estos se diferencian en macrófagos, fagocitan lipoproteínas de baja densidad oxidadas (oxLDL) y dan origen a células espumosas que contribuyen al entorno proinflamatorio y al desarrollo de la lesión ateromatosa. *Fuente: Adaptado de Gong, S., Li, Y., Yan, K., & Ning, K. (2025). The crosstalk between endothelial cells, smooth muscle cells, and macrophages in atherosclerosis. International Journal of Molecular Sciences, 26(3), 1452. https://doi.org/10.3390/ijms26031452*

2.2.2.1 Lipoproteína lipasa

Hay relación directamente proporcional entre el avance de la ERC y los niveles descontrolados de lípidos séricos.

Lacount.et.al. (2025) compara que el cuerpo humano en su fisiología base tiene la capacidad de eliminar los triglicéridos gracias a la *lipoproteína lipasa (LPL)*, una enzima que hidroliza los triglicéridos de los quilomicrones y de las VLDL en sangre periférica. En cambio, durante una alteración crónica a nivel renal, la regulación de la LPL disminuye y las lipoproteínas que tienen más composición de triglicéridos en membrana como la VLDL no se degradan bien dado a su catabolismo retardado, y se acumulan en sangre periférica.

Más allá de que se alteren los niveles séricos de estas moléculas, se puede concluir que no solo importa cuánto colesterol hay, sino como son las partículas y su composición.

2.2.2.2 Lectina-Colesterol Acetiltransferasa

Es la enzima clave para el transporte inverso de colesterol, actúa como principal factor precursor de la eliminación del exceso de colesterol en tejidos periféricos.

Este esterifica el colesterol presente en la capa más superior de la HDL y posteriormente atrayéndolo hacia el núcleo. Actúa como un limpiador superficial, que atrapa el colesterol en el núcleo impidiendo que este pueda liberarse al torrente sanguíneo, y que llegue al hígado para su correcta conversión a bilis y excreción en las heces.

2.2.3 ABCA1

La formación de las lipoproteínas de alta densidad (HDL) requiere de la participación del ATP binding cassette (ABCA1).

Segrest et. al (2022) sugiere que este cuenta con un mecanismo de túnel hidrofóbico que anteriormente se tomaba como floppasa, en donde solo movía lípidos de una capa

a otra. Pero en el reciente estudio se evidenció que este se adapta al mecanismo de túnel hidrofóbico.

De acuerdo con los modelos de representación. El fosfolípido es “secuestrado” de la membrana externa y pasa a través de un cavidad y llega a una región específica denominada “Gateway” que identifica y extrae el lípido de la membrana.

Posteriormente este pasa por el orificio anular o “annulus” que esta es la porción que principalmente actúa como un túnel alargado que se encarga de conducir los fosfolípidos hacia la ApoA-I.

En diversas literaturas se ha mencionado que en enfermedades en donde el ABCA1 está mutado se genera una acumulación patológica de los esteres colesterol en tejidos, y principalmente en macrófagos. Esto se debe a la incapacidad de expulsar el colesterol de la célula.

2.2.4 Función antioxidante, antiinflamatoria y endotelial del HDL

Las HDL son un complejo multimolecular que es capaz de proporcionar una potente protección ante los lípidos oxidativos proaterogénicos, pero su función antioxidante puede verse alterada en enfermedades ligadas a trastornos metabólicos, como la ERC.

Estas moléculas no solos son colesterol bueno, sino que dependen fuertemente de su composición, dado a que es factor clave de sus propiedades.

2.2.4.1 Disminución de la función antiinflamatoria

Durante la ERC se reduce la capacidad de las lipoproteínas de alta densidad de inhibir la expresión de las citoquinas proinflamatorias, tales como IL-1β, IL-6 y TNF-α en macrófagos.

Como consecuencia, se favorece un estado proinflamatorio a nivel sistémico.

De esta manera, se genera un ambiente urémico que propicia las modificaciones estructurales en cual se oxidan los componentes de HDL, y se altera la ApoA-I, proteína fundamental en la función del HDL. En este contexto se inhibe significativamente su síntesis hepática. Lo que causa un deterioro paulatino en la actividad antiinflamatorio en pacientes urémicos

2.2.4.2 Actividad vasodilatadora

Las HDL no solo transportan el colesterol, sino que también tienen la propiedad de estimular la producción de óxido nítrico. En condiciones normales, el óxido nítrico (NO) es esencial para mantener una homeostasis vascular y la adecuada función endotelial. La pérdida de esta función se asocia con un aumento de la concentración de SDMA (dimetilarginina simétrica), un biomarcador sensible a la alteración en la capacidad de filtración glomerular. En este contexto, el SDMA inhibe la producción de NO, lo que favorece la aparición de hipertensión y el daño vascular.

Es muy importante mencionar que esta disfunción se puede presentar en etapas tempranas de la ERC. Inclusive se ha observado una recuperación parcial luego del trasplante renal exitoso.

2.2.4.3 Reducción de la actividad antioxidante

En pacientes con ERC la actividad antioxidante de las HDL se encuentra reducida, pudiendo ser incluso nula en casos puntuales. Esta alteración compromete la capacidad de atenuar el estrés oxidativo e inflamación causados por las LDL oxidadas. **Pavanello, C., & Ossoli, A. (2023)**

2.2.5 Definición de enfermedad renal crónica (ERC)

La enfermedad renal crónica es una alteración caracterizada por el daño a nivel estructural y funcional. Se define como la pérdida progresiva y, generalmente, irreversible de la función renal en la cual los riñones no llegan a filtrar debidamente los desechos metabólicos, ni el exceso de líquido de la sangre.

La disminución de la filtración glomerular es medible con un marcador de función renal, la *tasa de filtración glomerular estimada (TFGe).* Se considera que hay un daño en el funcionamiento renal cuando la TFGe es inferior a 60 mL/min/1,73 m² que persiste a un periodo monitorizado en tres meses sin causa específica.

Aunque la ERC no se clasifica como una enfermedad metabólica, si está estrechamente ligada a múltiples alteraciones metabólicas, tales como: trastornos hidroelectrolíticos. Y el desequilibrio ácido-base.

2.2.6 Clasificación de la ERC

A nivel mundial, la ERC ha aumentado entre un 10% a un 15% en poblaciones adultas em la región del occidente. En el año 2002 la Kidney Disease Outcomes Quality Intitative, Fundación nacional de riñón, Sentó una guía para la clasificación de la ERC mediante los criterios de diagnóstico, y el estadio según la TFG.

2.2.6.1 Criterios de diagnóstico

Según la KDIGO, la ERC se considera por la presencia sostenida por un tiempo igual o mayor de tres (3) meses.

- TFGe es inferior a 60 mL/min/1,73 m²
- Daño renal (Alteraciones estructurales, o indicadores en orina)

2.2.6.2 Clasificación según la TFG

- G1 (Normal o alto) = ≥90 TFG/ml/min/1,73 m²
- G2 (Leve disminución) = 60-89 TFG/ml/min/1,73 m²
- G3a (Leve a moderadamente disminuida) = 45-59 TFG/ml/min/1,73 m²
- G3b (Moderada a severamente disminuida) = 30-44 TFG/ml/min/1,73 m²
- G4 (Disminución severa) = 15-29 TFG/ml/min/1,73 m²
- G5 (Insuficiencia renal) = <15 TFG/ml/min/1,73 m²

En ausencia de evidencia de daño renal, ni la categoría G1 ni G2 cumplen como criterio para la determinación de la ERC

2.2.7 Factores de riesgo y progresión del daño renal

La ERC es considerada uno de los mayores riesgos asociados a la salud pública global. El riesgo de deterioro renal está mediado por una serie de factores que incluyen la su genotipo, comorbilidades y estilo de vida.

- Genotipo, incluye todas su características heredadas. La raza, predisposición al desarrollo de enfermedades renales por antecedentes familiares.
- Comorbilidades, continúan siendo en todas las patología los principales perfiles de riesgo. Infecciones virales (hepatitis C, VIH). Entre otras al diabetes mellitus, hipertensión arterial, obesidad, hiperlipidemia.
- El estilo de vida puede llegar a ser un detonante fundamental. Tales como, el tabaquismo, alcoholismo, uso excesivo de AINEs

2.3 Fisiopatología de la dislipidemia en la ERC

Preponderadamente, la dislipidemia ha sido vinculada al contexto de la enfermedad cardiovascular. Sin embargo, su impacto a la homeostasis renal no ha sido ampliamente

documentado. Y el deterioro que puede llegar a causar a nivel de la fisiología renal puede llegar ser subestimado. A pesar del rol critico que estos pueden llegar a causar en la microvasculatura y el parénquima renal su estrecha relación con la lipotoxicidad renal ha permanecido en segundo plano. La lipotoxicidad se ha correlacionado con la disfunción cardiaca, renal, endocrina e inclusive muscular. Su relación con la alteración renal no comienza en el mismo riñón, sino que es una serie de eventos que lleva a la acumulación de toxinas urémicas intravasculares que van a alterar el metabolismo de los lípidos en sangre. Estos evento son**: La inhibición de LPL por acción de la toxina urémicas, La falla en la maduración por LCAT, y la modificación por carbamilación.**

2.3.1 Inhibición de la Lipoproteína Lipasa (LPL)

En el espacio intravascular, el metabolismo lipoproteico es afectado por la acción de las toxinas urémicas. **Holmar, J., et al. (2022),** concluyó que en un ambiente urémico las principales toxinas disruptoras del metabolismo lipídico son la: Sulfato de p-Cresilo **(PCS),** Ácido Indol-3-Acético **(IAA),** Indoxil **(IS).** La LPL gracias a una serie de mecanismos reguladores la LPL es capaz de suprimir la activación de esta sea, necesaria para regular el desequilibrio del metabolismo lipídico, Y al estar compuesta de elementos *Cis-activos* es capaz de regular o potenciar reacciones por acción de factores de transcripción. Es importante conocer que en los pacientes con ERC los mecanismo reguladores se inhiben

Estos mecanismos reguladores no son más que una porciones cortas de ADN que van a determinar el comportamiento de la LPL dependiendo a quién se una, un activador, o un supresor. Entre esos, la regulación transcripcional, la regulación postranscripcional, traslacional y postraduccional

2.3.1.1 La regulación transcripcional:

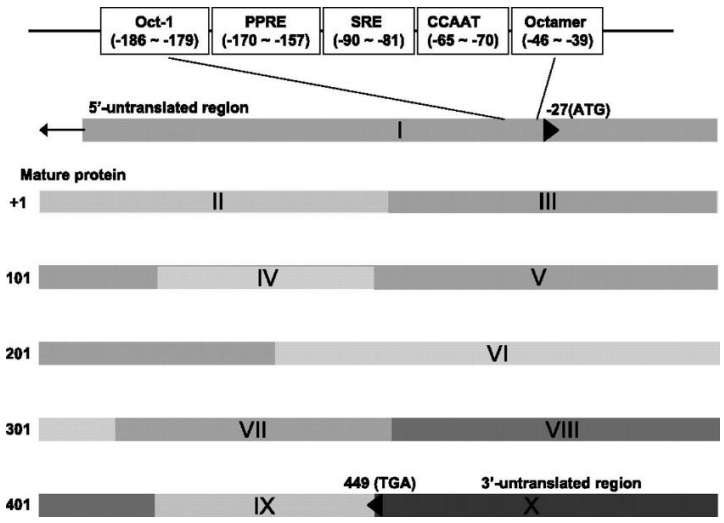


Figura 3. Estructura del gen LPL. *Hong Wang y Robert H. Eckel Revista Americana de Fisiología-Endocrinología y Metabolismo.* ***https://doi.org/10.1152/ajpendo.90920.2008***

Este mecanismo actúa en base a cuatro (4) elementos:

Elementos de respuesta metabólica:

La LPL no se produce de manera automática. Su producción va a depender del ambiente en el que se encuentre, en otras palabras, va a estar mediado por la concentración se lípidos en sangre.

