كليـــــة الـطب
و الصيدلة - مراكش
FACULTE DE MEDECINE
ET DE PHARMACIE - MARRAKECH

**Année 2026** **These N° 135**

# Dyslipidemia in Adult Chronic Kidney Disease Patients at CHU Mohammed VI: Prevalence, Clinical Associations, and Integrated Cardiovascular and Renal Risk Assessment (2022-2024)

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**THESE :**

**PRÉSENTÉ ET SOUTENUE PUBLIQUEMENT LE 24/04/2026**

**PAR**

**M. Bassam Bachiri Taoufiq**

Né le 19/08/2000 à Marrakech.

**POUR L'OBTENTION DU DOCTORAT EN MÉDECINE**

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## MOTS-CLES:

Chronic kidney disease; Dyslipidemia; Hypertriglyceridemia; Low HDL-C; Albuminuria; eGFR; Cardiovascular risk; KDIGO risk

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## JURY

| | | |
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| Mme. | I. Laouad<br>Professeur de Néphrologie | **Président** |
| Mme. | W. Fadili<br>Professeur de Néphrologie | **Rapporteur** |
| Mme. | S. Karimi<br>Professeur de Cardiologie | **Jury** |
| Mme. | S. Zaoui<br>Professeur de Pharmacologie | |
| M. | A. Meftah<br>Professeur d'Endocrinologie | |

# Serment d'Hippocrate

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me le demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.


Acknowledgement

## Professor L. Laouad (Nephrology) — Chair of the Jury

*I respectfully thank you for accepting to chair this jury and for honoring this work with your presence. Your scientific rigor, high standards, and breadth of academic perspective give this defense a particular significance. I was deeply appreciative of the careful attention you devoted to reviewing this manuscript and of the quality of your remarks, always precise and fair. Beyond the honor, your chairmanship represents for me both a reference point and a source of inspiration. Please accept the expression of my highest consideration and sincere gratitude.*

## Professor W. Fadili (Nephrology) — Rapporteur

*I extend my most sincere thanks for accepting to serve as rapporteur for this thesis. Your attentive reading, availability, and the precision of your comments have strengthened the scientific solidity of this manuscript. I especially appreciated your ability to combine high standards with genuine kindness—standards that elevate, and kindness that reassures. Your guidance brought clarity and direction to this work, and your humanity made the burden lighter to carry. Please accept the assurance of my deep respect and gratitude.*

## Professor S. Karimi (Cardiology) — Member of the Jury

*I thank you for accepting to be part of this jury and for dedicating your time to the evaluation of this thesis. Your cardiology expertise provided a valuable cross-disciplinary perspective and brought greater clinical depth to the interpretation of the results. I was touched by the interest you showed in this work and by the relevance of your remarks. Your rigorous yet constructive feedback helped deepen the reflection and strengthen the coherence of the manuscript. Please accept the expression of my respectful gratitude.*

## Professor S. Zaoui (Pharmacology) – Member of the Jury

*I express my profound gratitude for the honor you give me by accepting to judge this work. Your pharmacology perspective—precise and illuminating—added essential value, particularly regarding therapeutic aspects and the critical appraisal of treatments. I appreciated the depth of your reading and the quality of your observations, expressed with rigor and balance. Your contribution strengthened both the academic weight of the manuscript and its clinical relevance. Please accept the expression of my highest consideration and sincere thanks.*

## Professor A. Meftah (Endocrinology) – Member of the Jury

*I warmly thank you for accepting to be part of this jury and for offering your expert perspective on this thesis. Your experience in endocrinology enriched the metabolic approach and helped clarify the complex links between endocrine dimensions and renal outcomes. I was grateful for the relevance of your remarks and for the kindness with which you accompanied your evaluation. Your contribution enhanced the scientific quality and clinical coherence of this manuscript. Please accept the expression of my deep respect and gratitude.*

### To my mother, Soumia Elidrissi Maaroufi

*Mom, if this work has come to life, it is because you have always been my first certainty. In your prayers, I found paths when I could see only walls. In your patience, I learned that we grow quietly, day after day. You carried my fatigue without counting it, and you celebrated my small victories as if they were entire worlds. May these pages be a humble reflection of everything your love has built within me.*

### To my father, Mohamed Bachiri Taoufiq

*Dad, you taught me the straightness of one's steps and the dignity of effort. You made perseverance a discipline and silence a strength. When doubt appeared, your example reminded me that one does not retreat from what deserves to be accomplished. Thank you for your steady confidence, your constant support, and for that quiet pride that warms more than long speeches. This work bears your imprint—the imprint of a man who lifts others by example.*

### To my sister, Mahacine Bachiri Taoufiq

*My sister, thank you for being that simple and precious bond—the one that reassures, brings a smile, and keeps you standing. Your presence alone was sometimes enough to lighten heavy days. You knew how to encourage without pressure, love without conditions, and believe in me with a certainty I often lacked. In this journey, you were gentleness, stability, and a sisterly refuge. I am happy to share this moment with you and to place my gratitude here in writing.*

### To my parents-in-law and brothers-in-law

*To you, who welcomed me with generosity, thank you for your trust and support. You offered my path a rare serenity: that of a home where one feels respected, understood, and carried. During demanding periods, your kindness was a breath of relief. Thank you for your reassuring words, your simple gestures, and your quiet way of supporting without noise. Please accept the expression of my deep gratitude and respect.*

*To my wife, Zakia Khachia*

*Zakia, there are loves that beautify life, and others that hold it upright. You have been both. You walked with me through long nights of work, absences, and silences filled with fatigue, and you never let the storm take over the peace. When I doubted, you brought me back to myself with a gentleness that asks for nothing but gives everything. You loved this project the way you love me: with patience, loyalty, and that calm strength that reassures without a sound.*

*If this thesis has a soul, it is yours that protected it. And if I put rigor into it, I put into it above all what your love taught me: to endure, to believe, to move forward... and to return to you.*


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| 223 | SBAI Asma | MCHab | Informatique |
| 224 | EL AMIRI My Ahmed | MCHab | Chimie de Coordination bio-organnique |
| 225 | ABISSY Meriem | MC | Microbiologie |
| 226 | SLIOUI Badr | MC | Radiologie |
| 227 | CHEGGOUR Mouna | MC | Biochimie |
| 228 | BELARBI Marouane | MC | Néphrologie |
| 229 | LALAOUI Abdessamad | MC | Pédiatrie |
| 230 | ESSAFTI Meryem | MC | Anesthésie-réanimation |
| 231 | RACHIDI Hind | MC | Anatomie pathologique |
| 232 | FIKRI Oussama | MC | Pneumo-phtisiologie |
| 233 | EL HAMDAOUI Omar | MC | Toxicologie |
| 234 | EL HAJJAMI Ayoub | MC | Radiologie |
| 235 | BOUMEDIANE El Mehdi | MC | Traumato-orthopédie |
| 236 | RAFI Sana | MC | Endocrinologie et maladies métaboliques |
| 237 | JEBRANE Ilham | MC | Pharmacologie |
| 238 | LAKHDAR Youssef | MC | Oto-rhino-laryngologie |
| 239 | LGHABI Majida | MC | Médecine du Travail |
| 240 | AIT LHAJ El Houssaine | MC | Ophtalmologie |
| 241 | RAMRAOUI Mohammed-Es-said | MC | Chirurgie générale |
| 242 | EL MOUHAFID Faisal | MC | Chirurgie générale |
| 243 | AHMANNA Hussein-choukri | MC | Radiologie |
| 244 | AIT M’BAREK Yassine | MC | Neurochirurgie |
| 245 | ELMASRIOUI Joumana | MC | Physiologie |
| 246 | FOURA Salma | MC | Chirurgie pédiatrique |
| 247 | LASRI Najat | MC | Hématologie clinique |
| 248 | BOUKTIB Youssef | MC | Radiologie |
| 249 | MOUROUTH Hanane | MC | Anesthésie-réanimation |
| 250 | BOUZID Fatima zahrae | MC | Génétique |
| 251 | MRHAR Soumia | MC | Pédiatrie |
| 252 | QUIDDI Wafa | MC | Hématologie |
| 253 | BEN HOUMICH Taoufik | MC | Microbiologie-virologie |
| 254 | FETOUI Imane | MC | Pédiatrie |
| 255 | FATH EL KHIR Yassine | MC | Traumato-orthopédie |
| 256 | NASSIRI Mohamed | MC | Traumato-orthopédie |
| 257 | AIT-DRISS Wiam | MC | Maladies infectieuses |
| 258 | AIT YAHYA Abdelkarim | MC | Cardiologie |
| 259 | DIANI Abdelwahed | MC | Radiologie |
| 260 | AIT BELAID Wafae | MC | Chirurgie générale |
| 261 | ZTATI Mohamed | MC | Cardiologie |
| 262 | HAMOUCHE Nabil | MC | Néphrologie |
| 263 | ELMARDOULI Mouhcine | MC | Chirurgie Cardio-vasculaire |
| 264 | BENNIS Lamiae | MC | Anesthésie-réanimation |
| 265 | BENDAOUD Layla | MC | Dermatologie |
| 266 | HABBAB Adil | MC | Chirurgie générale |

| 267 | CHATAR Achraf | MC | Urologie |
|---|---|---|---|
| 268 | OUMGHAR Nezha | MC | Biophysique |
| 269 | HOUMAID Hanane | MC | Gynécologie-obstétrique |
| 270 | YOUSFI Jaouad | MC | Gériatrie |
| 271 | NACIR Oussama | MC | Gastro-entérologie |
| 272 | BABACHEIKH Safia | MC | Gynécologie-obstétrique |
| 273 | ABDOURAFIQ Hasna | MC | Anatomie |
| 274 | TAMOUR Hicham | MC | Anatomie |
| 275 | IRAQI HOUSSAINI Kawtar | MC | Gynécologie-obstétrique |
| 276 | EL FAHIRI Fatima Zahrae | MC | Psychiatrie |
| 277 | BOUKIND Samira | MC | Anatomie |
| 278 | LOUKHNATI Mehdi | MC | Hématologie clinique |
| 279 | ZAHROU Farid | MC | Neurochirugie |
| 280 | MAAROUFI Fathillah Elkarim | MC | Chirurgie générale |
| 281 | EL MOUSSAOUI Soufiane | MC | Pédiatrie |
| 282 | BARKICHE Samir | MC | Radiothérapie |
| 283 | ABI EL AALA Khalid | MC | Pédiatrie |
| 284 | AFANI Leila | MC | Oncologie médicale |
| 285 | EL MOULOUA Ahmed | MC | Chirurgie pédiatrique |
| 286 | LAGRINE Mariam | MC | Pédiatrie |
| 287 | DAFIR Kenza | MC | Génétique |
| 288 | CHERKAOUI RHAZOUANI Oussama | MC | Neurologie |
| 289 | ABAINOU Lahoussaine | MC | Endocrinologie et maladies métaboliques |
| 290 | BENCHANNA Rachid | MC | Pneumo-phtisiologie |
| 291 | EL GUAZZAR Ahmed | MC | Chirurgie générale |
| 292 | OULGHOUL Omar | MC | Oto-rhino-laryngologie |
| 293 | AMOCH Abdelaziz | MC | Urologie |
| 294 | ZAHLAN Safaa | MC | Neurologie |
| 295 | EL MAHFOUDI Aziz | MC | Gynécologie-obstétrique |
| 296 | CHEHBOUNI Mohamed | MC | Oto-rhino-laryngologie |
| 297 | LAIRANI Fatima ezzahra | MC | Gastro-entérologie |
| 298 | SAADI Khadija | MC | Pédiatrie |
| 299 | TITOU Hicham | MC | Dermatologie |
| 300 | EL GHOUL Naoufal | MC | Traumato-orthopédie |
| 301 | BAHI Mohammed | MC | Anesthésie-réanimation |
| 302 | RAITEB Mohammed | MC | Maladies infectieuses |
| 303 | DREF Maria | MC | Anatomie pathologique |
| 304 | ENNACIRI Zainab | MC | Psychiatrie |
| 305 | BOUSSAIDANE Mohammed | MC | Traumato-orthopédie |
| 306 | JENDOUZI Omar | MC | Urologie |
| 307 | MANSOURI Maria | MC | Génétique |
| 308 | ERRIFAIY Hayate | MC | Anesthésie-réanimation |
| 309 | BOUKOUB Naila | MC | Anesthésie-réanimation |
| 310 | OUACHAOU Jamal | MC | Anesthésie-réanimation |
| 311 | EL FARGANI Rania | MC | Maladies infectieuses |
| 312 | IJIM Mohamed | MC | Pneumo-phtisiologie |
| 313 | AKANOUR Adil | MC | Psychiatrie |
| 314 | ELHANAFI Fatima Ezzohra | MC | Pédiatrie |
| 315 | BOUROUMANE Mohamed Rida | MC | Anatomie |

| 316 | IJDDA Sara | MC | Endocrinologie et maladies métaboliques |
|---|---|---|---|
| 317 | GHARBI Khalid | MC | Gastro-entérologie |
| 318 | ATBIB Yassine | MC | Pharmacie clinique |
| 319 | MOURAFIQ Omar | MC | Traumato-orthopédie |
| 320 | ZAIZI Abderrahim | MC | Traumato-orthopédie |
| 321 | HENDY Iliass | MC | Cardiologie |
| 322 | HATTAB Mohamed Salah Koussay | MC | Stomatologie et chirurgie maxillo faciale |
| 323 | DEBBAGH Fayrouz | MC | Microbiologie-virologie |
| 324 | OUASSIL Sara | MC | Radiologie |
| 325 | KOUYED Aicha | MC | Pédopsychiatrie |
| 326 | DRIOUICH Aicha | MC | Anesthésie-réanimation |
| 327 | TOURAIF Mariem | MC | Chirurgie pédiatrique |
| 328 | BENNAOUI Yassine | MC | Stomatologie et chirurgie maxillo faciale |
| 329 | SABIR Es-said | MC | Chimie bio organique clinique |
| 330 | LAATITIOUI Sana | MC | Radiothérapie |
| 331 | IBBA Mouhsin | MC | Chirurgie thoracique |
| 332 | SAADOUNE Mohamed | MC | Radiothérapie |
| 333 | TLEMCANI Younes | MC | Ophtalmologie |
| 334 | SOLEH Abdelwahed | MC | Traumato-orthopédie |
| 335 | OUALHADJ Hamza | MC | Immunologie |
| 336 | BERGHALOUT Mohamed | MC | Psychiatrie |
| 337 | EL BARAKA Soumaya | MC | Chimie analytique-bromatologie |
| 338 | KARROUMI Saadia | MC | Psychiatrie |
| 339 | EL-OUAKHOUMI Amal | MC | Médecine interne |
| 340 | AJMANI Fatima | MC | Médecine légale |
| 341 | ZOUITEN Othmane | MC | Oncologie médicale |
| 342 | MENJEL Imane | MC | Pédiatrie |
| 343 | BOUCHKARA Wafae | MC | Gynécologie-obstétrique |
| 344 | ASSEM Oualid | MC | Pédiatrie |
| 345 | ELHANAFI Asma | MC | Médecine physique et réadaptation fonctionnelle |
| 346 | ABDELKHALKI Mohamed Hicham | MC | Gynécologie-obstétrique |
| 347 | ELKASSEH Mostapha | MC | Traumato-orthopédie |
| 348 | EL OUAZZANI Meryem | MC | Anatomie pathologique |
| 349 | HABBAB Mohamed | MC | Traumato-orthopédie |
| 350 | KHAMLIJ Aimad Ahmed | MC | Anesthésie-réanimation |
| 351 | EL KHADRAOUI Halima | MC | Histologie-embryologie-cyto-génétique |
| 352 | ELKHETTAB Fatimazahra | MC | Anesthésie-réanimation |
| 353 | SIDAYNE Mohammed | MC | Anesthésie-réanimation |
| 354 | ZAKARIA Yasmina | MC | Neurologie |
| 355 | BOUKAIDI Yassine | MC | Chirurgie Cardio-vasculaire |
| 356 | NABIL Mehdi | MC | Anesthésie-réanimation |
| 357 | KAAKOUA Mohamed | MC | Oncologie médicale |
| 358 | FIQHI Mohammed Kamal | MC | Stomatologie et chirurgie maxillo faciale |
| 359 | BEN ELHEND Salah | MC | Radiologie |
| 360 | KHERRAB Anass | MC | Rhumatologie |
| 361 | AWATI El Mehdi | MC | Hématologie |
| 362 | HAOUANE Mohamed Amine | MC | Anatomie pathologique |
| 363 | BOUABBADI Salah eddine | MC | Ophtalmologie |

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|---|---|---|---|
| 364 | MOUNIR Reda | MC | Chirurgie Cardio-vasculaire |
| 365 | AHCHOUCH Siham | MC | Hématologie clinique |
| 366 | AZRIOUIL Ouahb | MC | Traumato-orthopédie |
| 367 | CHALOUAH Badr | MC | Traumato-orthopédie |
| 368 | EL BEJJAJ Iatimad | MC | Anatomie pathologique |
| 369 | BABA Zineb | MC | Rhumatologie |
| 370 | OUSSAYEH Imane | MC | Anesthésie-réanimation |
| 371 | KASSAL Ghizlane | MC | Pédiatrie (Néonatologie) |
| 372 | RACHID Chaynez | MC | Pneumo-phtisiologie |
| 373 | BALILI Khaoula | MC | Neurologie |
| 374 | IGARRAMEN Tariq | MC | Biophysique |
| 375 | EL MAGHTOUM Hicham | MC | Anesthésie-réanimation |
| 376 | KAOUANI Douaa | MC | Pédiatrie |
| 377 | ESSOLI Samira | MC | Médecine Communautaire |
| 378 | HABCHANE Amal | MC | Pharmacologie |
| 379 | CHARIK Mohamed Amine | MC | Cardiologie |
| 380 | MEZDID Chaymae | MC | Anatomie |
| 381 | ROUHI Salma | MC | Hématologie |
| 382 | EL OUARRADI Assia | MC | Microbiologie-virologie |
| 383 | JOULAL Hajar | MC | Médecine interne |
| 384 | AOUROUD Hala | MC | Physiologie |

*Liste arrêtée le 11/02/2026*


Abbreviations

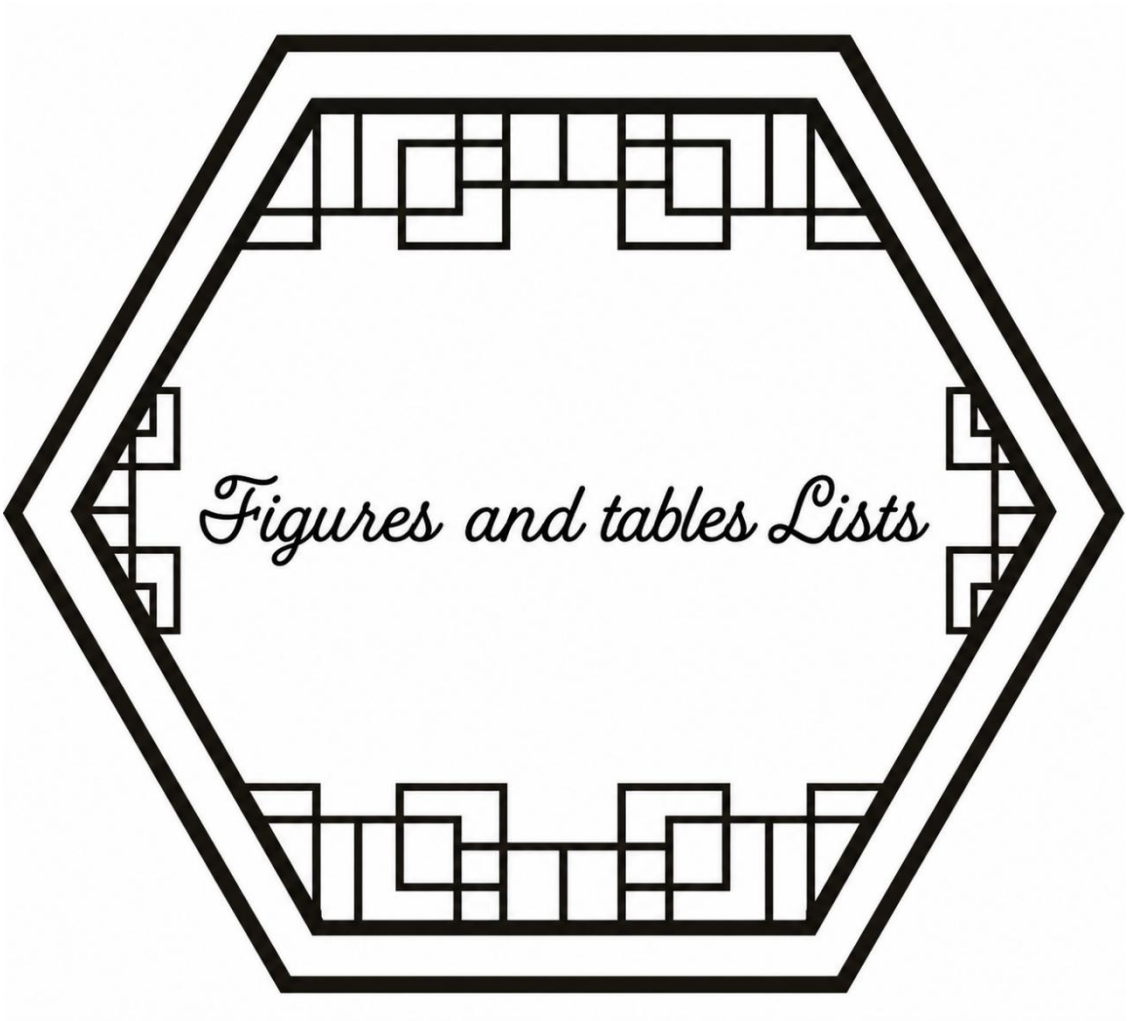
# Abbreviations

| | |
|---|---|
| **ABCA1** | ATP-binding cassette transporter A1 |
| **ABCG1** | ATP-binding cassette transporter G1 |
| **ABCG5** | ATP-binding cassette transporter G5 |
| **ABCG8** | ATP-binding cassette transporter G8 |
| **ACAT** | Acyl-CoA:cholesterol acyltransferase |
| **ACAT2** | Acyl-CoA:cholesterol acyltransferase 2 |
| **ACC** | Acetyl-CoA carboxylase |
| **ACR** | Albumin-to-creatinine ratio |
| **ADA** | American Diabetes Association |
| **AHA** | American Heart Association |
| **AKD** | Acute kidney disease |
| **AKI** | Acute kidney injury |
| **ANCA** | Anti-neutrophil cytoplasmic antibodies |
| **ApoA-I** | Apolipoprotein A-I |
| **ApoB-100** | Apolipoprotein B-100 |
| **ApoB-48** | Apolipoprotein B-48 |
| **ApoC-II** | Apolipoprotein C-II |
| **ApoC-III** | Apolipoprotein C-III |
| **ARBs** | Angiotensin II receptor blockers |
| **ASCVD** | Atherosclerotic cardiovascular disease |
| **ATF6** | Activating transcription factor 6 |
| **BMI** | Body mass index |
| **BP-D** | Diastolic blood pressure |
| **BP-S** | Systolic blood pressure |
| **BU** | Urine dipstick proteinuria |
| **c-ANCA** | Cytoplasmic anti-neutrophil cytoplasmic antibodies |
| **CCI** | Charlson Comorbidity Index |
| **CE** | Cholesteryl esters |
| **CETP** | Cholesteryl ester transfer protein |
| **CGA** | Cause, GFR category, and albuminuria category |
| **CHU** | Centre Hospitalier Universitaire |

| | |
|---|---|
| **CI** | Confidence interval |
| **CKD** | Chronic kidney disease |
| **CKD-EPI** | Chronic Kidney Disease Epidemiology Collaboration |
| **cLDL** | Carbamylated low-density lipoprotein |
| **CLDs** | Cytosolic lipid droplets |
| **CM** | Chylomicrons |
| **CPT1** | Carnitine palmitoyltransferase 1 |
| **CPT2** | Carnitine palmitoyltransferase 2 |
| **CRP** | C-reactive protein |
| **DAMPs** | Damage-associated molecular patterns |
| **DBP** | Diastolic blood pressure |
| **DDR** | DNA-damage response |
| **DGAT** | Diacylglycerol acyltransferase |
| **DRP1** | Dynamin-related protein 1 |
| **ECM** | Extracellular matrix |
| **eGFR / EGFR** | Estimated glomerular filtration rate |
| **EMT** | Epithelial–mesenchymal transition |
| **ER** | Endoplasmic reticulum |
| **ESKD** | End-stage kidney disease |
| **ESRD** | End-stage renal disease |
| **FA** | Fatty acids |
| **FAO** | Fatty acid oxidation |
| **FATP2** | Fatty acid transporter 2 |
| **FFA** | Free fatty acids |
| **FXR** | Farnesoid X receptor |
| **GFR** | Glomerular filtration rate |
| **Hb** | Hemoglobin |
| **HbA1c** | Glycated hemoglobin |
| **HD** | Hemodialysis |
| **HDL** | High-density lipoprotein |
| **HDL-C** | High-density lipoprotein cholesterol |
| **HL** | Hepatic lipase |
| **HMGB1** | High-mobility group box 1 |