- PPAR **(Elemento de respuesta al receptor al receptor activado por proliferadores de peroxisomas)**. Este se encarga de regular la producción de la LPL en base a factores como la dieta, ayuno, ejercicio.

- Durante la ERC la acción del PPAR se ve inhibida, gracias a que las toxinas actúan como reguladores negativos. Es decir, frenos que no permite la producción de LPL indistintamente de los niveles séricos de lípidos presentes.

- LXR y SRE-2 **(reguladores /receptores de oxiesteroles, y esteroles)** Estos elementos determinan el exceso de colesterol celular y ayuda a eliminar el exceso de lípidos celulares.

Elementos de control basal:

El sistema humano tiene la capacidad de producir una gran cantidad de enzimas para catalizar varias reacciones en el cuerpo simultáneamente. Los elementos de control basal cumplen con la función de producir enzimas, constantemente, aunque no haya algún estímulo externo. Es decir que en la ERC como hay una falla del riñón, se acumulan toxinas que actúan como reguladores negativos que generan un aumento descontrolado del factor de necrosis tumoral alfa (TNF-α) y este impide la unión al factor de transcripción nuclear Y a la caja CCAAT e impide del debido funcionamiento de la LPL al tratar de disminuir el colesterol excedente o células saturadas.

2.3.1.2 La regulación postranscripcional:

La principal característica de la LPL radica en estar unida a una unidad igual. Pero es importante saber que en la ERC la traducción de la LPL puede verse bloqueada inactivando la producción la proteína estabilizadora. En situaciones normales, la LPL se glicosila en el retículo endoplásmico con su homólogo que sería el aminoácido asparagina.

En caso tal que durante el proceso a través de retículo endoplásmico haya un mal plegamiento de la LPL por un mal uso o ausencia de calcio, esta se reserva para ser

posteriormente destruida. Y el calcio no es solo utilizado como un estabilizador del plegamiento de la LPL, sino que de ella depende la homeostasis para los siguientes procesos necesarios para llegada de la LPL al lumen vascular.

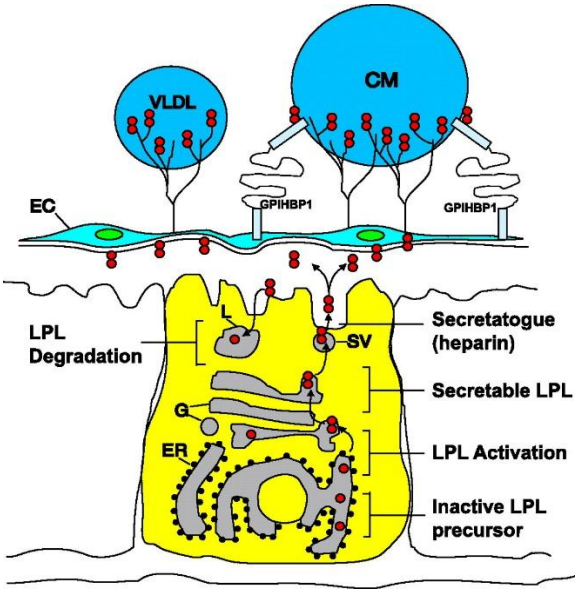


Figura 4. Anclaje luminal mediado por la GPIHBP1. *Hong Wang y Robert H. Eckel Revista Americana de Fisiología-Endocrinología y Metabolismo.* ***https://doi.org/10.1152/ajpendo.90920.2008***

La funcionalidad de LPL ya sintetizada va a depender de la capacidad que esta tiene de migrar y translocarse al lumen vascular. Si esta no está bien ubicada en espacio endotelial no puede interactuar debidamente con la con moléculas no proteicas precursoras de un función, como la apolipoproteína C-II. **Wolska *et. al.* (2020)** describe la ApoC-II como el cofactor activador de la funciones en la lipoproteína lipasa.

Es decir, en ambas situaciones, la regulación transcripcional. Y postranscripcional implican una alteración funcional en la LPL, proliferando la concentración de triglicéridos a nivel vascular. Dado a la incapacidad de depurar las partículas lipídicas se condiciona un ambiente tóxico, que, posteriormente, por una serie de factores fisiopatológicos más van a promover un estado proinflamatorio mediador para el avance de la ERC.

2.3.2 Hipertrigliceridemia, y la formación de remanentes lipoproteicos

Luego de saber cómo se inhibe la depuración de lípidos mediado por la LPL, la gran interrogante sería*: ¿Qué ocurre con los remanentes que no han sido depurados y se mantienen en la vasculatura?*

Al alterarse la cinética de los lípidos en el espacio intravascular, se da origen a una serie de eventos fisiopatológicos hasta llegar a la lipotoxicidad renal.

2.3.2.1 Retraso en la tasa de aclaramiento de los triglicéridos.

Durante la ERC el cuerpo pierde la capacidad de poder eliminar los desechos del cuerpo, no solo en el ámbito de toxinas en el torrente sanguíneo, también pierde la dinamia lipídica a nivel intravascular. Esto quiere decir que el proceso desde la producción, hasta la eliminación de grasas presenta un fallo crítico.

Erróneamente se suele pensar que, en la ERC, el cuerpo aumenta la producción de triglicéridos, pero este aumento se debe al fallo en el metabolismo plasmático. La enzima encargada de catabolizar los lípidos, la lipoproteína lipasa, disminuye su actividad y al no poder hidrolizar las moléculas de grasa causa un falso aumento de estos componentes plasmáticos, este se debe a que mantiene las porciones no hidrolizadas, junto a las agregadas por la dieta.

Esto, no solo se afecta la acción de la lipoproteína lipasa, sino que también se observa una notable alteración en las proteínas reguladores del metabolismo. Entre estas la CETP (proteína transportadora de ésteres de colesterol) esta proteína juega un rol fundamental en el transporte reverso del colesterol. La fisiología está estructurada en su libre circulación en el espacio plasmático, permitiendo que los lípidos extraídos por el HDL-c y posteriormente almacenados como ésteres de colesterol en el interior de la

partícula sean intercambiados con los triglicéridos presente en el LDL, es decir que los ésteres de colesterol pasan a las lipoproteínas baja densidad proteica, mientras que los triglicéridos pasan al HDL. Las moléculas cargadas por ésteres de colesterol o sea el LDL post intercambio, van a ser reconocidas por los receptores de lipoproteínas de baja densidad (LDLR). Estas, se unen por la presencia de ApoB-100 en la superficie de las moléculas de LDL y gracias a esta unión se produce una endocitosis de la partícula del LDL para ser degradada en aminoácidos, colesterol libre, ácidos grasos entre otros para ser desechado al intestino mediante la bilis.

La partícula de HDL, es metabolizada de una manera distinta, ya que esta no entra directamente al hepatocito, sino que dependiente de la acción de los receptores de Scavenger clase B tipo I (SR-B1), que a diferencia de los receptores de lipoproteínas de baja densidad (LDLR) estos se no incorporan a la molécula de HDL mediante una endocitosis, sino más bien, por medio de una captación selectiva que facilita la transferencia de esteres de colesterol. EL SR-B1 se une a la ApoA-1 en el HDL que permite un flujo bidireccional entre el hepatocito. Y la partícula de HDL. Es decir que los ésteres de colesterol en el núcleo de la HDL van a pasar a través de un canal lipofílico que se va a formar gracias a su unión.

De lo contrario, cuando ser cursa con una ERC, estas vías de procesamiento se ven saturadas lipídicamente

2.4 Correlaciones entre los biomarcadores y la molécula de HDL-C mientras se cursa con una enfermedad renal crónica.

La presente sección se enfoca en evaluar la interacción matemática y clínica entre el perfil lipídico y la función renal, tomando como eje central la correlación entre el colesterol

de lipoproteínas de alta densidad (HDL-C) y la creatinina sérica. Desde el planteamiento metodológico de esta investigación, se postula la existencia de una correlación inversa o negativa de carácter significativo. Esto implica en términos probabilísticos que la reducción progresiva de las concentraciones circulantes de HDL-C se vincula directamente con una retención y elevación proporcional de la creatinina plasmática en la población de estudio. Esta premisa no solo responde a una lógica fisiopatológica, sino que se encuentra robustamente respaldada por la evidencia epidemiológica e internacional más reciente, la cual permite desglosar este fenómeno desde diversas perspectivas numéricas.

2.4.1 Correlación creatinina y HDL- C

Para comprender la magnitud de esta asociación en la población geriátrica, es imperativo analizar el estudio observacional desarrollado por (Srivastava S, 2022) Esta investigación examinó de forma transversal a una cohorte de adultos mayores con una edad media de 75 años, un grupo etario con una vulnerabilidad intrínseca al declive funcional orgánico. Los resultados de dicho estudio pusieron de manifiesto que los individuos que padecían de hipoalfa-lipoproteinemia crónica —definida analíticamente como niveles de HDL-C inferiores al umbral crítico de 50 mg/dL— presentaban una tasa sustancialmente mayor de disfunción renal evidenciada por la acumulación de metabolitos nitrogenados. Al aplicar un análisis estadístico multivariado para controlar variables confesoras como la edad, el sexo y la presencia de comorbilidades cardiovasculares, los autores reportaron un *Odds Ratio* (OR) ajustado que osciló entre **1.85 y 2.10** (Sp < 0.01). En el contexto de la interpretación de datos, este indicador demuestra que un adulto mayor con déficit cuantitativo de HDL-C posee hasta el doble de probabilidad de desarrollar hipercreatininemia en comparación con aquellos que

mantienen un perfil lipídico óptimo, sugiriendo que la pérdida de esta lipoproteína precede o agrava el compromiso de la filtración glomerular.

Complementando este hallazgo, el macroestudio longitudinal de carácter masivo ejecutado por (Takaaki Kosugi, 2024) aportó la validación matemática y predictiva necesaria a través del seguimiento temporal de una muestra superior a los 760,000 participantes. Al someter los datos a modelos robustos de regresión lineal y correlación, los investigadores lograron demostrar que las concentraciones de HDL-C por debajo de **40 mg/dL** muestran una pendiente de asociación negativa constante frente a los valores de creatinina sérica. Los coeficientes de correlación obtenidos en este análisis fluctuaron en un rango de **r = -0.28 a r = -0.42**, manteniendo una rigurosa significancia estadística de **p < 0.001** Metodológicamente, el signo negativo en estos coeficientes es la evidencia matemática directa que convalida la hipótesis de proporcionalidad inversa: a medida que el valor numérico del HDL-C se desplaza de manera decreciente en el eje de las variables, el valor de la creatinina sérica experiencia un incremento sistemático debido a la reducción en la capacidad de aclaramiento del nefrón.