| | |
|---|---|
| **IDL** | Intermediate-density lipoprotein |
| **IQR** | Interquartile range |
| **IRE1α** | Inositol-requiring enzyme 1 alpha |
| **KDIGO** | Kidney Disease: Improving Global Outcomes |
| **KFRE** | Kidney Failure Risk Equation |
| **LAL** | Lysosomal acid lipase |
| **LCAT** | Lecithin–cholesterol acyltransferase |
| **LDL** | Low-density lipoprotein |
| **LDL-C** | Low-density lipoprotein cholesterol |
| **LDLR** | Low-density lipoprotein receptor |
| **LPL** | Lipoprotein lipase |
| **LRP1** | LDL receptor-related protein 1 |
| **LXR** | Liver X receptor |
| **MA-24H** | 24-hour microalbuminuria |
| **MAG** | Monoacylglycerol |
| **MDA** | Malondialdehyde |
| **MPO** | Myeloperoxidase |
| **mtDNA** | Mitochondrial DNA |
| **MTP / MTTP** | Microsomal triglyceride transfer protein |
| **NCEP ATP III** | National Cholesterol Education Program Adult Treatment Panel III |
| **NKD** | No kidney disease |
| **NPC1L1** | Niemann–Pick C1-like 1 |
| **OR** | Odds ratio |
| **oxLDL** | Oxidized low-density lipoprotein |
| **p-ANCA** | Perinuclear anti-neutrophil cytoplasmic antibodies |
| **PCR** | Protein-to-creatinine ratio |
| **PCTV** | Pre-chylomicron transport vesicles |
| **PD** | Peritoneal dialysis |
| **PERK** | Protein kinase RNA-like endoplasmic reticulum kinase |
| **PL** | Phospholipids |
| **PON1** | Paraoxonase 1 |
| **PRRs** | Pattern-recognition receptors |

| | |
|---|---|
| **PU-24H** | 24-hour proteinuria |
| **RCT** | Reverse cholesterol transport |
| **RECORD** | REporting of studies Conducted using Observational Routinely-collected health Data |
| **ROS** | Reactive oxygen species |
| **SBP** | Systolic blood pressure |
| **SD** | Standard deviation |
| **sdLDL** | Small dense low-density lipoprotein |
| **SPSS** | Statistical Package for the Social Sciences |
| **SR-BI / SR-B1** | Scavenger receptor class B type I |
| **TC** | Total cholesterol |
| **TECs** | Tubular epithelial cells |
| **TG** | Triglycerides |
| **TGRL** | Triglyceride-rich lipoproteins |
| **TICE** | Transintestinal cholesterol excretion |
| **TLRs** | Toll-like receptors |
| **TNF** | Tumor necrosis factor |
| **UPR** | Unfolded protein response |
| **VLDL** | Very-low-density lipoprotein |
| **VLDL-R** | Very-low-density lipoprotein receptor |
| **WHO** | World Health Organization |


Figures and tables Lists

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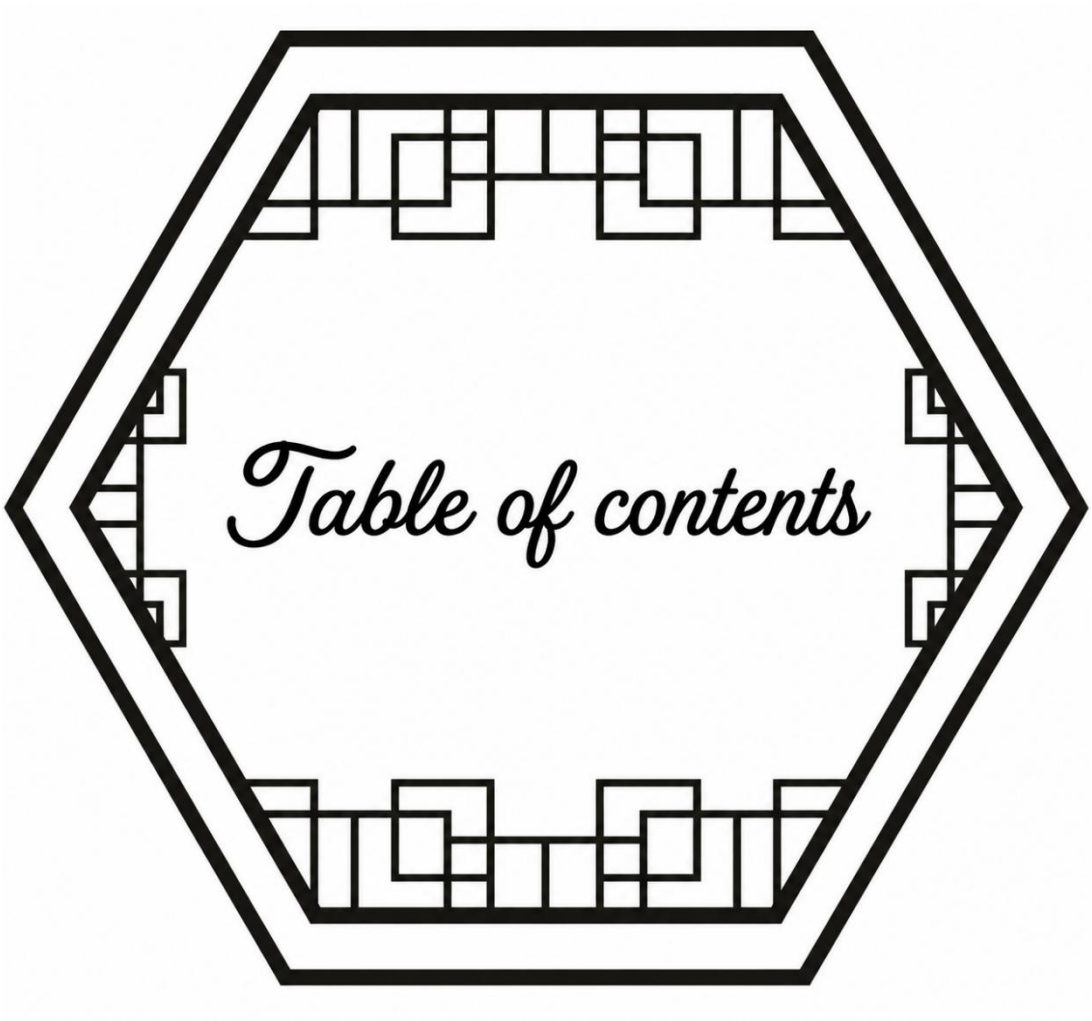
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Introduction

# I. Introduction:

Chronic kidney disease (CKD) is defined by abnormalities of kidney structure or function that persist for more than three months and has become a major global public health problem because of its association with kidney failure, cardiovascular disease, and premature mortality (1,2). Contemporary classification frameworks, particularly the Kidney Disease: Improving Global Outcomes (KDIGO) approach, have refined CKD evaluation by integrating the underlying cause with glomerular filtration rate (GFR) and albuminuria categories. This classification is clinically important because reduced estimated glomerular filtration rate (eGFR) and increased albuminuria provide complementary prognostic information regarding renal progression, cardiovascular events, and death (1). Accordingly, CKD should not be viewed as an isolated reduction in renal filtration, but rather as a complex systemic disorder associated with substantial metabolic, inflammatory, and vascular disturbances (2).

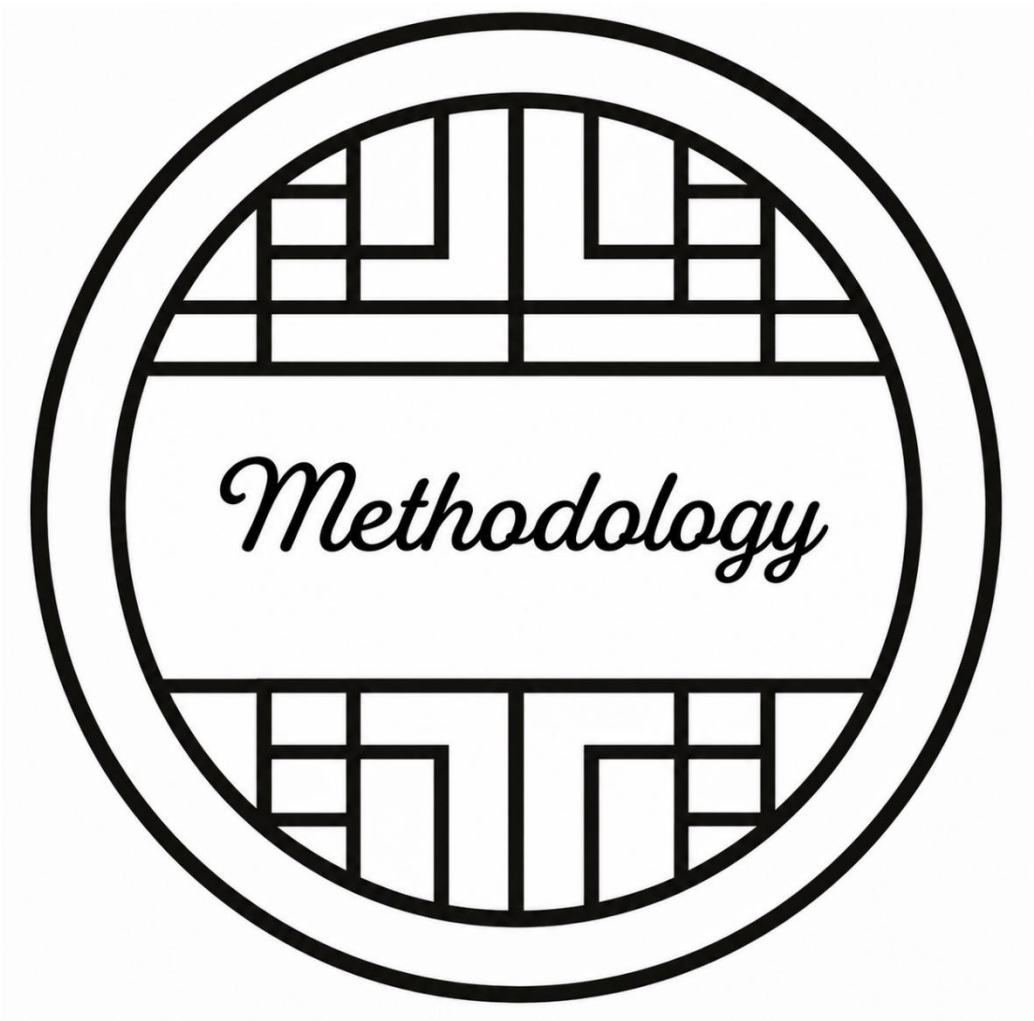
Among the metabolic abnormalities observed in CKD, dyslipidemia occupies a central place. Lipid disorders are frequent in patients with renal disease and contribute to the marked cardiovascular burden that characterizes this population (3,4). However, dyslipidemia in CKD does not fully mirror the classic pattern seen in the general population. In predialysis CKD, the most typical abnormalities are hypertriglyceridemia, reduced high–density lipoprotein cholesterol (HDL–C), and qualitative changes in lipoprotein composition, including triglyceride–rich remnants, oxidized low–density lipoproteins, and dysfunctional HDL particles (3,4). In some settings, particularly heavy proteinuria, nephrotic states, or diabetic kidney disease, elevations in total cholesterol and low–density lipoprotein cholesterol (LDL–C) may also become prominent (3,4). These disturbances are clinically relevant because they may amplify atherosclerotic risk while also reflecting the metabolic consequences of renal injury itself.

Beyond their cardiovascular implications, lipid abnormalities may also participate directly in renal damage. Growing experimental and translational evidence supports the concept that dysregulated lipid handling in the kidney can lead to ectopic lipid accumulation and lipotoxicity (4,5). Excessive uptake of fatty acids and oxidized lipoproteins, impaired fatty acid β–oxidation, altered cholesterol efflux, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, and inflammatory activation have all been implicated in renal cell injury (5,6). These mechanisms may affect multiple renal compartments, including podocytes, tubular epithelial cells, mesangial cells, and endothelial cells, thereby promoting albuminuria, tubulointerstitial fibrosis, and progressive loss of kidney function (5,6). In this perspective, dyslipidemia is not merely a coexisting comorbidity of CKD but may represent one component of a broader cardio–renal–metabolic axis involved in disease progression.

Nevertheless, the relationship between dyslipidemia and renal severity remains incompletely defined in clinical practice. Although many studies have reported associations between lipid abnormalities and markers such as eGFR decline, proteinuria, or albuminuria, the findings are not entirely consistent across populations (3,5). This heterogeneity likely reflects differences in study design, case mix, underlying nephropathy, CKD stage distribution, degree of proteinuria, and the lipid definitions used. In addition, routine lipid measurements quantify circulating fractions but may not fully capture qualitative abnormalities such as HDL dysfunction, oxidized lipoproteins, or tissue lipid accumulation, all of which may be biologically important in CKD (3,4,7). As a result, the precise clinical meaning of individual lipid abnormalities in relation to renal impairment and integrated renal risk stratification remains an area of ongoing investigation.

This question is particularly relevant in hospital-based populations from low- and middle-income settings, where patients are often diagnosed at more advanced stages and where local epidemiologic data remain limited. In Moroccan tertiary-care practice, CKD patients commonly present with multiple overlapping cardio-metabolic comorbidities, yet the burden and pattern of dyslipidemia in this context are insufficiently documented. Better characterization of lipid abnormalities in such patients may improve understanding of their cardio-renal risk profile and help clarify whether specific lipid fractions are more closely linked to renal impairment, albuminuria burden, or overall prognostic risk.

In this context, we conducted a cross-sectional study at CHU Mohammed VI in Marrakech over the period 2022 to 2024 to evaluate dyslipidemia in adult patients with chronic kidney disease. The objectives of this work were to determine the prevalence and pattern of lipid abnormalities in this population, to examine the relationship between blood lipid levels and renal function, and to assess these findings within an integrated cardiovascular and renal risk framework using markers such as eGFR, albuminuria, and KDIGO risk stratification. By doing so, this study aims to contribute locally relevant data on the interaction between dyslipidemia and CKD in routine tertiary-care practice.


Methodology

# II. Methodology

## 1. Design and period of study.

This investigation was conducted using a cross-sectional observational design. Such a design provides a contemporaneous "snapshot" of exposures and outcomes in the study population, enabling the estimation of prevalence and the examination of associations between variables without any manipulation of exposure.

Within this methodological framework the study covered a three-year interval extending from January 1, 2022, to December 31, 2024, inclusively. This duration was selected to ensure the accrual of a sufficiently representative cross-sectional sample of adult patients with chronic kidney disease (CKD) evaluated within the medical departments of CHU Mohammed VI. Data extraction and dataset construction were conducted over a dedicated one-year collection phase, during which eligible medical records from the 2022–2024 period was systematically reviewed and anonymized for analysis.

## 2. Study Setting

The study was conducted at the **Centre Hospitalier Universitaire (CHU) Mohammed VI, Marrakech, Morocco**, a tertiary university hospital serving the Marrakech-Safi region and providing specialized inpatient and outpatient care.

Relevant data were systematically extracted from hospital records within the medical departments of CHU Mohammed VI, specifically *Nephrology, Endocrinology, Rheumatology, Internal Medicine, and Cardiology*, for the study period spanning from January 2022 to December 2024.

## 3. Study Population and Sampling

The source population for this cross-sectional investigation is defined by the chronic kidney disease patient's flow and demographic coverage within the catchment area served by CHU Mohammed VI, as described in Section 2.

Between 2022 and 2024, **1,000** patient records were retrieved from the CHU Mohammed VI databases and screened for eligibility. A standardized extraction sheet was used to ensure consistent application of inclusion and exclusion criteria and to verify the availability of variables necessary for analysis.

### 3.1. Inclusion and Exclusion Criteria

**The Inclusion Criteria comprises:**

- Time and setting: Managed/seen in the target departments (nephrology, internal medicine, cardiology, endocrinology, rheumatology) at CHU Mohammed VI between 01/01/2022 and 31/12/2024.
- Age: ≥ 16 years
- Data Availability

- Index window rule satisfied: Renal and lipid measurements available within 30 days' time window to represent the same cross-sectional "snapshot." (See section 4.1)

**The Exclusion Criteria includes:**

- Missing Key data that prevents classification.
- Acute Kidney Injury (AKI) and Acute Kidney Disease (AKD) Patients
- Absence of chronic kidney disease (CKD).
- Pregnancy
- Long-term corticosteroids treatments >3months.
- Diabetes type I
- Hypothyroidism.

## 3.2. Participants Flow:

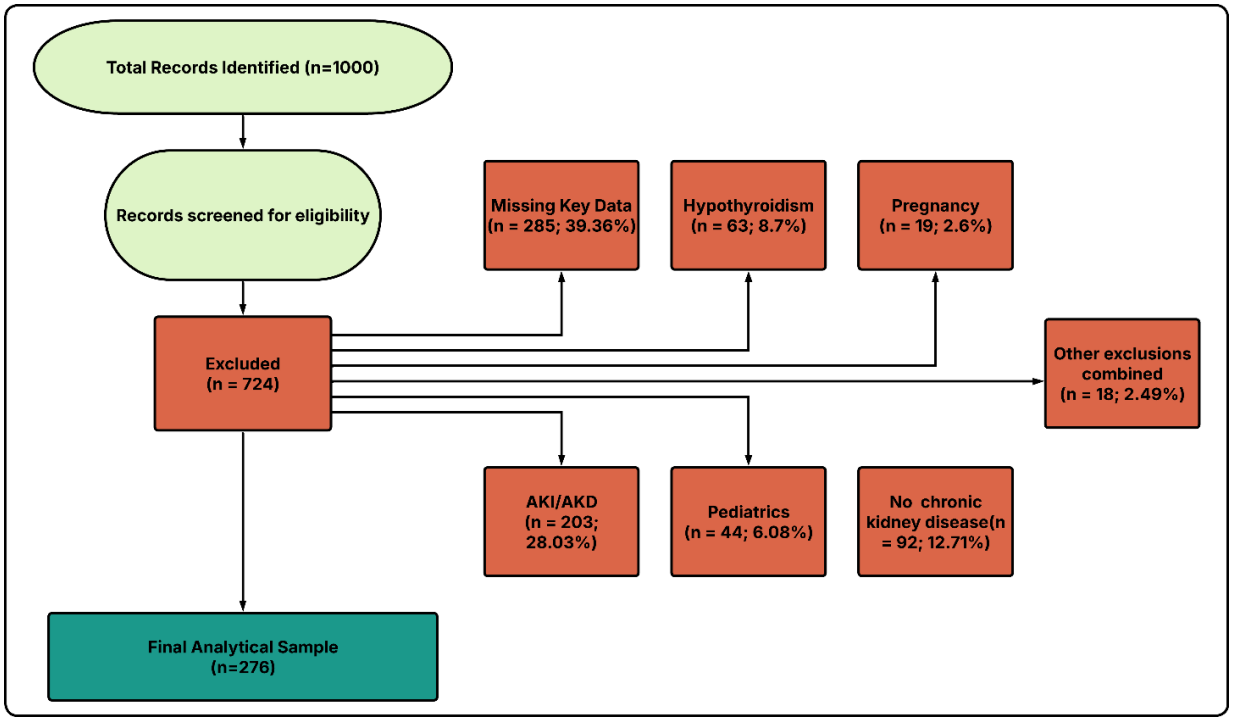



*Figure 1: Flow diagram of record screening, exclusions, and final analytical sample (n=276).*

A total of 1,000 patient records were identified from the nephrology, internal medicine, cardiology, endocrinology, and rheumatology departments at CHU Mohammed VI between **01/01/2022 and 31/12/2024**.

After screening eligibility criteria, **724 records** were excluded according to predefined criteria in section 3.1. The main exclusion reasons were **missing key data** (**n = 285; 39.36%** of excluded records) and **AKI/AKD** (**n = 203; 28.03%**), followed by Absence of CKD (n =92; 12.71%) then **hypothyroidism** (**n = 63; 8.7%**), **pediatric age (<16 years)** (**n = 44; 6.08%**), and **pregnancy** (**n = 19; 2.6%**). The remaining exclusions were due to other criteria (**n = 18; 2.9%**), including long-term corticosteroid therapy (>3 months), type I Diabetes.

The final analytic sample included **276 patients**.

# 4. Index date and measurement time window

## 4.1. Definition of the index date

To ensure a standardized cross-sectional assessment in this retrospective dataset, an **index date** was defined for each eligible patient.

In the present study, the index date corresponded to the **Lipid Panel** in the standardized extraction sheet, defined as the date of the patient's **lipid profile measurement**, which served as the anchor for linking renal, metabolic, inflammatory, and anthropometric variables. When multiple lipid profiles were available during the study period (January 2022–December 2024), a single index assessment was retained per patient to maintain one observation per individual (cross-sectional snapshot). The **earliest eligible lipid assessment** within the study period was selected to minimize duplication and preserve independence of observations.

## 4.2. Acceptable time window around the index date

In routine clinical practice, laboratory and clinical measurements are rarely obtained on the same day. To standardize variable ascertainment and minimize information bias due to heterogeneous timing of data capture in routinely collected records, we anchored all measurements to an **index date** using predefined time windows. For the cross-sectional description at baseline, values were considered valid if recorded within **±30 days** of the index date.

Beyond baseline description, the **index-date anchoring approach was also central to defining CKD chronicity**, because it allowed creatinine/eGFR values to be positioned consistently **both before and after** the index date. Specifically, creatinine measurements **preceding the index date** were used to document pre-existing renal impairment (retrospective evidence), while creatinine measurements obtained **≥3 months (≥90 days) after the index date** were used to confirm persistence over time (prospective evidence). By integrating **past** and **future** creatinine data relative to a single reference point (the index date), this method reduced misclassification from transient kidney function changes and enabled a more robust classification of patients into **CKD** versus **NKD** (no kidney disease), based on the chronicity criterion.

## 4.3. Managing multiple measurements within the time window

When multiple measurements for the same variable were available within the accepted time window, a deterministic rule was applied to avoid selective reporting and to ensure reproducibility. Specifically, the **measurement closest in time to the index date** (minimum absolute difference in days) was retained as the primary value. This approach is frequently used in routinely collected health data studies, where defining "baseline" requires explicit rules to mitigate bias from healthcare process patterns and uneven measurement frequency.

If two measurements were equidistant from the index date, priority was given to the value recorded **on or after** the index date to maintain consistent forward anchoring from the lipid assessment. The final analytical dataset therefore represented **one harmonized set of measurements per patient** corresponding to the index assessment period.

In summary, defining a patient-specific **index date** based on the lipid profile enabled a standardized and reproducible cross-sectional "snapshot" across this retrospective cohort, while ensuring one observation per individual. The use of a **predefined ±30-day measurement window** around the index date allowed consistent linkage of routinely collected clinical and laboratory data despite real-world variability in testing schedules, thereby limiting timing-related information bias and reducing arbitrary data selection. Moreover, anchoring renal function to the same index date facilitated a more rigorous CKD classification by incorporating **both retrospective creatinine/eGFR evidence** (before index) and **prospective confirmation of chronicity** (≥90 days after index), decreasing misclassification due to transient kidney function changes. Finally, applying deterministic selection rules for multiple measurements (closest-to-index, with a predefined tiebreaker) strengthened transparency and reproducibility, resulting in a harmonized analytical dataset aligned with the study's methodological framework.

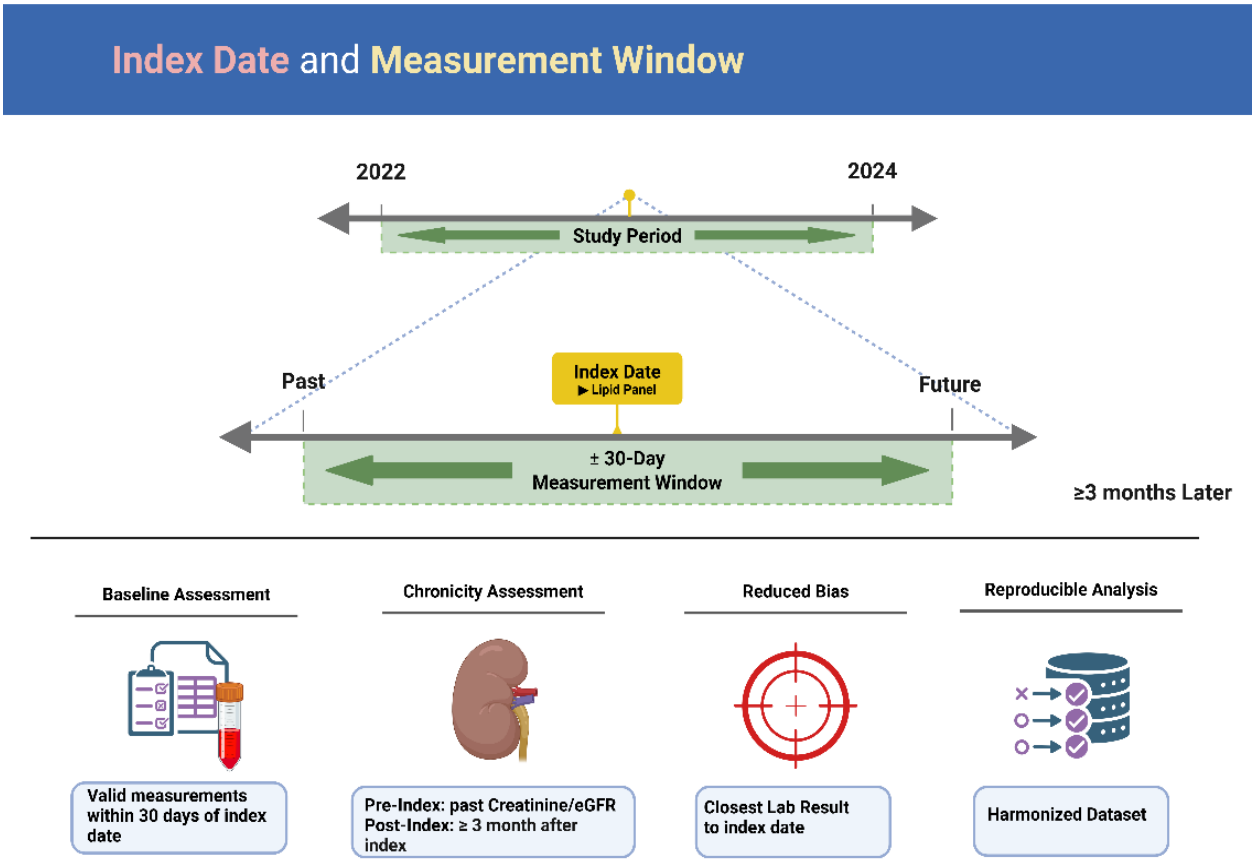



*Figure 2: Operational Framework for Index Date Definition and Measurement Window.*

# 5. Variables and operational definitions

## 5.1. Demographic and socioeconomic variables

- **Age (years)**: calculated from date of birth; analyzed as a continuous variable.
- **Age groups**: categorized age variable using pre-defined cut points of **≤40, 40-60, >60**.
- **Sex/Gender**: recorded as binary category (Male (M)/Female (F)) as documented in the medical record.
- **Insurance**: type of medical coverage/insurance as documented; analyzed as categorical.