La importancia de profundizar en este análisis radica en que la creatinina sérica, al ser un subproducto del catabolismo muscular metabólicamente estable, depende casi exclusivamente de la eficacia de la filtración glomerular para su depuración. Cuando la literatura científica actual demuestra estos niveles de correlación negativa (r negativos y *Odds Ratios* elevados), está evidenciando que el déficit de HDL-C altera de forma sistémica la microvasculatura renal, promoviendo microangiopatías subclínicas que lesionan el aparato filtrante. Al disminuir el flujo plasmático renal efectivo por la falta de protección endotelial del HDL-C, el riñón pierde su capacidad de depurar la creatinina a la velocidad metabólica requerida, provocando su acumulación sérica. Por lo tanto, los

antecedentes presentados justifican plenamente el análisis estadístico individualizado de estas dos variables, consolidando al HDL-C disminuido no solo como un trastorno lipídico aislado, sino como un indicador indirecto y temprano del compromiso en la función excretora renal en el adulto mayor.

2.4.2 Correlación entre la TFG y HDL-C

La Tasa de Filtración Glomerular Estimada (eTFG) constituye el indicador clínico de elección y el estándar de oro para la monitorización de la función renal depurativa, así como para la estadificación de la Enfermedad Renal Crónica (ERC) según los lineamientos internacionales de las guías KDIGO. En la población de adultos mayores, si bien la senescencia renal fisiológica se caracteriza por una pérdida progresiva y cronológica de nefronas funcionales, la presencia concomitante de alteraciones metabólicas —específicamente el descenso de las concentraciones séricas de colesterol de lipoproteínas de alta densidad (HDL-C)— actúa como un acelerador exógeno y un predictor independiente de este deterioro hemodinámico y estructural.

Al analizar este fenómeno a nivel molecular, encontramos que la relación clínica entre ambas variables es directa. Esto significa que cuando el HDL-C baja, la tasa de filtración glomerular disminuye de forma mucho más rápida. Detrás de esto hay un mecanismo fisiopatológico claro: al no haber suficientes partículas de HDL funcionales, el riñón pierde esa protección natural contra la inflamación, antioxidantes y de transporte reverso de colesterol inherentes a las partículas de HDL-C funcionales. Bajo condiciones de hipoalfalipoproteinemia (definida clínicamente como un HDL-C < 40 mg/dL en varones y < 50 / mg/dL en mujeres) se suprime la estimulación de la enzima óxido nítrico sintasa endotelial (eNOS), lo que disminuye la biodisponibilidad de óxido nítrico y desencadena una vasoconstricción refleja en la arteriola aferente del glomérulo. Esta alteración

hemodinámica reduce la presión hidrostática intraglomerular, comprometiendo de forma inmediata el volumen de ultrafiltrado plasmático por unidad de tiempo.

Paralelamente, el fracaso en el aclaramiento de lípidos aterogénicos promueve la acumulación lipídica en las células del mesangio renal. Las células mesangiales fagocitan estas lipoproteínas oxidadas y activan una cascada proinflamatoria local que reclutas macrófagos, mimetizando el proceso de aterogénesis sistémica. Este fenómeno de “aterosclerosis glomerular” induce el desarrollo de glomeruloesclerosis microvascular, daño podocitario y fibrosis tubulointersticial. La destrucción histológica de la barrera de filtración se traduce clínicamente en un descenso sostenido de la TFG por debajo del umbral crítico de los 60 mL/min/1.73 m^2 el cual delimita la transición hacia el Estadio G3a (disfunción renal moderada), una etapa donde las complicaciones metabólicas del adulto mayor se agudizan.

La pertinencia de esta correlación se encuentra sólidamente respaldada por evidencia epidemiológica de cohortes longitudinales a gran escala. Estudios como el Atherosclerosis Risk in Communities (ARIC), desarrollado por (Fan Wang, 2013) colaboradores en poblaciones geriátricas con una media de edad de 75 a 53 años, demostraron que los pacientes ubicados en los estadios moderados de disfunción renal (TFG entre 30 y 59 mL/min/1.73 m^2) exhiben de forma concomitante niveles séricos de HDL-C críticamente reducidos en comparación con aquellos que mantienen una función renal preservada (90 mL/min/1.73 m^2).

Asimismo, análisis estadísticos multivariables liderados por investigadores como (Sadiya S. Khan, 2023) colaboradores corroboraron la solidez de esta asociación mediante el coeficiente de correlación de Pearson, el cual objetivó una relación lineal

positiva directa entre el HDL-C sérico y la TFG ($r = 0.16$; $p < 0.01$). Tras ajustar los modelos de regresión logística por variables confesoras tradicionales como la edad, el sexo, el índice de masa corporal, la hipertensión arterial y la diabetes mellitus, los resultados confirmaron que el riesgo relativo de presentar una filtración glomerular deficiente se magnifica exponencialmente en los estratos de edad más avanzada cuando coexiste el déficit de HDL-C. Estos descubrimientos metodológicos consolidan la premisa de que la monitorización conjunta del perfil lipídico y la TFG (calculada preferencialmente mediante la ecuación de precisión CKD-EPI para evitar la subestimación funcional en geriatría) es vital para predecir el ritmo de progresión del daño renal en el adulto mayor.

2.4.3 HDL-C Disminuido y Albuminuria

Una correlación clínica, fisiopatológica e inversamente proporcional, profundamente respaldada por la investigación nefrológica y metabólica contemporánea, entre el descenso de los niveles plasmáticos de colesterol de lipoproteínas de alta densidad (HDL-C) y el incremento progresivo y severo en la tasa de excreción urinaria de albúmina (albuminuria). En la población geriátrica, esta relación no se limita a un simple epifenómeno o a un hallazgo estadístico secundario derivado del síndrome metabólico; por el contrario, representa un eje patogénico activo y bidireccional.

La pérdida cuantitativa y cualitativa del HDL-C que actúa como un inductor directo e independiente del daño ultraestructural crónico sobre la barrera de filtración glomerular (TFG), acelerando de forma drástica la transición hacia la enfermedad renal crónica terminal. Si queremos entender por qué existe esta relación tan marcada, primero debemos revisar cómo trabaja el HDL-C en condiciones normales. Fisiológicamente, esta lipoproteína cumple un papel protector muy importante en el endotelio y el epitelio renal. En condiciones normales, las partículas de HDL son las encargadas exclusivas de

mediar el Transporte Reverso de Colesterol (TRC). Este proceso homeostático remueve el exceso de colesterol libre y fosfolípidos de los tejidos periféricos a través de la interacción directa con los transportadores de casete de unión a ATP A1 y G1 (ABCA1 y ABCG1) localizados en la membrana de las células residentes del glomérulo, especialmente en las células mesangiales y los podocitos. Cuando las concentraciones de HDL-C circulante caen de forma crítica, este eflujo lipídico celular se colapsa por completo, desencadenando un fenómeno conocido como lipotoxicidad renal. La acumulación intracelular de ésteres de colesterol y ácidos grasos saturados dentro del podocito altera gravemente la dinámica de su citoesqueleto de actina.

Los podocitos son células terminales altamente especializadas cuyos pedicelos abrazan los capilares glomerulares, formando los diafragmas de hendidura que constituyen el “colador” molecular final del riñón. La investigación de (baohai shao, 2020) afirma que la reducción cuantitativa de las partículas de HDL se acompaña de un remodelamiento patológico de su proteoma superficial, caracterizado por la pérdida de la enzima antioxidante paraoxonasa 1 (PON1) y la apolipoproteína A-I (ApoA-I). Al verse privado de este escudo protector, el glomérulo queda indefenso ante las especies reactivas del oxígeno (ERO) y las lipoproteínas de baja densidad oxidadas (LDLox). Este estrés oxidativo masivo induce el borramiento, la retracción y la fusión de los pedicelos podocitarios. Al destruirse la arquitectura geométrica de la TFG, el riñón pierde su selectividad de tamaño, lo que permite que la albúmina plasmática atraviese la membrana basal y se filtre de manera masiva hacia el espacio urinario. A nivel microvascular, la correlación se hace evidente desde las etapas más tempranas y subclínicas del deterioro renal, sirviendo como un indicador predictivo de disfunción endotelial.

El estudio longitudinal publicado por (Ren M, 2021) demostró de manera concluyente que un perfil lipídico con HDL-C disminuido constituye un factor de riesgo independiente y estadísticamente significativo para el desarrollo de albuminuria de bajo grado (definida como una relación albúmina/creatinina en orina [UACR] entre 11 y 30 mg/g) en la población de adultos mayores.

Los autores destacan que el déficit de HDL-C apaga las vías de señalización dependientes del receptor Scavenger de clase B tipo 1 (SR-B1), las cuales normalmente estimulan a la enzima óxido nítrico sintasa endotelial (eNOS) para producir óxido nítrico, el principal vasodilatador y protector capilar. La consecuente disfunción microvascular y la degradación de la glucocálix endotelial (la capa de carga negativa que repele a la albúmina) provocan microfugas proteicas iniciales.

Este fenómeno ocurre de forma prematura, mucho antes de que los marcadores azoados convencionales detecten una caída franca en la Tasa de Filtración Glomerular estimada (TFG), consolidando al descenso de HDL-C como un biomarcador clínico de alerta temprana. la literatura médica más reciente describe que esta correlación evoluciona de manera deletérea en forma de un círculo vicioso metabólico que perpetúa la enfermedad en el paciente geriátrico. Según la revisión clínica dirigida por (Steven Lacount, 2025) la presencia de albuminuria persistente y el estado inflamatorio sistémico crónico de bajo grado propio de la senescencia (inflammaging) inducen una regulación a la baja (downregulation) en la transcripción génica de la ApoA-I en el hígado y una inhibición de la enzima lecitina-colesterol aciltransferasa (LCAT). La deficiencia de LCAT impide la maduración de las partículas de HDL nacientes a su forma esférica activa, deprimiendo aún más los niveles de HDL-C funcional en el plasma. De este modo, el sistema entra en una retroalimentación positiva patológica: a mayor pérdida urinaria de

albúmina, menor es la concentración de HDL-C disponible, lo que exacerba la inflamación local mediada por el factor nuclear kappa B (NF-\kappa B), acelera la esclerosis del mesangio y precipita la transición descontrolada desde una microalbuminuria incipiente hacia una macroalbuminuria franca o una insuficiencia renal establecida.

2.4.4 Correlación de la Cistatina C

En el estudio de variables cuantitativas continúas aplicadas a poblaciones en edades avanzadas, la literatura científica internacional describe de forma unánime una interacción de carácter estrictamente inverso o negativo entre las concentraciones circulantes de colesterol de alta densidad (HDL-C) y los niveles séricos de Cistatina C. Este comportamiento bivariado establece que el decremento progresivo de la fracción lipídica se asocia, de manera proporcional y constante, con una elevación sistémica de este biomarcador de filtración glomerular. A nivel ultraestructural y analítico, las fluctuaciones concomitantes de ambas moléculas coexisten dentro de un mismo eje de deterioro microvascular, donde la caída en los niveles de HDL-C se vincula de manera directa con la pérdida de la integridad hidrodinámica y estructural de la barrera de ultrafiltración del ovillo capilar. Este daño microangiopático restringe el aclaramiento físico de la Cistatina C a través de las hendiduras podocitarias glomerulares, provocando que la proteína experimente una retención sostenida en el espacio intravascular al no ser depurada ni catabolizada eficientemente por las células tubulares proximales. Esto consolida una dinámica de codependencia donde el punto mínimo de la curva de concentración de HDL-C coincide de forma lineal con el punto máximo de acumulación plasmática de la Cistatina C, trazando una pendiente negativa constante en los gráficos de dispersión bivariado.