## 5.2. Clinical classification variables

- **Anemia:** Anemia was defined using sex-specific hemoglobin thresholds measured closest to the index date:
    - **Men (M): Hb < 13.0 g/dL**
    - **Women (F): Hb < 12.0 g/dL**
- **Diabetes:** was defined by any of the following at/near index date:
    - **HbA1c ≥ 6.5%**, and/or
    - **Fasting plasma glucose ≥ 1.26 g/L** (8)
    - **Recorded Diagnosis in the patient health records.**

- **CKD or NKD:** The binary variable **"CKD" vs "NKD"** was an *etiologic classification* created to distinguish patients with **chronic kidney disease** from those **without evidence of CKD** at the time of the study period. Patients were classified as having **chronic kidney disease (CKD)** or **No kidney disease (NKD)** according to KDIGO criteria. CKD was defined as evidence of kidney structure or abnormality **persisting for ≥3 months**. Therefore, **chronicity was not inferred from a single abnormal test**.
    - A patient was classified as **CKD** if:
        - A kidney abnormality was present at/around index.
            - reduced eGFR <60ml/min/1.73m².
            - and/or marker of kidney damage.
            - and/or structural abnormality,

      **And**

        - **Chronicity (≥3 months)** was proved by:
            - repeat abnormal labs ≥90 days apart **or**
            - structural chronicity on ultrasound **or**
            - documented prior CKD/nephropathy consistent with objective findings.

- A patient was classified as **NKD (No chronickidney disease)**, if:
  - eGFR was **≥60 mL/min/1.73 m²** and **no markers of kidney damage** were present (ACR <30 mg/g; no documented persistent proteinuria; no structural abnormalities),

  **Or**

  - An abnormal kidney measure was **isolated** (single abnormal eGFR/ACR) **without evidence of chronicity**, consistent with KDIGO's caution that such findings may represent AKI/AKD rather than CKD.

This variable was constructed to ensure that analyses of dyslipidemia–kidney relationships were not biased by misclassifying **acute kidney injury/acute kidney disease** as chronic disease. In addition, it helped in excluding patients with no chronic kidney disease.

- **Diagnosis:** was defined as the **overall clinical condition(s)** for which the patient was managed, as documented in admission notes, discharge summaries. It could include both **renal and extra-renal diseases** and may explicitly mention kidney disease.
- **Nephropathy type and subtype:** used to characterize CKD etiology. This "cause" domain is essential because etiology can be associated with *both* CKD severity and lipid abnormalities.
  - Nephropathy Type: broad etiologic class (five mutually exclusive groups).
  - Nephropathy Subtype: specific etiologic diagnosis within each group.

The classification of Nephropathy types and subtypes are resumed in table 1.

***Table 1: Etiologies of End-Stage Renal Disease (ESRD)**: Major Categories and Representative Subtypes. Reference: Rout P, Aslam A. End-Stage Renal Disease. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2025 Jan- [updated 2025 Jun 22].(9)*

| *Category* | Subtypes (examples) |
|---|---|
| *Vascular diseases* | Renal artery stenosis; ANCA-positive vasculitides (c-ANCA/p-ANCA); ANCA-negative vasculitides; atheroembolic kidney disease; hypertensive nephrosclerosis; renal vein thrombosis |
| *Primary glomerular diseases* | Membranous nephropathy; Alport syndrome; IgA nephropathy; focal segmental glomerulosclerosis; minimal change disease; membranoproliferative glomerulonephritis; complement-related diseases (atypical HUS, C3 glomerulopathy, dense deposit disease); rapidly progressive (crescentic) glomerulonephritis |
| *Tubulointerstitial diseases* | Drug-induced TIN (e.g., sulfonamides, allopurinol); infectious causes (viral/bacterial/parasitic); Sjögren syndrome; tubulointerstitial nephritis and uveitis syndrome; chronic hypokalemia; chronic hypercalcemia; sarcoidosis; multiple myeloma cast nephropathy; heavy metals; radiation nephritis; polycystic kidneys; cystinosis and other inherited diseases; chronic interstitial nephritis in agricultural communities (Mesoamerican nephropathy/CINAC) |
| *Urinary tract obstruction* | Benign prostatic hypertrophy; urolithiasis; urethral stricture; tumors; neurogenic bladder; congenital obstructive anomalies; retroperitoneal fibrosis; reflux nephropathy |
| *Systemic causes of glomerular disease* | Diabetes mellitus; systemic lupus erythematosus; rheumatoid arthritis; mixed connective tissue disease; scleroderma; mixed cryoglobulinemia; endocarditis; hepatitis B/C; syphilis; HIV; parasitic infection; heroin use; gold (historical); penicillamine; amyloidosis; light-chain deposition disease; neoplasia; thrombotic thrombocytopenic purpura; Shiga-toxin or *Streptococcus pneumoniae*-related HUS; IgA vasculitis (Henoch-Schönlein purpura) |

## 5.3. Anthropometrics and obesity-related variables

- **Weight (kg), Height (m).**
- **Body mass index (BMI, kg/m²)**: computed as

$$BMI = \frac{W}{H^2}$$

**Whereas:**

- **H: Height in meter.**
- **W: Weight in Kg.**

- **BMI category**: categorized using standard adult BMI thresholds.

*Table 2: Body Mass Index (BMI) classification.*

| BMI (kg/m²) | Category / Class |
|---|---|
| < 18.5 | Underweight |
| 18.5–24.9 | Normal weight |
| 25.0–29.9 | Overweight |
| ≥30.0 | Obesity |

## 5.4. Blood pressure variables

- **Systolic** and **diastolic blood pressure (mmHg)**
- **Hypertension Status (binary: Yes/No)** was defined using a composite rule based on (i) measured blood pressure, (ii) documented history/diagnosis, and (iii) antihypertensive treatment at/around the index date:
    - **Hypertension = "Yes"** if any of the following criteria were met:
        - Elevated BP at index date.
        - SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, consistent with the conventional office threshold used in major hypertension guidelines.
        - Documented hypertension.
        - Anti-hypertensive treatment.
        - Active prescription or documented chronic use of antihypertensive medication at/around the index date.
    - **Hypertension = "No"** if none of the above criteria were present and both SBP and DBP were available and below the threshold.

## 5.5. Renal function measures and eGFR categorization:

- **Creatinine:** recorded as a continuous laboratory value in mg/L
- **Urea in g/L**
- **eGFR:** We used the CKD-EPI GFR estimation.
- **eGFR Categorization:** For staging, eGFR was categorized according to KDIGO GFR categories.

*Table 3: KDIGO classification of estimated glomerular filtration rate (eGFR) categories (mL/min/1.73 m²).*

| eGFR category | eGFR (mL/min/1.73 m²) | Comment |
|---|---|---|
| G1 | ≥ 90 | Normal or high |
| G2 | 60–89 | Mildly decreased |
| G3a | 45–59 | Mildly to moderately decreased |
| G3b | 30–44 | Moderately to severely decreased |
| G4 | 15–29 | Severely decreased |
| G5 | < 15 | Kidney failure |

## 5.6. Kidney Damage Markers and ACR estimation /categorization:

Kidney damage marker englobes **urinary**, and **structural** markers:

- **Urine dipstick protein** corresponds to the **semi-quantitative dipstick protein result** recorded in the urinalysis report as **negative/trace/+/++/>++**. In this study, dipstick protein was treated as a **categorical marker of kidney damage**
- **Albuminuria (mg/L)** represents the **spot urine albumin concentration** (mg/L)
- **Micro-Albuminuria (mg/L)** represents the **spot urine microalbumin concentration** (mg/L)
- **Proteinuria (mg/L)** is the **spot urine total protein concentration** (mg/L). **Creatinuria (mg/L)** is the **spot urine creatinine concentration** (mg/L). When both spot protein and spot urine creatinine were available, these values were used to obtain a spot **protein-to-creatinine ratio** (PCR).
- **PU-24H** corresponds to **24-hour proteinuria** (g/24 h), representing total protein excretion over a timed collection; it was treated as a quantitative marker of kidney damage and reported descriptively
- **MA-24H** corresponds to **24-hour microalbuminuria** (mg/24 h), representing 24-hour urinary albumin excretion and similarly served as a quantitative kidney damage marker when available.
- **PCR (mg/g)** is the **spot urine protein-to-creatinine ratio** expressed in mg/g. It was either directly recorded or derived from spot protein and creatinuria. The equation used is as follows

$$PCR\ (mg/g) = \frac{Urine\ protein\ (mg/L)}{Urine\ creatinine\ (g/L)}$$

- **ACR** represents the **Albuminuria to creatinuria ration in mg/g.**

$$ACR\ (mg/g) = \frac{Urine\ Albumine\ (mg/L)}{Urine\ creatinine\ (g/L)}$$

- **Imaging variable: renal ultrasound**: Renal ultrasound findings were extracted from radiology reports/clinical documentation. At minimum, ultrasound was coded as **Normal** vs **abnormal**. If consistent details were available, abnormal findings may be subclassified (e.g., reduced kidney size, increased echogenicity/cortical thinning, cystic disease, obstruction).

- **ACR Categorization**

Finally, **ACR Category** corresponds to the categorical albuminuria stage derived from ACR classified as **A1 (<30 mg/g), A2 (30–300 mg/g), or A3 (>300 mg/g)** in accordance with KDIGO albuminuria categories.

*Table 4: ACR Categorization as with KDIGO Standards.*

| A1 | A2 | A3 |
|---|---|---|
| Normal–mild increase | Moderate increase (Micro-albuminuria) | Severe increase (Macro-Albuminuria) |
| <30mg/g | 30–300mg/g | >300mg/g |

## 5.7. Laboratory covariates (metabolic, nutritional, and hematologic)

- **Hb (g/dL)**: anemia marker and CKD phenotype indicator.
- **Glucose** and **HbA1c (%)**: metabolic status/diabetes control.
- **Albuminemia (g/L)** and **proteinemia (g/L)**: nutritional/inflammatory state; hypoalbuminemia may reflect protein loss and can influence lipid patterns.
- **Uric acid.**

## 5.8. Lifestyle variables

- Smoking
- Alcohol
- physical activity

## 5.9. Dyslipidemia (definitions and thresholds)

### 5.9.1. Binary dyslipidemia Status and type

- **Dyslipidemia = "Yes"** if at least one abnormal fraction was present at the index assessment:
  - TC ≥2.00 mg/L **or**
  - LDL-C ≥1.30 mg/L **or**
  - TG ≥1.50 mg/L **or**
  - HDL-C <0.40 mg/L (men) / <0.50 mg/L (women).
- **Dyslipidemia = "No"** if none of these abnormalities were present.

### 5.9.2. Lipid profile components

The lipid profile included available serum lipid fractions measured in routine care and recorded in **mg/L**: **total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TG)**.

Each lipid fraction was described using standard clinical categories from NCEP ATT III(10):

- **Total cholesterol (TC):**
  - desirable <2.00;
  - borderline high 2.00–2.39;
  - high ≥2.40 mg/L
- **LDL-C:**
  - optimal <1.29.
  - borderline high 1.30–1.59.
  - high 1.60–1.89.
  - very high ≥1.90 mg/L
- **HDL-C:**
  - low <0.40 mg/L (men),
  - <0.50 mg/L (women);
- **Triglycerides (TG):**
  - normal <1.50.
  - borderline high 1.50–1.99.
  - high 2.00–4.99.
  - very high ≥5.00 mg/L.

### 5.9.3. lipid-lowering treatment

Lipid-lowering therapy was operationalized using **three linked variables** to capture (i) **exposure status**, (ii) **therapeutic class**, and (iii) **specific agent and dose** at the time of lipid assessment. This approach was chosen to ensure transparent exposure definition in a retrospective cross-sectional dataset and to allow adjustment for treatment-related confounding when analyzing lipid levels and dyslipidemia phenotypes.

- **Lipid treatment status (Yes / No / Unknown)**: A categorical variable indicating whether the patient was receiving any lipid-lowering therapy at/around the index date.
  - **Yes:** a lipid-lowering medication was documented as active treatment.
  - **No:** no lipid-lowering medication was documented at/around the index date.
  - **Unknown:** treatment information was missing, contradictory, or not interpretable from the available record (e.g., medication list absent; unclear documentation).

- **Type of lipid treatment taken (therapeutic class)**: A categorical (or multi-label) variable capturing the **class(es)** of lipid-lowering therapy documented at/around index date.
  - **Statin** (HMG-CoA reductase inhibitor)
  - **Fibrate**
  - **Omega-3**
  - **Unknown**
- **Molecule and dose:** A structured variable capturing the **active molecules** and the **daily dose** as documented at/around index date.
  - **Molecule:** generic name(s) (e.g., atorvastatin, rosuvastatin, simvastatin, ezetimibe, fenofibrate).
  - **Dose:** recorded as **mg/day**

## 5.10. Comorbidity and risk scores

**Age-adjusted Charlson Comorbidity Index (ACCI):** Comorbidity burden was quantified using the **age-adjusted Charlson Comorbidity Index (ACCI)**, which combines (1) the standard Charlson comorbidity score (weighted comorbid conditions) and (2) an **age component**. Specifically, **1 additional point was added for each decade of age above 40 years**, and this age score was added to the Charlson comorbidity score to obtain the final ACCI (11).

*Table 5: Age-adjusted Charlson Comorbidity Index (CCI) scoring system (11).*

| *Comorbidities* | Points | *Comorbidities* | Points |
|---|---|---|---|
| *< 50 years* | 0 | Peptic ulcer disease | 1 |
| *50-59 years* | +1 | Mild liver disease | 1 |
| *60-69 years* | +2 | Diabetes (without end-organ damage) | 1 |
| 70-79 years | +3 | Hemiplegia | 2 |
| ≥ 80 years | +4 | Moderate-to-severe renal disease | 2 |
| Myocardial infarction | 1 | Diabetes with chronic complications (end-organ damage) | 2 |
| Congestive heart failure | 1 | Solid tumor (without metastasis) | 2 |
| Peripheral vascular disease | 1 | Leukemia | 2 |
| Cerebrovascular disease / TIA | 1 | Lymphoma | 2 |
| Dementia | 1 | Moderate or severe liver disease | 3 |
| Chronic pulmonary disease | 1 | Metastatic solid tumor | 6 |
| Connective tissue / rheumatologic disease | 1 | AIDS | 6 |

- **KDIGO risk category (CKD prognosis heat map)** was defined using the KDIGO "**Prognosis of CKD by GFR and albuminuria categories**" grid (see table 6), which combines:
  - **eGFR category (G1–G5)** and
  - **Albuminuria category (A1–A3, based on ACR)** to assign a prognosis/risk stratum.

*Table 6: KDIGO 2024 CKD prognosis risk heat map combining eGFR (G1–G5) and albuminuria (A1–A3).*

| CKD is classified based on:<br>• Cause (C)<br>• GFR (G)<br>• Albuminuria (A) | | | | A1 | A2 | A3 |
|---|---|---|---|---|---|---|
| | | | | Normal to mildly increase | Micro – albuminuria | Macro – albuminuria |
| | | | | <30 mg/g | 30–300 mg/g | >300 mg/g |
| GFR Catégories (ml/min/1.73²) Description and Range | G1 | Normal or high | ≥90 | Low | Moderate | High |
| | G2 | Mildly decreased | 60–89 | Low | Moderate | High |
| | G3a | Mildly to moderately decreases | 45–59 | Moderate | High | Very High |
| | G3b | Moderately to severely decreased | 30–44 | High | Very High | Very High |
| | G4 | Severely decreased | 15–29 | Very High | Very High | Very High |
| | G5 | Kidney failure | <15 | Very High | Very High | Very High |

- **KFRE 5-year risk (Kidney Failure Risk Equation):** was defined as the **predicted probability (%) of treated kidney failure** (initiation of **dialysis or kidney transplantation**) within **5 years**, calculated using the validated **4-variable KFRE model (Age, Sex, eGFR** (mL/min/1.73m²)**, Urine ACR**)
  - **Eligibility / scope (important to state):** KFRE is intended for patients with **CKD stages G3–G5** (i.e., eGFR <60 mL/min/1.73m²), and outputs **2- and 5-year** kidney failure risk.
- **ASCVD risk (10-year risk):** ASCVD risk was operationalized as the 10-year predicted probability (%) of a first atherosclerotic cardiovascular disease (ASCVD) event, estimated at the index date using the American Heart Association (AHA) PREVENT-ASCVD equation (sex-specific, race-free), validated for adults aged 30–79 years without known cardiovascular disease.
  - For each eligible participant, the required predictors were entered: age, sex, systolic blood pressure, antihypertensive treatment (yes/no), lipid-lowering therapy (yes/no), smoking status, diabetes status, body mass index (BMI), HDL-cholesterol, non-HDL-cholesterol, and eGFR, non-HDL-cholesterol.
  - Because albuminuria was available in our dataset, we used the kidney-enhanced optional PREVENT model by additionally entering urine albumin-to-creatinine ratio

(UACR/ACR, mg/g) to personalize the risk estimate. When UACR was missing, the base PREVENT-ASCVD estimate (required predictors only) was retained.

- The resulting ASCVD risk was recorded as a continuous percentage (%) for analysis.

The table below presents a summary of the variables used in the study. (table7)

*Table 7: Summary of the variables used in the study.*

| Domain | Variables | Domain | Variables |
|---|---|---|---|
| Sociodemographic | Origin | Kidney Damage Markers | BU (Proteinuria) |
| | Insurance | | Proteinuria (mg/L) |
| | Age | | Creatinuria (mg/L) |
| | Age groups | | Microalbuminuria (mg/L) |
| | Gender | | PU 24h (g/24h) |
| Nephropathy | Nephropathy Type | | MA 24h (mg/24h) |
| | Nephropathy Subtype | | PCR (mg/g) |
| Diagnosis | Diagnosis | | Renal Ultrasound |
| Kidney status | CKD, NKD | | ACR (mg/g) |
| Renal function | Urea (g/L) | | ACR Category |
| | Creatinine (mg/L) | Metabolic | Glucose (g/L) |
| | eGFR (CKD-EPI) | | HbA1c (%) |
| | eGFR (CKD-EPI) Stage | | Diabetes |
| Hematology | Hb (g/dL) | | Uric Acid (mg/L) |
| | Anemia | Inflammation | Proteinemia (g/L) |
| Lipid Profile | Total Cholesterol (g/L) | | Albuminemia (g/L) |
| | HDL-C (g/L) | | Ferritinemia (ng/mL) |
| | LDL-C (g/L) | | CRP |
| | Triglycerides (g/L) | Blood pressure | Systolic pressure |
| | Dyslipidemia (Yes/No) | | Diastolic pressure |
| | Type of Dyslipidemia | Lifestyle | Physical activity |
| Lipid Treatment | Type of lipid treatment | | Alcohol |
| | Molecule and Dose | | Smoking Status |
| Anthropometrics | Weight | CV risk | ASCVD Risk |
| | Height | CKD prognosis | KDIGO risk |
| | BMI and BMI Category | | KFRE 5y |
| | | Comorbidity | CCI index |
| | | | CCI 10y Survival |
| | | | Hypertension |

# 6. Statistical Analysis

All statistical analyses were performed using **IBM SPSS Statistics version 31.0.2.0**.

Normality of continuous variables was evaluated using the Shapiro–Wilk test in conjunction with visual assessment of histograms and Q–Q plots. The results of these distributional assessments informed the choice between parametric and non-parametric analyses.

Continuous variables were summarized as **mean ± standard deviation (SD)** when approximately normally distributed and as **median (interquartile range, IQR)** when non-normally distributed.

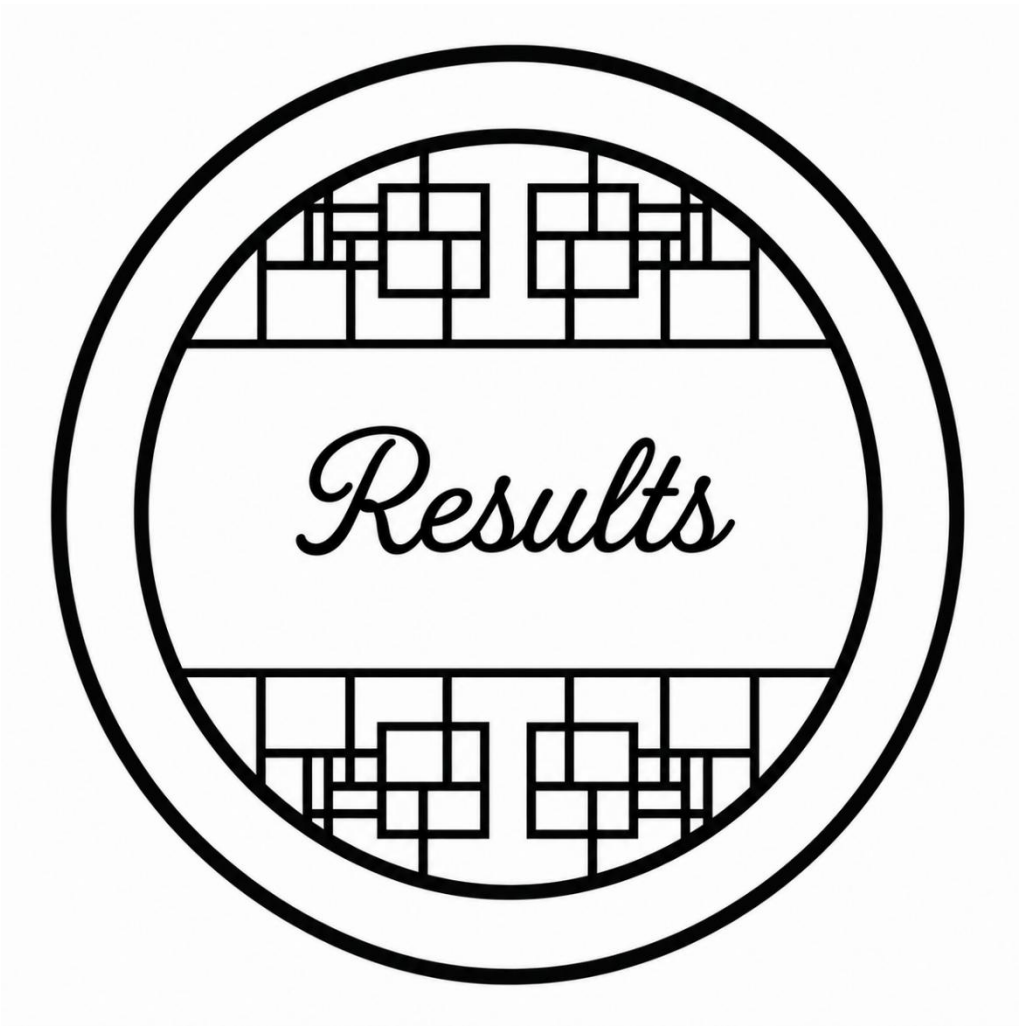
Categorical variables were summarized as **counts and percentages**.

For **group comparisons**, normally distributed continuous variables were compared using the **independent-samples t-test** (two groups) or **one-way ANOVA** (>2 groups), whereas non-normally distributed variables were compared using the **Mann–Whitney U test** (two groups) or the **Kruskal–Wallis's test** (>2 groups).

For **categorical variables**, associations between proportions were evaluated using the **Pearson Chi-square ($\chi^2$) test**. When expected cell counts were small (e.g., any expected count <5 or sparse contingency tables), the **Fisher's exact test** was used instead of $\chi^2$. When contingency tables exceeded 2×2 and sparse cells were present, an exact approach (Fisher's exact where available) or appropriate corrections were applied, and where relevant, **standardized residuals** were inspected to identify the categories contributing most to overall $\chi^2$ significance.

To assess **associations** between dyslipidemia and renal outcomes beyond unadjusted comparisons, **regression analyses** were planned according to outcome type. For **binary outcomes** (e.g., CKD vs NKD; dyslipidemia yes/no), **binary logistic regression** was performed, and results were expressed as **odds ratios (OR)** with **95% confidence intervals (CI)**.

All tests were **two-sided**, and statistical significance was set at $p < 0.05$.


Results

# III. Results:

## I. Descriptive Analysis:

### I.1. Population Sociodemographic and lifestyle characteristics:

#### I.1.1. Gender Distribution:

Among the study population (**N = 276**), **females accounted for 177 participants (64.1%)**, whereas **males accounted for 99 participants (35.9%). (see figure 3)**

This indicates a predominantly female sample with a sex ratio of 1.78 female to 1 man (F/M = 1.78/1).