Esta dirección analítica y su comportamiento epidemiológico se encuentran ampliamente avalados por investigaciones clínicas contemporáneas que describen con precisión la robustez de este vínculo molecular. Al evaluar el comportamiento bivariado en cohortes masivas de edad avanzada, los hallazgos del estudio epidemiológico Atherosclerosis Risk in Communities (ARIC), reportados por (Shreya Srivastava, 2022) colaboradores en su análisis sobre función renal y niveles lipídicos en adultos mayores, demuestran que el declive de la tasa de filtración glomerular calculada mediante la Cistatina C no se comporta como un evento bioquímico aislado, sino que guarda una estrecha relación inversa con perfiles lipídicos deficientes.

Los datos de esta cohorte describen que los sujetos con los valores más críticos de hipoalfalipoproteinemia exhiben, de forma simultánea, las mayores concentraciones de Cistatina C sérica, definiendo esta correspondencia lineal como un reflejo directo de una disfunción microvascular sistémica donde la reducción del filtrado corre en paralelo con el agotamiento de las fracciones lipídicas de alta densidad. Por su parte, el estudio poblacional dirigido por (Fan Wang, 2013) y colaboradores publicados en la revista PLOS ONE aborda esta interdependencia analítica mediante modelos de regresión multivariante y coeficientes producto-momento, reportando una correlación negativa altamente significativa entre el HDL-C y la Cistatina C circulante. Un acierto crucial en dicha publicación es el efecto de interacción biológica condicionado por el envejecimiento, describiendo que la pendiente de esta correlación inversa se agudiza y se vuelve estadísticamente más robusta a medida que avanza la edad de los individuos evaluados debido a la susceptibilidad acumulada del endotelio renal ante la ausencia de la fracción lipídica protectora.

Asimismo, las investigaciones transversales de estadificación renal recopiladas en el Journal of Clinical Nephrology and Renal Care (P Ravi Kumar, 2020) por investigadores que analizan las ecuaciones de Cistatina C y su correlación con lípidos confirman que el comportamiento de esta proteína responde de forma lineal y predecible ante los descensos del HDL-C, avalando que el aclaramiento disminuido de este marcador coexiste con el déficit de la fracción lipídica y permitiendo trazar una línea de asociación continua, homogénea y libre de interferencias antropométricas entre el estado de la microcirculación capilar y la retención molecular precoz en el compartimento intravascular del sujeto evaluado.

La determinación inferencial de esta relación bivariado dentro de una revisión cuantitativa se ejecuta mediante el análisis de covariación estadística, seleccionando la prueba matemática idónea según el comportamiento previo de la distribución de la muestra evaluada a través de los algoritmos analíticos de Shapiro-Wilk o Kolmogórov-Smirnov con corrección de Lilliefors. Ante datos que siguen una distribución normal, se aplica el coeficiente de correlación producto-momento de Pearson, el cual computa la covariancia de las variables normalizada por el producto de sus desviaciones estándar para medir el grado de asociación lineal entre el perfil lipídico y el biomarcador renal a través de la fórmula:

$$r = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2 \sum_{i=1}^{n}(Y_i - \bar{Y})^2}} \quad (\text{Ec. } 1)$$

Por el contrario, si los datos muestran asimetría o distribuciones libres de supuestos, se ejecuta el coeficiente de correlación por rangos de Spearman (rho), el cual evalúa la

monotonicidad de la relación de dos variables a través de las diferencias de rangos asignados a cada par de datos intersujeto mediante la ecuación:

$$\rho = 1 - \frac{6 \sum_{i=1}^{n} d_i^2}{n(n^2 - 1)} \text{ (Ec. 2)}$$

De acuerdo con los parámetros estándar reportados en las investigaciones, el vector resultante de la correlación debe arrojar de manera invariable un coeficiente con signo negativo, situándose habitualmente en un rango de magnitud moderado a fuerte, comprendido entre r -0.50 \le r \le -0.75. Este signo negativo constituye la evidencia matemática fundamental de la relación inversa del modelo, demostrando estadísticamente que ambas variables se mueven en direcciones opuestas donde al aproximarse el HDL-C a sus rangos mínimos, la Cistatina C sérica tiende hacia sus valores máximos. La significancia asintótica del constructo se supedita a un valor crítico de probabilidad de error tipo I inferior al 5% ($p < 0.05$) bajo un intervalo de confianza bilateral del 95%, un comportamiento estadístico robusto que permite rechazar formalmente la hipótesis nula de independencia y demuestra que la covariación entre el descenso del HDL-C y la elevación de la Cistatina C es un fenómeno real, reproducible y con un alto poder estadístico predictivo dentro de la población de estudio.

2.4.5 Correlación del BUN

El nitrógeno ureico en sangre (BUN, Blood Urea Nitrogen) es un indicador bioquímico ampliamente utilizado para valorar el metabolismo proteico y la capacidad excretora renal. Su concentración refleja la cantidad de urea circulante generada a partir del catabolismo de aminoácidos en el hígado y eliminada principalmente por vía renal.

Cuando existe compromiso funcional del riñón, especialmente a nivel glomerular o por alteraciones hemodinámicas renales, sus niveles séricos tienden a incrementarse.

En relación con el metabolismo lipídico, diferentes estudios han demostrado que las alteraciones renales suelen coexistir con perfiles de HDL-C disminuido, particularmente en adultos mayores. Un estudio poblacional realizado por (You A, 2021) en 4,649 adultos mayores mostró que la reducción de la función renal se asoció de forma independiente con niveles bajos de HDL-C, evidenciando una relación significativa entre deterioro renal y dislipidemia. Investigaciones recientes como la de (Lan Q, 2021) reportaron que valores elevados de BUN en población geriátrica se relacionan con mayor riesgo cardiovascular y mayor carga de daño metabólico, reforzando su utilidad como marcador pronóstico en adultos mayores.

En el artículo (Blanca Guadalupe Baez-Duarte, 2022) observaron que índices lipídicos que incluyen HDL, como el índice TG/HDL, presentaron asociación significativa con BUN y otros marcadores de daño renal, sugiriendo que la disminución del HDL puede acompañarse de alteraciones tempranas en biomarcadores nitrogenados antes de que aparezca enfermedad renal avanzada.

El BUN se cuantifica, principalmente, mediante métodos enzimáticos basados en ureasa, los cuales ofrecen buena sensibilidad analítica. Sin embargo, su interpretación debe contextualizarse en el adulto mayor, ya que factores como deshidratación, ingesta proteica elevada o cambios metabólicos relacionados con el envejecimiento pueden modificar sus valores.

En conjunto, la evidencia científica que existe una relación inversa entre HDL-C y BUN, donde la disminución del HDL-C se asocia con elevación del nitrógeno ureico,

reflejando un posible estado de compromiso renal temprano y mayor vulnerabilidad cardiometabólica en adultos mayores.

2.5 Antecedentes históricos

Los términos colesterol bueno y colesterol malo han sido acuñados desde hace más de una década. Junto con su descubrimiento, se evidenció que, debido a su composición bioquímica, el colesterol no viaja libremente por la sangre. En su estructura, posee una porción polar que permite a las macromoléculas lipoproteicas encargadas de su transporte interactuar mediante puentes de hidrógeno con los grupos polares de los fosfolípidos y las proteínas presentes en la superficie de la lipoproteína.

Las lipoproteínas son partículas sumamente complejas que se caracterizan por poseer en su superficie una monocapa de fosfolípidos y colesterol libre. En su núcleo presentan una región de naturaleza hidrófoba. Compuesta, principalmente por lípidos no polares, como los ésteres de colesterol y los triglicéridos. Cabe destacar que las lipoproteínas difieren tanto en su contenido lipídico como en su composición proteica. Una vez comprendido lo anterior, podemos describir cada una de estas moléculas. Las lipoproteínas plasmáticas se pueden clasificar comúnmente en siete: Quilomicrones, Resto de quilomicrones, VLDL, IDL, LDL, HDL y Lp(a).

2.6 Magnitud del problema

A nivel mundial la problemática por población que padecen de enfermedad renal cada vez es más grande, se estima de uno de cada diez adultos en el mundo padece de ERC, entre ellos la población que más suele desarrollar esta patología es la población adulta específicamente individuos mayores de 50 años.

Al ser una enfermedad de progresión asintomática, en la mayoría de los caso, esta puede llegar a estadios avanzados, evitando que se pueda dar un tratamiento menos invasivo, procurando su calidad de vida.

2.7 Bases legales

Ley 64 de 2012 sobre Derecho de Autor y Derechos Conexos establece que:

TÍTULO V

CONTENIDO DEL DERECHO DE AUTOR

CAPÍTULO II

DERECHOS MORALES

ARTÍCULO 46: “Corresponde exclusivamente al autor la facultad de resolver sobre la divulgación total o parcial de la obra y, en su caso, el modo de hacer dicha divulgación.

Nadie puede dar a conocer, sin el consentimiento de su autor, el contenido esencial de la obra antes de que él lo haya hecho o la obra se haya divulgado.”

ARTÍCULO 47 “El autor tiene el derecho de ser reconocido como tal, determinando que la obra lleve las indicaciones correspondientes y de resolver si la divulgación ha de hacerse con su nombre, seudónimo o signo, o en forma anónima.”

ARTÍCULO 48 “El autor tiene, incluso frente al propietario del objeto material que contiene la obra, el derecho de prohibir toda deformación, mutilación, alteración o cualquier otro atentado a la misma, que pueda poner en peligro el decoro de la obra o su reputación como autor”

CAPÍTULO III

METODOLOGÍA

Metodología

3.1 Tipo y diseño de investigación

El presente estudio tendrá un diseño tipo revisión bibliográfica de tipo descriptivo, analítico con un enfoque correlacional que está dirigido a consolidar las evidencias científicas con respecto a los niveles bajos de HDL-C y su correlación con los biomarcadores de disfunción renal en adultos mayores.

Este diseño permitirá evaluar la relación existente en base al análisis crítico de estudios previamente publicados. No implica una recolección de datos primarios, ni una intervención directa a la población, permitiendo así unificar los distintos enfoques y disminuir la heterogeneidad de conclusiones.

3.2 Población

Dado que el presente estudio corresponde a una revisión bibliográfica, su población está basada en el compendio de artículos científicos, extraídos de base de datos internacionales, y revistas indexadas, los cuales fueron seleccionados tomando en cuenta su concordancia con las características de título, a los objetivos generales y específicos del estudio. Esta selección se enfocó principalmente, en evidencias científicas que reflejen la lipotoxicidad renal basada en las dislipidemias y hayan sido editadas en el periodo comprendido desde el 2020 y 2025.

3.3 Muestra

A partir de la población, se evaluaron una serie de artículos mediante un muestreo no probabilístico, que mantuviera concordancia con los objetivos de la revisión. Descartando el manejo de muestras biológicas, ni intervención directa con humanos o animales; se

evitó tomar de referencia expedientes clínicos, ni datos de pacientes de una institución en específico que alteren los derechos de propiedad del artículo. De este modo guiado por los criterios de inclusión y exclusión, se delimitó que la muestra quedó compuesta de siete (7) artículos científicos. Para optimizar el desarrollo de la investigación estas fuentes se distribuyeron entre los investigadores, finalizando el primer investigador con cuatro (4) artículos, y al segundo investigador tres (3) artículos.

3.4 Criterios de elegibilidad

3.4.1 Criterios de inclusión:

- Artículos publicados en los últimos (cinco) 5 años
- Estudios realizados en una población adulta mayor de (cincuenta) 50 años
- Publicaciones que analicen la relación entre las alteraciones metabólicas lipídicas en la partícula de HDL, y los principales biomarcadores de función renal tales como creatinina sérica, tasa de filtración glomerular, proteinuria y nitrógeno ureico en sangre.

3.4.2 Criterios de exclusión:

- Artículos que enfoquen el aspecto cardiovascular.
- Estudios realizados con pacientes pediátricos.
- Investigaciones que se enfoquen únicamente en pacientes bajo los efecto de fármacos que alteren su metabolismo lipídico.

3.5 Técnicas de recolección de datos

Para determinar el proceso desde la elección del título, hasta el análisis formal de cada uno de los artículos; se determinaron una serie de etapas, y actividades enfocadas para el desarrollo de la investigación basándose en la tabla 1.

Tabla 1. Etapas del Proceso de Investigación sobre HDL-C y Disfunción Renal

Etapa	Métodos	Actividades	Materiales	Procedimientos
1. Revisión / Planificación documental	Definición del tema y objetivos	Delimitación del alcance	Guías metodológicas y criterios de búsqueda	Establecer qué se va a investigar y cómo
2. Selección	Aplicación de criterios de inclusión y exclusión	Implementación del diagrama de flujo PRISMA	Artículos a texto completo y con acceso libre	Filtrar estudios útiles y confiables
3. Síntesis	Análisis documental	Extracción y organización de información clave	Fichas y matrices de análisis	Sistematización de datos
4. Análisis	Análisis comparativo	Comparación de conclusiones entre artículos	Literatura seleccionada	Identificación de coincidencias

Etapa	Métodos	Actividades	Materiales	Procedimientos
5. Discusión	Discusión académica	Elaboración del informe final	Documento final	Redacción y divulgación de conclusiones

3.6 Herramientas de recolección de datos

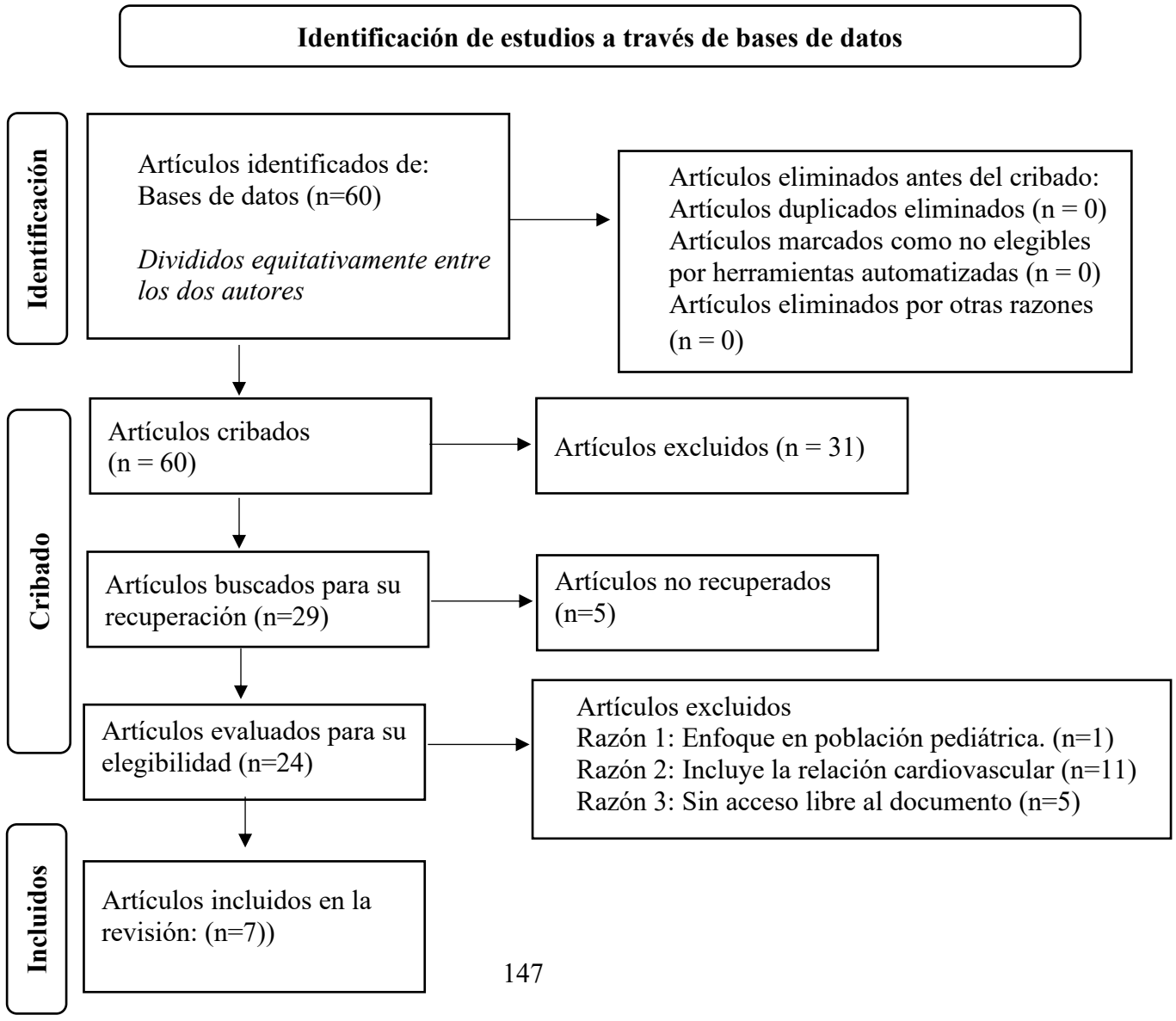
La herramienta utilizada en esta revisión se basó en una matriz de análisis bibliográfico diseñada para la sistematización de información y optimización de la recopilación de la evidencias. De esta misma manera, se utilizó Microsoft Excel para plasmar, registrar y ordenar la evidencia de los siete artículos.

3.7 Procesamiento y análisis de la información

Junto a las metodologías mencionadas anteriormente para el correcto desarrollo de la recolección de datos, el procesamiento de la información se desarrolló en base al diagrama de flujo propuesto por la declaración PRISMA para revisiones bibliográficas. Antes de poder determinar los siete (7) artículos expuestos en la revisión se llevó un proceso de filtración y depuración de que nos permitió mantener los artículos que se adaptaban más a nuestros objetivos.

Figura 5. Diagrama de flujo de procesamiento en selección y análisis de información

Nota: Adaptado de Page et.al (2021)



3.8 Aspectos éticos de la investigación

En concordancia con el reglamento de citación y referenciación requerido por la institución, se respetó la propiedad intelectual de los autores referenciados, evitado el uso indebido de la información, manteniendo fidelidad a su autoría. Nuestra máxima prioridad fue mantener a rigor la utilización adecuada de las normas del estilo APA (7.ª edición).

En cuanto a consideraciones éticas, se puede garantizar que se dio estricto cumplimiento a la declaración de Helsinki. Dado a que el presente estudio es una revisión bibliográfica y no implica la participación directa de sujetos humanos ni el uso de datos clínicos confidenciales, no se requirió consentimiento informado de parte una institución hospitalaria para el debido análisis de datos.

CAPÍTULO IV

PRESENTACIÓN Y ANÁLISIS DE LA INFORMACIÓN

4.1 Presentación de la información

Con el propósito de romper el esquema tradicional de un análisis descriptivo, individualizado; consolidamos los hallazgos teóricos en los siete (7) artículos aplicando las matrices comparativas en la secuencia lógica del Estado del arte, siguiendo así la etapa de comprensión, para desglosar el artículo de manera analítica y descriptiva; la etapa de reflexión crítica en donde el objetivo principal es que se pueda sintetizar los hallazgos científicos, y compararlos con los criterios de elegibilidad y justificar que cumplan con tus criterios de inclusión; y por último, la etapa de naturalización que nos permite explicar la metodología en el ámbito práctico de laboratorio.

Esta estrategia nos permite sintetizar de manera más integrada cada una de las variables en los artículos.

El análisis de la información empieza directamente en la etapa 3, posteriormente a la 4 y 5 exceptuando a la etapa 1 y 2 que ya fueron abordadas de manera tácita, correspondientes a la contextualización y a la clasificación de las fuentes utilizadas para la revisión.

4.1.1 Caracterización documental de la muestra

Tabla 2. Caracterización de la muestra documenta seleccionada

Código	Autor(es) y año	Título del artículo	País, o lugar de desarrollo
A1	Sun, Y, et al. (2025)	Association of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and chronic kidney disease in Elderly insights from NHANES	Estados Unidos
A2	Xu, Z. et al. (2024)	Understanding the heterogeneity and dysfunction of HDL in chronic kidney disease: insights from recent reviews	China
A3	Patel., A. et al. (2025)	A Study of Lipid Profile in Pre-Dialysis Chronic Kidney Disease Patients in Tertiary Care Hospital, South Gujarat	India

A4	Pavanello, C et al. (2023)	HDL and chronic kidney disease	Italia
A5	Weldegiorgis, M., & Woodward, M. (2022).	Elevated triglycerides and reduced high-density lipoprotein cholesterol are independently associated with the onset of advanced chronic kidney disease: a cohort study of 911,360 individuals from the United Kingdom.	Reino Unido
A6	You, A. et al. (2021)	Association Between Renal Dysfunction and Low HDL Cholesterol Among the Elderly in China	China
A7	Dopierała, M. et al. (2025)	New and Emerging Biomarkers in Chronic Kidney Disease	Polonia

Nota: Códigos fueron asignados a partir de la A1-A7 representando cada artículo, para su fácil identificación en las siguientes descripciones.