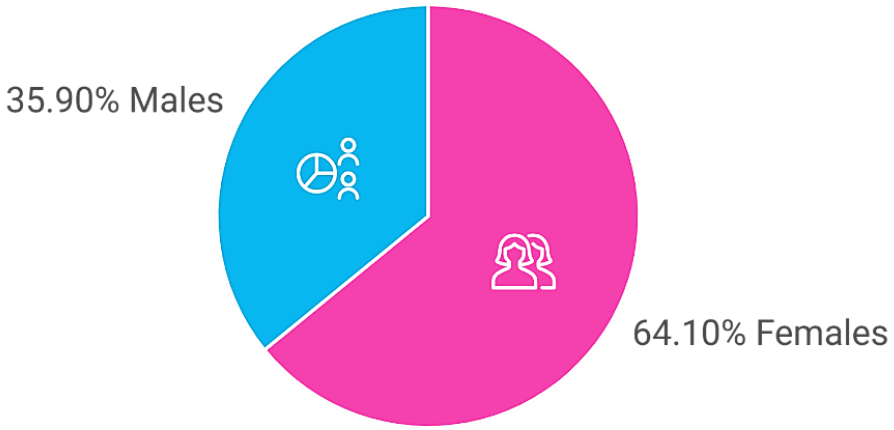



**Figure 3 Proportion of Male and Female Participants**

#### I.1.2. Age Distribution:

In this study, the mean age was **45.18 years** (SD **16.98**), corresponding to approximately **28.2 years (mean − 1 SD)** to **62.16 years (mean + 1 SD)**. The median age is 45 years (IQR: 31.00–58.00). (see figure 4)

Ages ranged from **16** to **87 years**, and the distribution was approximately symmetric.

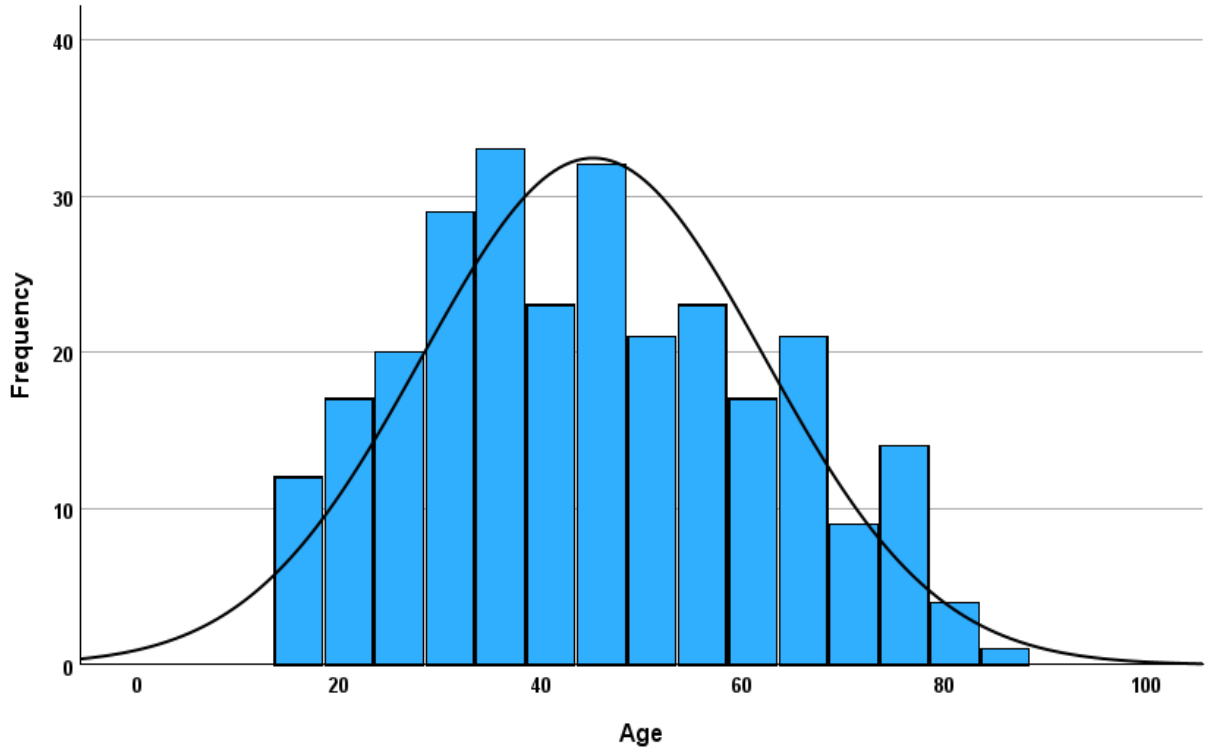



*Figure 4 Distribution of Age in the Study Population with normal curve.*

When categorized into clinically interpretable age groups, **119 patients (43.1%)** were aged **≤40 years**, **94 (34.1%)** were aged **40–60 years**, and **63 (22.8%)** were aged **>60 years** (See figure 5).

Overall, the study was relatively young-to-middle aged, with three-quarters of participants aged ≤60 years, and one quarter aged >60 years.

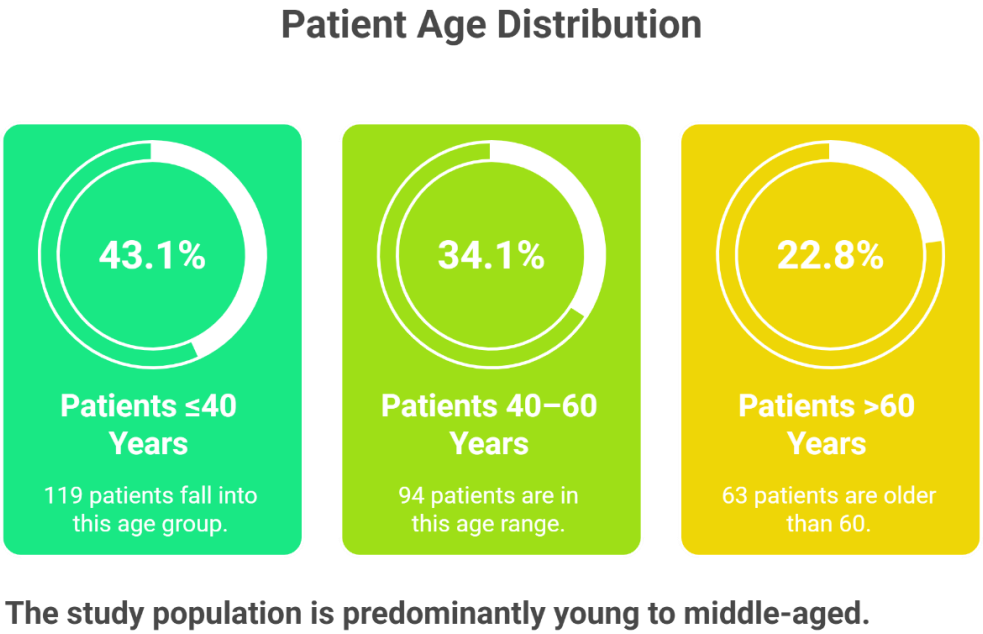



*Figure 5 Distribution of Participants According to Age Groups*

### I.1.3.Insurance Distribution:

Among the 276 included patients, health coverage was predominantly provided through **CNSS** (**n = 179; 64.8%**), followed by **self-pay ("Payant")** (**n = 71; 25.7%**) and **CNOPS** (**n = 22; 8.0%**). Other insurance categories were rare, representing **1.5%** of the sample (**FAR: n = 2; 0.7%, OCP: n = 1; 0.4%, SANLAM assurance: n = 1; 0.4%**). (see figure 6)

This distribution indicates that the study population was mainly composed of patients covered by national insurance schemes CNSS.

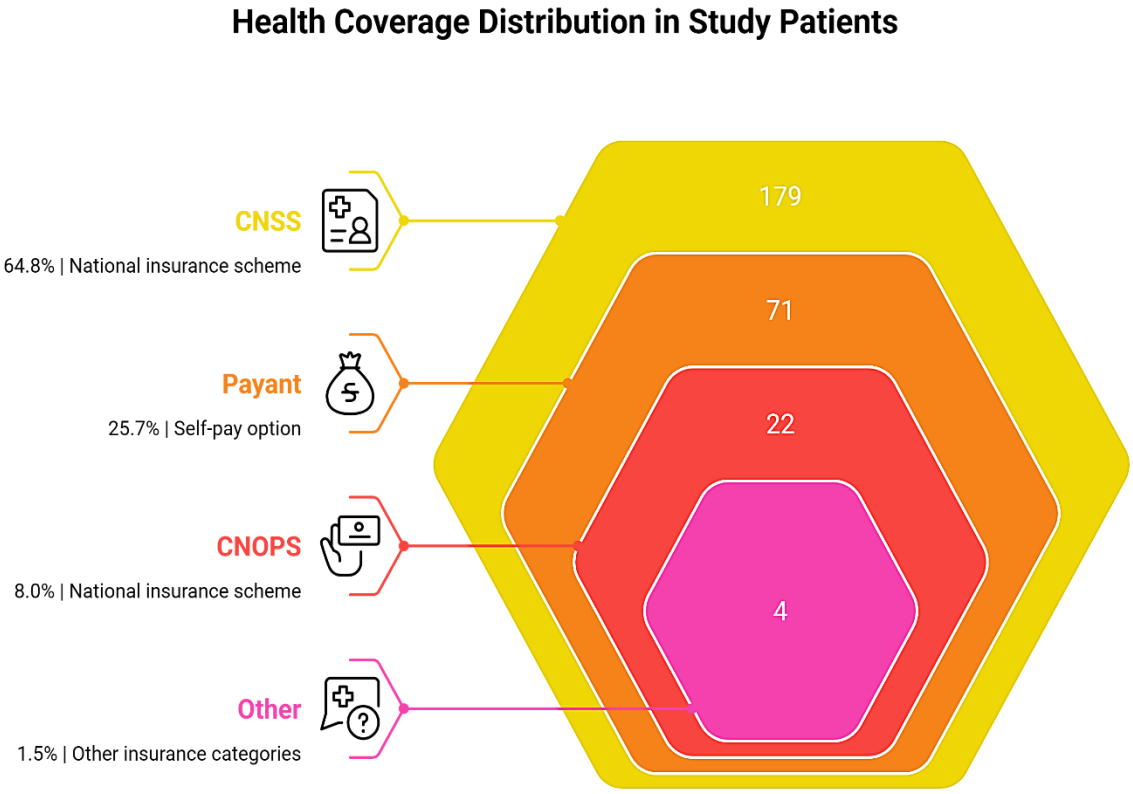



*Figure 6 Distribution of Participants According to Health Insurance Coverage*

### I.1.4.Smoking, Alcohol and Physical Activity Distribution:

- **Smoking status.**

Smoking exposure was limited in this cohort. The vast majority of patients had no recorded history of smoking (n = 244; 88.4%), whereas only a small proportion were active smokers at the time of assessment (n = 29; 10.5%). A past history of smoking was uncommon, being documented in only n = 3 patients (1.1%). (see table 8)

Overall, ever-smoking exposure, whether current or former, was identified in n = 32 patients (11.6%), indicating that the study population was predominantly composed of non-smokers.

- **Alcohol consumption.**

Alcohol consumption was not identified in the study population, with 0 patients having documented alcohol use. (see table 8)

- **Physical activity.**

Recorded levels of physical activity indicated that most patients had a moderate degree of daily activity (n = 180; 65.2%). In contrast, nearly one-third of the cohort was documented as having a sedentary lifestyle (n = 92; 33.3%), whereas only a very small minority engaged in vigorous physical activity (n = 4; 1.4%). (see table 8)

Overall, these findings suggest that reduced physical activity was common in this population, while high-intensity activity was exceptional.

*Table 8 Distribution of Lifestyle Characteristics Among Study Participants*

| Domain | Category | Frequency (n) | Percent (%) |
|---|---|---|---|
| Smoking status | Current | 29 | 10.5 |
| | Former | 3 | 1.1 |
| | Never | 244 | 88.4 |
| Alcohol | No | 276 | 100 |
| | Yes | 0 | 0.0 |
| Physical activity | Extremely Active | 0 | 0.0 |
| | Vigorously active | 4 | 1.4 |
| | Moderately active | 180 | 65.2 |
| | Sedentary | 92 | 33.3 |

## I.2. Population Anthropometric characteristics:

Weight, height, and BMI data were available for 186 (67.4%), with 90 (32.6%) missing values for these measures.

*Table 9 Summary of anthropometric characteristics of the study population*

| Variable | Median |
|---|---|
| Weight (kg) | 70 [59.3-80] |
| Height (m) | 1.60 [1.56-1.68] |
| Body mass index (kg/m²) | 26.44 [21.99-31.21] |

**Body weight** showed substantial variability, with a mean of 71.55 ± 20.26 kg and a median of 70 kg [IQR 59.3–80], ranging from 31 to 153 kg.