4.2 Etapa 3: comprensión de los fenómenos

4.2.1 Estudio 1

Association of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and chronic kidney disease in Elderly insights from NHANES. Sun, Y., Li, Z. & Feng, N. *Sci Rep.* **15**, 12611 (2025). https://doi.org/10.1038/s41598-025-96299-7

Tabla 3. Comprensión de fenómenos; estudio 1

Se buscó establecer las relaciones entre los índices de lipídicos, y la ERC, se consideraron los criterios de inclusión /exclusión para su debido análisis en la matriz correspondiente**.**

Formulación del problema	Revista/año / Autor/ámbito	Objetivos	Criterios elegibilidad	Tipo de estudio	Muestra	Variables principales	Métodos de recolección de datos	Instrumentos
El envejecimiento celular es una de las mayores predisposiciones para el desarrollo de enfermedades	*Sci Rep.* (Scientific reports), 2025, Sun, Y. et al. EE.UU.	Establecer la relación que hay entre el índice lipídico (NHHR) y el desarrollo	Criterios de inclusión: Personas mayores de 60 años residentes en los Estados unidos	Estudio transversal, observacional, retrospectivo, de carácter epidemiológico	El estudio estuvo desarrollado en base a datos recopilados entre el 2003 y	Presencia o ausencia de la ERC. Demografía: Sexo, raza, edad, escolaridad,	Se consideró la base de datos de la NHANES, que es recopilada por la	Utilizó R (versión 4.2.0) y el software Empower

crónicas. Y en adultos mayores la probabilidad de desarrollar una ERC es sumamente alto. Las alteraciones que pueden hacer a nivel de moléculas lipídicas son clave para el desarrollo de la relación proporcional del deterioro renal y la dislipidemia		de una enfermedad renal crónica.	considerando especialmente personas obesas (IMC>30). Criterios de exclusión: Individuos menores de 60 años, que no presentan datos en la NHHR, ni en seguimiento por ERC.		2016. En total se tomaron datos de 3715 participantes en donde el 49.9% eran hombres y un 50% eran mujeres.	estado civil, índice de pobreza. Comorbilidades: Diabetes, Tabaquismo, hipertensión, enfermedad cardiovascular u otras enfermedades crónicas.	NCHS, y las CDC	

Nota. ERC: Enfermedad Renal Crónica; NHHR: Ratio de colesterol lipoproteico de densidad no alta/colesterol lipoproteico; IMC: Índice de Masa Corporal; NCHS: Centro Nacional de Estadísticas de Salud; NHANES: Encuesta Nacional de examen de salud y Nutrición; CDC: Centros para el Control y la Prevención de Enfermedades.

4.2.2 Estudio 2

Understanding the heterogeneity and dysfunction of HDL in chronic kidney disease: insights from recent reviews.

Xu, Z., Yang, S. y Cui, L. *BMC Nephrol* **25**, 400 (2024). https://doi.org/10.1186/s12882-024-03808-3

Tabla 4. Comprensión de fenómenos; estudio 2

Establecimos características fisiopatológicas y comorbilidades que pueden aumentar la progresión de la ERC. Se extrajo el fundamento conceptual agregada a la matriz de análisis.

Formulación del problema	Revista/año/ autor/ámbito	Objetivos	Criterios elegibilidad	Tipo de estudio	Muestra	Variables principales	Métodos de recolección de datos	Instrumentos
En los últimos años la ERC ha supuesto una gran problemática en el ámbito de salud pública. Durante la ERC la homeostasia del cuerpo está alterada. Esto quiere decir que	*BMC Nefrology*, 2024, Xu, Z. China	Evaluar la alteraciones en el metabolismo los lípidos, principalmente en la HDL-C y su importancia en el transporte reverso de	Criterios de inclusión: Metaanálisis, revistas indexadas, y artículos científicos que describan el fundamento fisiopatológico de la ERC	Revisión sistemática con un enfoque analítico, descriptivo, y conceptual.	El acervo bibliográfico seleccionado minuciosamente respetando los criterios de elegibilidad, a la vanguardia	Alteración en la microvasculatura. Comorbilidades metabólicas como él esté oxidativo, diabetes, síndrome urémico.	Se determinó un tamizaje por cribado para la exclusión de los artículos menos adecuados.	Herramientas para el registro de datos junto a guías estandarizadas.

muchas de las funciones normales del cuerpo se encuentran afectadas, entre ellas el equilibrio metabólico específicamente cuando el HDL-C se vuelve disfuncional debido a la pérdida de su capacidad protectora, antioxidante y antinflamatorio.		colesterol y la pérdida de la capacidad antiaterogénica. Describir la lipotoxicidad y caracterizarla con la ERC.			del enfoque en la progresión del daño renal, y el impacto de las lipoproteínas a la toxicidad renal.			

Nota. ERC: Enfermedad Renal Crónica; HDL-C: Lipoproteínas de Alta Densidad.

4.2.3 Estudio 3

A study of lipid profile in pre-dialysis chronic kidney disease patients in tertiary care hospital, south Gujarat.

Patel, A., Goyani, R., Dudhrejiya, R., Varma, V., & Naik, G. (2025). The European Journal of Cardiovascular Medicine, 15, 912–917. https://doi.org/10.61336/ejcm/25-04-147

Tabla 5. Comprensión de fenómenos; estudio 3

Establecimos características fisiopatológicas y comorbilidades que puede aumentar la progresión de la ERC. Se extrajo el fundamento conceptual agregada a la matriz de análisis.

Formulación del problema	Revista/año/ autor/ámbito	Objetivos	Criterios elegibilidad	Tipo de estudio	Muestra	Variables principales	Métodos de recolección de datos	Instrumentos
La ERC ha sido clasificada una de las mayores causa de muerte a nivel mundial. Su impacto en la población es cada vez más frecuente.	*The European Journal of Cardiovascular Medicine*, 2025, Patel, A. India	Determinar la prevalencia de pacientes con alteraciones en el metabolismo lipídico a causa de la progresión de la ERC y	Criterios de inclusión: Pacientes adultos, con ERC bajo manejo por prediálisis en estadios 1 a 5. Criterios de exclusión:	Estudio de tipo transversal, observacional, retrospectivo.	50 pacientes adultos, atendidos en el GMERS. Mediante un muestreo intención, no probabilístico con un predominio de estadio 5	Antecedentes de hipertensión arterial, condiciones demográficas (Sexo, raza, edad, escolaridad, estado civil, índice de	Análisis químicos (séricos) crio preservados a -20°C. Registro de las muestras procesadas en analizadores automáticos	Epi Info. CDC versión 7.

La progresión del daño renal eventualmente encamina al paciente y al personal de salud a recurrir a la diálisis, en la mayoría de los casos desconociendo loa marcadores de riesgo aterogénico que pueden prever temprano, y preservar la integridad de los riñones		evaluar los patrones de dislipidemias en distintas etapas de la ERC.	Mujeres embarazadas, bajo tratamiento con estatinas.		al 75% y 24% en estadio 4.	pobreza), perfil lipídico completo.	del laboratorio centra de referencia.	

Nota. ERC: Enfermedad Renal Crónica; HDL-C: Lipoproteínas de Alta Densidad; CDC: Centro de Control y prevención de Enfermedades; GMERS: facultad de medicina y hospital general.

4.2.4 Estudio 4

HDL and chronic kidney disease.

Pavanello, C., & Ossoli, A. (2023). *Atherosclerosis plus*, *52*, 9–17. https://doi.org/10.1016/j.athplu.2023.04.001

Tabla 6. Comprensión de fenómenos; estudio 4

Se sintetizó la relación entre la HDL-C y su correlación ciertos comportamientos enzimáticos que prolongan la lipotoxicidad renal.

Formulación del problema	Revista/año / autor/ámbito	Objetivos	Criterios elegibilidad	Tipo de estudio	Muestra	Variables principales	Métodos de recolección de datos	Instrumentos
Una de las mayores problemáticas en la ERC es que el cuerpo humano no tiene la capacidad de depurar toxinas por sí mismo, afectando directamente el catabolismo de	*ELSEVIER*, 2023, Pavanello, Ch. Et al. Italia	Resumir las alteraciones metabólicas o genéticas que pueden propiciar la progresión de la ERC y su relación con las dislipidemias y su	Criterios de inclusión: Enfoque directo al metabolismo lipídico. Criterios de exclusión: Estudios enfocados a pacientes	Revisión sistemática, descriptiva, retrospectiva.	El corpus documental que fue seleccionado base a sus criterios de elegibilidad.	Presencia de la ERC, uso de estatinas, niveles de colesterol sérico, y triglicéridos.	Integración conceptual de los datos bibliográficos, y revistas indexadas.	Diagramas de flujo metabólico, registro de datos en aplicaciones de Microsoft Word.

las grasas, causando así un falso aumento de triglicéridos. Las alteraciones propias de la ERC impiden que las vías de procesamiento de las grasas actúen de manera correcta permitiendo que las moléculas lipídicas se mantengan más tiempo en el espacio plasmático.		disminución en la partícula de HDL-C. Se evalúa las probables estrategias para disminuir la progresión de la ERC.	tratados con estatinas					

Nota. ERC: Enfermedad Renal Crónica; HDL-C: Lipoproteínas de Alta Densidad; CDC: Centro de Control y prevención de Enfermedades.

4.2.5 Estudio 5

Elevated triglycerides and reduced high-density lipoprotein cholesterol are independently associated with the onset of advanced chronic kidney disease: a cohort study of 911,360 individuals from the United Kingdom.Weldegiorgis, M., & Woodward, M. (2022). *BMC nephrology*, *23*(1), 312. https://doi.org/10.1186/s12882-022-02932-2

Tabla 7. Comprensión de fenómenos; estudio 5

Se revisó el estudio para resaltar que los triglicéridos altos y el HDL bajo son factores independientes que predicen el avance hacia un daño renal grave.

Formulación del problema	Revista/año/ autor/ámbito	Objetivos	Criterios elegibilidad	Tipo de estudio	Muestra	Variables principales	Métodos de recolección de datos	Instrumentos
Aunque las alteraciones en las concentraciones de lípidos plasmáticos son factores de riesgo firmemente establecidos para la	*BMC Nephrology*, 2022 Weldegiorgis, M. et al. Reino unido	Evaluar de manera prospectiva y a gran escala si el (TC), (TG), (LDL-C), (HDL-C) están asociados de forma independient	Criterios de inclusión: Individuos activos registrados en la base de datos CPRD entre enero de 2000 y marzo de 2014, con	Estudio observacional, retrospectivo, y de cohorte.	Una cohorte masiva de 911,360 individuos pertenecientes al (CPRD), vinculada a registros hospitalarios de altas	Concentraciones séricas de Colesterol Total (TC), Triglicéridos (TG), LDL-C y HDL-C	Extracción automatizada de expedientes clínicos electrónicos anonimizados del CPRD.	Datos analíticos procedentes de laboratorios clínicos automatizados integrados al sistema de salud del Reino Unido

morbimortalidad cardiovascular, su impacto directo e independiente sobre el riesgo de desarrollar Enfermedad Renal Crónica (ERC) avanzada en la población general seguía siendo controvertido e inconsistente en la literatura científica		e con la aparición de ERC avanzada (estadios 4-5).	edades entre 20 y 79 años, un (IMC 15-60) Criterios de exclusión: Pacientes que tuvieran menos de 2 años de datos de seguimiento tras su medición basal para minimizar el riesgo de causalidad inversa.		médicas y registros			

Nota. ERC: Enfermedad renal crónica; TC: Colesterol total; TG: Triglicéridos; LDL-C: Lipoproteínas de baja densidad, HDL-C: Lipoproteínas de alta densidad; CPRD: *Clinical Practice Research Datalink*; IMC: índice de masa corporal.

4.2.6 Estudio 6

Association Between Renal Dysfunction and Low HDL Cholesterol Among the Elderly in China

You, A., Li, Y., Tomlinson, B., Yue, L., Zhao, K., Fan, H., Liu, Z., Zhang, Y., & Zheng, L. (2021). *Frontiers in cardiovascular medicine*, *8*, 644208. https://doi.org/10.3389/fcvm.2021.644208

Tabla 8. Comprensión de fenómenos; estudio 6

Se encontró que a medida que cae la tasa de filtración de los riñones, aumenta el riesgo de presentar el colesterol HDL bajo, lo que convierte a la falla renal en un aviso directo de esta alteración.

Formulación del problema	Revista/año/ autor/ámbito	Objetivos	Criterios elegibilidad	Tipo de estudio	Muestra	Variables principales	Métodos de recolección de datos	Instrumentos
Al presentar disminución en las concentraciones de HDL-C se observa una alteración renal que supone estar vinculada con una	*Frontiers in Cardiovascular Medicine* / Año: 2021 / Autores: Aijun You China	Evaluar de manera transversal si la disfunción renal (medida a través de la eGFR) está asociada de forma	Criterios de inclusión: Individuos comunitarios de 60 años o más Criterios de exclusión: Individuos con ausencia	Estudio observacional, transversal.	4,649 pacientes seleccionados en base a los criterios de elegibilidad	TFG, datos demográficos de los participantes, consumo de alcohol, y uso de medicamentos.	A través de datos registrados en cuestionarios estandarizados	Medición de analitos a través del analizador cobas 8000 de Roche diagnostics

población de adultos mayores.		independiente con la presencia de niveles bajos de HDL-C en una población anciana de base comunitaria en China.	simultánea de mediciones de HDL-C y creatinina sérica					

Nota. ERC: Enfermedad renal crónica; eGFR: Tasa de Filtración Glomerular estimada.

4.2.7 Estudio 7

New and Emerging Biomarkers in Chronic Kidney Disease

Dopierała, M. Department of Nephrology, Transplantology and Internal Medicine, Poznan University of Medical Sciences, 61-701 Poznan, Poland *Biomedicines* 2025, *13*(6), 1423; https://doi.org/10.3390/biomedicines13061423

Tabla 9. Comprensión de los fenómenos

Se revisó el estudio para resaltar que los triglicéridos altos y el HDL bajo son factores independientes que predicen el avance hacia un daño renal grave.

Formulación del problema	Revista/año/ autor/ámbito	Objetivos	Criterios elegibilidad	Tipo de estudio	Muestra	Variables principales	Métodos de recolección de datos	Instrumentos
Los biomarcadores tradicionales (creatinina/albúmina) son insuficientes para predecir la transición a eventos cardiovasculares adversos	*Frontiers in Cardiovascular Medicine*, 2021 / (Revisión técnica de biomarcadores asociados a ERC y riesgo	Evaluar y sintetizar el valor pronóstico de biomarcadores inflamatorios y cardiovasculares emergentes	Criterios de inclusión: Estudios clínicos y observacionales que evalúan ficolinas, inflamasoma NLRP3, receptores	Revisión analítica observacional, retrospectivo.	Un considerable corpus documental científico que abarca múltiples cohortes de pacientes con ERC en diversos	Concentraciones séricas de marcadores (SIRI, NLR, CAR, Ficolinas, NLRP3, TNFR1/2, Calprotectina, Galectina-3, sST-2, GDF-15, suPAR)	Análisis comparativo y validación de marcadores mediante pruebas inmunológicas, citometría de flujo y ensayos	Datos analíticos procedentes de laboratorios clínicos automatizados integrados al sistema de salud del Reino Unido

(MACE) y la progresión de la ERC, la cual cursa como un estado de inflamación crónica sistémica.	cardiovascular).	en la progresión de la ERC y su asociación independiente con la mortalidad.	de TNF, calprotectina, SIRI, NLR, CAR, galectina-3, sST-2, GDF-15 y su par en el contexto de ERC. Criterios de exclusión: Estudios que no establecen una correlación significativa entre el marcador, la función renal y eventos cardiovasculares.		estadios (I-V) y con comorbilidades asociadas.		bioquímicos en pacientes con ERC.	

Nota. CAR: ratio proteína C reactiva-albúmina; ERC: enfermedad renal crónica; GDF-15: factor de diferenciación de crecimiento 15; MACE: eventos cardiovasculares adversos mayores; NLR: relación neutrófilo-linfocito; NLRP3: inflamasoma NLRP3; SIRI: índice de respuesta inflamatoria sistémica; sST-2: ST2 soluble; suPAR: receptor soluble del activador del plasminógeno tipo urocinasa; TNFR1/2: receptores del factor de necrosis tumoral 1 y 2.

4.3 Etapa 4: Reflexión para la acción crítica

4.3.1 Estudio 1: Asociación entre la relación colesterol no HDL/colesterol HDL y la enfermedad renal crónica en ancianos: información obtenida del estudio NHANES.

En este estudio de carácter transversal, observacional, retrospectivo, y de carácter epidemiológico realizado en Estados Unidos pone en evidencia una gran problemática de salud pública que aqueja a la población estadounidense o residente. Los autores utilizaron la base de datos de la NHANES para seleccionar 3715 participantes mayores de 60 años, con ERC, considerando, especialmente, a la población estadounidense o residente que cuenta con índice de masa corporal mayor a 30 kg/m^2. El objetivo principal fue establecer la relación que había entre un nuevo índice lipídico.

Entender la correlación entre la ERC con la dislipidemia es un tanto complejo, y más aún cuando hay un limitado acceso a información que realmente priorice la relación entre estas dos alteraciones.

Sun, Y. (2025) utiliza la base de datos de la NHANES comprendida entre 2003 a 2016. Junto a ello se revisaron alrededor de 71,058 participantes que fueron sometidos a una riguroso proceso de selección que priorizó a los 3715 que cumplían con los criterios de elegibilidad. Considerando la complejidad en la etapa de muestreo, los participantes fueron estratificados según características demográficas.

La cohorte del estudió estuvo compuesta por el 49,48% de los hombres y el 50, 52%. Dándonos así una relación equitativa que evita es sesgo por sexo. El autor menciona que el grupo racial más grande fueron los blancos no hispanos representando

el 58.59% es decir que los resultados de este estudio describirían en un contexto geográfico racial la población estadounidense.

Al evaluar los resultados, el autor reveló que la asociación en el índice NHHR en donde se asocia directamente con la ERC, arrojando un 35.99% de participantes con ERC y un 2,70 ± 1,13. Descartó la presencia de alguna disparidad por características demográficas, esto quiere decir que la lipotoxicidad renal actúa indiferente a la demografía, siendo el IMC la única excepción. De esta manera se puede concluir que, si el participante cursa un peso normal y una ERC, el índice lipídico NHHR le afectará indistintamente, pero si el participante cursa con un IMC>30 la aumenta exponencialmente la progresión de la ERC. De esta misma manera, se halló una fuerte prevalencia en el subgrupo de adulto mayores.

4.3.2 Estudio 2: Comprender la heterogeneidad y la disfunción de las HDL en la enfermedad renal crónica: perspectivas de revisiones recientes

La revisión evalúa grandes aspectos de la correlación entre el HDL y la ERC, desde la composición de las HDL hasta la inactivación de rutas catabólicas de las lipoproteínas séricas.

Entender la fisiopatología de la ERC y su factor de riesgo asociado a las dislipidemias puede ser algo complejo, ya que múltiples evidencias se enfocan en la implicación parénquimal y la pérdida de la capacidad antiaterogénica, en vez de enfocarse en los mecanismos que llevan a que haya cambios estructurales en las partículas de HDL cursando la ERC. Al revisar la heterogeneidad de las HDL logramos entender los múltiples factores que propician la progresión de la ERC.

Xu, Z. (2024) plantea la premisa que la mayoría de los autores mencionan como eje central al hígado como el principal responsable del catabolismo de las grasas, pero nuevos artículos contradicen la premisa basándose en la teoría de que, aunque el efecto del hígado sea directo, el de los riñones es indirecto, pero más complejo al momento de eliminar el componente lipídico.

El autor asevera que la disminución del HDL-C en la ERC está asociada directamente a la falta de regulación enzimática. Entre ellas se menciona la disminución de la proteína lipasa y consecuente a ello el aumento de los triglicéridos. También se menciona la expresión reducida de los ABCA1 que impide el transporte reverso del colesterol, aunado a ello se menciona la alteración en la estructura de la HDL-C que resultan en perdida en la función antiinflamatoria, y antioxidante propiciando el ambiente urémico, junto a la progresión de la ERC.

De esta manera este estudio, descriptivo concluyó con la teoría que además de las funciones antiaterogénica de la HDL-C, esta puede aumentar el riesgo de progresión al exacerbar el daño a nivel de células endoteliales, o simplemente a la liberación de radicales libres por el estrés oxidativo.

4.3.3 Estudio 3: Estudio del perfil lipídico en pacientes con enfermedad renal crónica en etapa prediálisis en un hospital de atención terciaria del sur de Gujarat

El desarrollo de este estudio de tipo observacional, transversal tiene como objetivo establecer un patrón en los distintos estadios de la ERC.

Patel, A. (2025) tomó de la base de datos del hospital cincuenta (50) pacientes con distintos estadios de la ERC, desde los que están en etapa de prediálisis, hasta los que ya habían recibido trasplante.

El autor expresa su preocupación en la creciente problemática en el país que busca desarrollar patrones con los niveles de lípidos séricos para usarlos como marcadores tempranos de daño renal que pueden evitar que el paciente llegue inclusive al tratamiento con diálisis.

Al realizar este estudio el autor consideró que los pacientes que se encontraran bajo tratamiento con inmunsupresores, embarazadas, y tratados con estatinas. La guía para clasificación de las variables estuvo basada en directrices de la KDIGO. Y, de esta misma manera, se seleccionaron a los pacientes ingresados a cuidados de atención terciaria, atendidos entre mayo 2022 a enero de 2024 basándose en un muestreo intencional, no probilístico para su debida cuantificación sérica en analizadores en el laboratorio central de referencia.

El autor recopiló los datos estadístico en el software Epi Info CDC, versión 7. Los resultados arrojaron una grave alteración en los niveles de lípidos séricos.

Al haber recopilado pacientes con algunas comorbilidades, se concluyó que la población de mediana a avanzada edad que esta actúan como un acelerador de lesión renal. Se determinó que el nexo entre le ERC y la dislipidemia es inevitable y ambos son consecuentes. Se destacó que los pacientes que no presentaban enfermades crónicas, a medida que la ERC se desarrollaban, empezaron tener muchas más alteraciones metabólicas que parcialmente corroboran nuestra expectativa de resultado.

4.3.4 Estudio 4: HDL y enfermedad renal crónica

Al igual que este estudio, muchos se enfocan en el impacto negativo que puede llegar a tener el deterioro de la función renal describiendo la relación entre el HDL-C y la progresión de la ERC. Pero esta no siempre se observa. Pavanello, C. (2023) en su escrito describe el estudio CRIC Rahman, M. (2014) e indica que la relación entre el HDL-C y el riñón no es directa, el autor analiza una cohorte de 3,939 paciente en donde se evidenció que los niveles séricos si presentan niveles oxidativos, pero, no predice el daño renal. Planteándonos la siguiente interrogante.

¿El HDL-C disminuido causa lesión renal, o es el daño en el parénquima renal que afecta el metabolismo lipídico?

Esta cohorte nos evidencia que los niveles plasmáticos de la HDL-C no causa directamente la progresión en la ERC, ni con la alteración de la TFG. Sino que, esta se debe a una cascada fisiopatológica de eventos multifactoriales tales como: el estrés oxidativo, inactivación de mecanismos antiinflamatorios, y retraso de la tasa de aclaramiento de los lípidos séricos; que no corresponde a una causalidad lineal directa, sino a un detonante metabólico que resulta en progresión de la ERC.

4.3.5 Estudio 5: Los niveles elevados de triglicéridos y la disminución del colesterol de lipoproteínas de alta densidad se asocian de forma independiente con la aparición de enfermedad renal crónica avanzada: un estudio de cohorte de 911.360 individuos del Reino Unido.

Este artículo de investigación desarrolla el papel del perfil lipídico como factor de riesgo independiente y no invasivo para el diagnóstico predictivo de la enfermedad renal crónica

(ERC) avanzada, especialmente útil en entornos clínicos donde se busca prevenir la progresión hacia estadios terminales. El informe establece que:

> Los factores de riesgo tradicionales, como la hipertensión y la diabetes, están bien establecidos, pero el papel de los lípidos en la progresión a la ERC avanzada sigue siendo controvertido. Los estudios anteriores han arrojado resultados contradictorios, posiblemente debido a la causalidad inversa, las diferencias en los ajustes por confusión, las definiciones de la ERC y el uso de estatinas. (Misghina Weldegiorgis, 2022, pág. 4)

Uno de los aportes centrales del documento es explicar la utilidad clínica del monitoreo de los triglicéridos y las lipoproteínas de alta densidad (HDL-C). En ese sentido, se señala que:

> Los triglicéridos elevados y el colesterol HDL reducido se asociaron de forma independiente con un mayor riesgo de desarrollar ERC avanzada. Por el contrario, el colesterol total y el colesterol LDL no se asociaron con la ERC avanzada después de ajustar por comorbilidades y el uso de estatinas. (Misghina Weldegiorgis, 2022, pág. 3)

A diferencia de otros reportes, este estudio clínico cuenta con una muestra directa masiva fundamentada en evidencia epidemiológica de gran escala, analizando registros de 911,360 individuos de una cohorte poblacional del Reino Unido. Asimismo, el documento destaca la relevancia de analizar estas fracciones de forma específica en subgrupos vulnerables:

> La fuerza de la asociación entre los triglicéridos y el colesterol HDL con la ERC avanzada fue mayor en las mujeres que en los hombres. Además, en adultos mayores de 60 años o más, los niveles bajos de HDL-C mantuvieron una correlación de riesgo sólida y significativamente alta para el inicio del daño renal. (Misghina Weldegiorgis, 2022, pág. 7)

En conjunto, este documento representa una fuente científica de alto nivel que respalda la incorporación del perfil de triglicéridos y HDL-C como herramientas clínicas válidas para orientar decisiones médicas y estrategias preventivas en la salud renal del adulto mayor.

4.3.6 Estudio 6: Asociación entre disfunción renal y niveles bajos de colesterol HDL en ancianos en China

Este artículo de investigación desarrolla el papel de la disfunción renal como un factor predictor independiente de niveles bajos de colesterol HDL en la población geriátrica, resultando una herramienta valiosa para la evaluación del perfil metabólico en adultos mayores que viven en la comunidad. El informe establece que:

> Aunque los niveles bajos de colesterol HDL son un marcador tradicional de riesgo cardiovascular, la asociación específica entre la disfunción renal y el HDL-C bajo en la población de adultos mayores que vive en la comunidad sigue siendo un área que requiere mayor claridad. (Aijun You, 2021)

Uno de los aportes centrales del documento es explicar la relación entre la Tasa de Filtración Glomerular estimada (eGFR) y las alteraciones lipídicas. En ese sentido, se señala que:

> La disfunción renal se asoció de forma independiente con la presencia de niveles bajos de colesterol HDL, observándose una relación dosis-respuesta donde la prevalencia de HDL-C bajo aumentaba progresivamente a medida que disminuía la eGFR. (Aijun You, 2021)

A diferencia de otros reportes, este estudio clínico aporta evidencia en una muestra poblacional de adultos mayores de 60 a 104 años, analizando a 4,649 participantes tras excluir aquellos con datos incompletos. Asimismo, el documento destaca la relevancia de considerar la función renal para entender la salud metabólica:

> La asociación independiente entre eGFR y HDL-C bajo se mantuvo constante tras realizar ajustes multivariables por edad, sexo, índice de masa corporal, tabaquismo, uso de medicamentos y comorbilidades como la diabetes y la hipertensión. (Aijun You, 2021)

En conjunto, este documento representa una fuente científica de alto nivel que respalda la incorporación del monitoreo de la función renal como un indicador estrechamente ligado al perfil lipídico, siendo fundamental para orientar decisiones clínicas y estrategias preventivas en la salud del adulto mayor.

4.3.7 Estudio 7: Nuevos biomarcadores emergentes en la enfermedad renal crónica

El análisis de los biomarcadores renales y cardiovasculares en el contexto de la enfermedad renal crónica (CKD) permite establecer una herramienta valiosa para la evaluación integral de la salud metabólica en pacientes con riesgo de deterioro renal progresivo. El informe establece que:

Aunque los marcadores tradicionales son útiles, la evaluación de biomarcadores específicos de secreción tubular, inflamatorios y cardiovasculares sigue siendo un área que requiere mayor claridad para optimizar la detección temprana y la estratificación del riesgo. (Mikołaj Dopierała, 2025)

Uno de los aportes centrales es explicar cómo diferentes perfiles de biomarcadores se relacionan con la progresión de la lesión renal y las complicaciones sistémicas. En ese sentido, se señala que:

La presencia de biomarcadores como KIM-1, NAG, uromodulina, Klotho y DKK-3 se asocia de forma independiente con la salud tubular, mientras que la elevación de marcadores inflamatorios (como NLRP3, TNFR1/2, SIRI) y cardiovasculares (como Galectina-3, sST2, GDF-15, suPAR) refleja la magnitud del daño y el riesgo de mortalidad cardiovascular, observándose una relación directa entre estos perfiles y el pronóstico del paciente. (Mikołaj Dopierała, 2025)

Este enfoque aporta evidencia sobre la relevancia de considerar la heterogeneidad de los biomarcadores para entender la patología renal compleja.

Asimismo, el documento destaca la importancia de integrar estas mediciones para la toma de decisiones clínicas:

La asociación independiente entre estos biomarcadores y el deterioro de la función renal se mantiene constante tras realizar ajustes por factores de riesgo metabólico, como el estado lipídico y la presencia de otras comorbilidades. (Mikołaj Dopierała, 2025)

En conjunto, este marco representa una fuente científica de alto nivel que respalda la incorporación de un monitoreo multifactorial de biomarcadores, esto es fundamental para orientar decisiones clínicas y estrategias preventivas en la salud del paciente renal.

4.4 Conclusiones y recomendaciones generales

4.4.1 Etapa 5: Reflexión para la acción crítica

Tras el análisis individual de los estudios incluidos en esta revisión, se evidencian coincidencias relevantes en torno al valor diagnóstico de los perfiles lipídicos y los biomarcadores tubulares en la enfermedad renal crónica (ERC). La mayoría de los autores coincide en que los niveles elevados de triglicéridos y una concentración reducida de colesterol HDL actúan como factores predictores independientes y significativos de la progresión hacia estadios renales avanzados, manteniendo una correlación clínica sólida, particularmente, en la población de adultos mayores. Esta asociación demuestra que las alteraciones en el metabolismo lipídico actúan como indicadores críticos del deterioro progresivo de la función renal.

Asimismo, la integración de biomarcadores especializados que abarcan indicadores de salud tubular como el KIM-1, la NAG y la uromodulina permite trascender las limitaciones de los métodos tradicionales, como la creatinina o la albúmina. Esta evaluación permite una estratificación del riesgo más precisa al aportar información específica sobre la integridad del daño tubular, facilitando la detección de la progresión de la ERC antes de alcanzar estadios terminales. En conjunto, esta evidencia respalda la implementación de un abordaje diagnóstico integral que combine el perfil metabólico con nuevos indicadores biomoleculares renales para frenar eficazmente el avance de la enfermedad.

Conclusiones

- Se determinan que la disminución cuantitativa y la disfunción cualitativa de la lipoproteína de alta densidad actúan como un marcador fisiopatológico precoz de daño endotelial e inflamación sistémica, lo que justifica plenamente su análisis clínico preventivo para identificar el compromiso renal mucho antes de que se manifiesten los síntomas clínicos avanzados de la patología.
- Los biomarcadores convencionales empleados en la rutina diagnóstica demostraron reflejar de manera proporcional el avance del daño tisular establecido en etapas tardías, pero carecen de la sensibilidad analítica necesaria en las fases iniciales, validando así la urgencia metodológica de incorporar índices lipídicos compuestos para optimizar el cribado oportuno.
- El desarrollo progresivo de la enfermedad renal crónica genera un entorno urémico adverso que inhibe de forma directa la actividad de enzimas metabólicas clave como la lipoproteína lipasa, lo cual bloquea el transporte reverso de colesterol y explica el mecanismo molecular recíproco por el que las alteraciones lipídicas aceleran el deterioro de la función renal.
- El estrés oxidativo crónico y los factores demográficos propios del envejecimiento celular amplifican la susceptibilidad y la citotoxicidad renal en la población mayor de 50 años, consolidando el motivo fundamental de esta investigación de establecer perfiles preventivos desde el laboratorio clínico aplicable a las necesidades de la salud pública panameña.

Recomendaciones

- Se propone incorporar en la práctica del laboratorio clínico el cálculo sistemático del índice lipídico compuesto mediante la relación entre el colesterol No-HDL y el HDL-C como una herramienta analítica accesible y altamente predictiva que permita un diagnóstico oportuno orientado a evitar que el paciente progrese hacia estadios terminales irreversibles de la patología.
- Se sugiere fortalecer de manera integral el enfoque de la medicina preventiva mediante la interpretación conjunta de los biomarcadores renales y metabólicos en lugar de analizar valores aislados, contribuyendo directamente a la reducción del impacto de las comorbilidades crónicas y garantizando un envejecimiento digno, saludable y de calidad para el adulto mayor.
- Se recomienda impulsar el uso formal y la validación en el laboratorio de parámetros analíticos alternativos de mayor sensibilidad analítica precoz tales como la Cistatina C y la Albuminuria, lo cual optimizará de forma significativa los recursos económicos del sistema de salud pública panameña mediante la detección temprana en fases reversibles.
- Se plantea desarrollar e implementar programas de capacitación sanitaria y educación comunitaria dirigidos específicamente a la población mayor de 50 años sobre el control estricto de los factores de riesgo metabólicos, empoderando activamente a los ciudadanos en su autocuidado y disminuyendo de este modo la incidencia crítica de la insuficiencia renal a nivel nacional.

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