**Height** was normally distributed, with a mean of 1.61 ± 0.09 m and a median of 1.60 m [IQR 1.56–1.68], ranging from 1.34 to 1.85 m.

**BMI** demonstrated non-normal distribution with a mean of 27.52 ± 7.8 kg/m² and a median of 26.44 kg/m² [IQR 21.99–31.21], ranging from 15.32 to 64.92 kg/m². Clinically, the average BMI falls in the overweight range, and the upper quartile lies in the obese range (≥30 kg/m²), reflecting a substantial burden of elevated adiposity in the cohort (overweight BMI ≥25, obesity BMI ≥30).

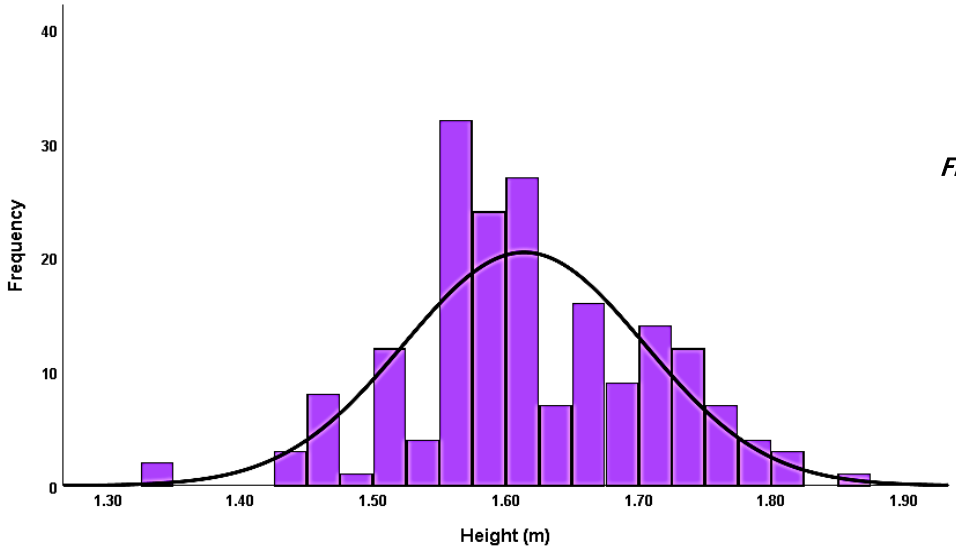



*Figure 7 Distribution of Height among participants*

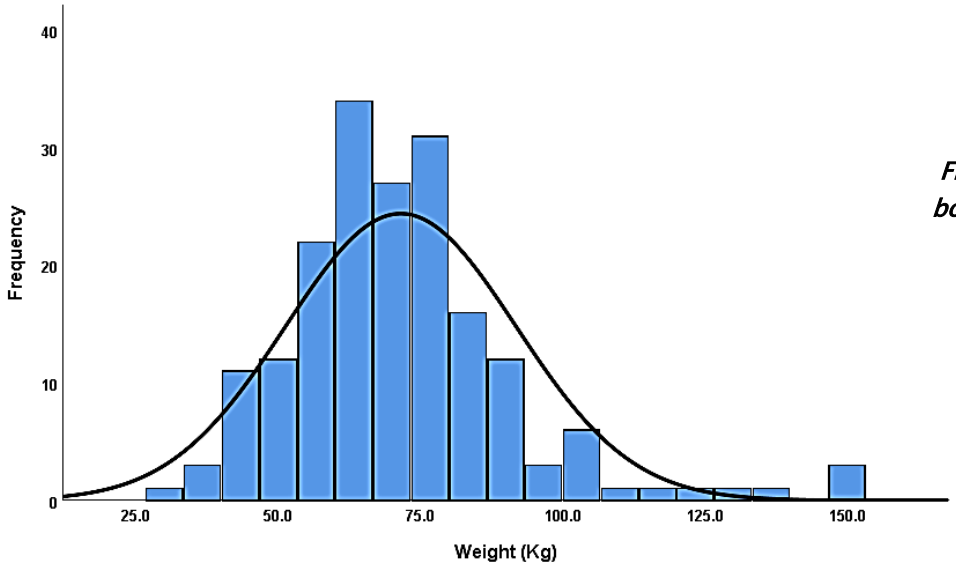



*Figure 8 Distribution of body weight in the study population*

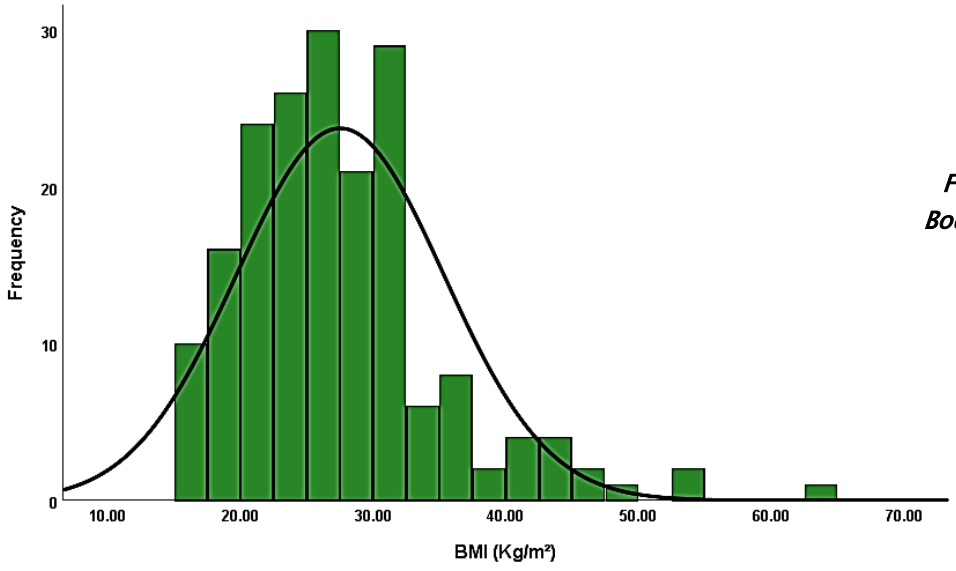



*Figure 9 Distribution of Body Weight Index (BMI) in the study population*

In the overall study population, body mass index categories were distributed as follows: normal weight in 61 patients (22.10%), overweight in 51 (18.48%), obesity in 59 (21.37%), and underweight in 15 (5.43%). While 90 (32.62%) patients had missing data for weight and/or height to calculate their Body mass index. (see figure10)

Among patients with available BMI classification data (n = 276), Normal represented the predominant category, affecting 61 patients (22.10%), followed by Obese weight in 59 (21.37%) and overweight in 51 (18.48%). Underweight was the least frequent category, observed in 15 patients (5.43%).

In conclusion, **excess weight was common**: **64.5%** were overweight or obese, which fell above the normal range without accounting for the missing data.

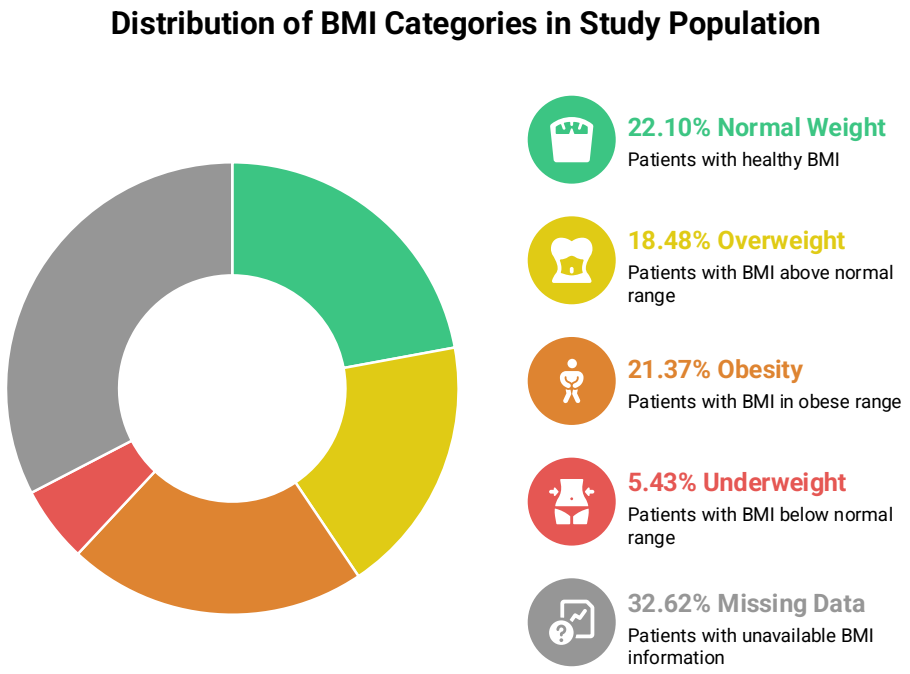



*Figure 10 Distribution of body mass index (BMI) categories in the study population*

## I.3. Comorbidity Burden in our study:

**Comorbidities were frequent in the study population.** Anemia was present in 159 patients (57.6%), while hypertension was observed in 117 patients (42.39%). Metabolic and endocrine disorders were also common, particularly diabetes in 91 patients (32.97%), including 74 cases (26.81%) with end-organ damage, and pre-diabetes in 46 patients (16.67%). Renal involvement was prominent, with moderate to severe renal disease reported in 171 patients (62.0%). Connective tissue diseases were identified in 41 patients (14.9%), whereas other comorbidities, such as chronic pulmonary disease (5.43%), gastrointestinal disorders, and cardiovascular conditions, were less frequent. (see table 10)

*Table 10 Prevalence of comorbidities in the study population*

| ***Comorbidities*** | **Frequency** | **Percentage (%)** |
|---|---|---|
| ***Anemia*** | 159 | 57.60 |
| ***Hypertension*** | 117 | 42.39 |
| ***Endocrinology/ Diabetology/ Metabolic*** | | |
| • *Pre-Diabetes* | 46 | 16.67 |
| • *Metabolic Syndrome* | 12 | 4.34 |
| • *Diabetes* | 91 | 32.97 |
| • *Diabetes without complication* | 17 | 6.16 |
| • *Diabetes with end-Organ Damage* | 74 | 26.81 |
| • *Others* | 8 | 2.89 |
| ***Cardiovascular disease*** | | |
| • *Valvulopathy* | 1 | 0.36 |
| • *Myocardial infarction* | 2 | 0.72 |
| • *Congestive heart failure* | 7 | 2.53 |
| • *Peripheral vascular disease* | 4 | 1.44 |
| • *Cerebrovascular disease* | 4 | 1.44 |
| ***Gastroenterology/ Hepatology*** | | |
| • *Peptic ulcer disease* | 5 | 1.8 |
| • *Mild Liver disease (Hepatic Steatosis, hepatitis B/C …)* | 4 | 1.44 |
| • *Moderate to severe liver disease (cirrhosis)* | 5 | 1.81 |
| ***Connective tissue disease*** | 41 | 14.9 |
| • *Grave's disease* | 1 | 0.36 |
| • *Lupus* | 20 | 7.24 |
| • *ANCA Vasculitis* | 4 | 1.44 |
| • *Gougerot's Disease* | 1 | 0.36 |
| • *Gout* | 1 | 0.36 |
| • *Others* | 14 | 5.07 |
| ***Nephrology*** | | |
| • *Moderate to severe renal disease* | 171 | 62.0 |
| ***Other Comorbidities*** | | |
| • *Dementia* | 4 | 1.4 |
| • *Chronic Pulmonary Disease* | 15 | 5.43 |
| • *Cerebrovascular disease or transient ischemic attack* | 4 | 1.4 |
| • *Hemiplegia* | 0 | 0 |
| • *Localized Solid tumor* | 5 | 1.81 |
| • *Leukemia* | 2 | 0.72 |
| • *Lymphoma* | 0 | 0 |
| • *Metastatic solid tumor* | 5 | 1.81 |
| • *AIDS* | 0 | 0 |
| • *Chronic Infection* | 2 | 0.72 |

### I.3.1.Charlson Comorbidity Index (CCI)

In this study, the **Charlson Comorbidity Index (CCI)** was available for all participants. The CCI had a **median of 3** (IQR **2–4**), with values ranging from **0 to 13**. The distribution was **right-skewed** (skewness **1.423)**, indicating that most patients clustered at lower scores with fewer patients presenting higher comorbidity burden.

When categorized, **11.6%** had **CCI = 0**, **37.3%** had **CCI between 1–2**, **32.6%** had **CCI between 3–4**, and **18.5%** had **CCI ≥ 5**. (see figure 11)

The derived **10-year survival estimate** showed a **mean ± SD of 95.43% ± 3.15**, with a **median of 95%** (IQR **94–97**) and values ranging from **82% to 100%**. (see figure 12)

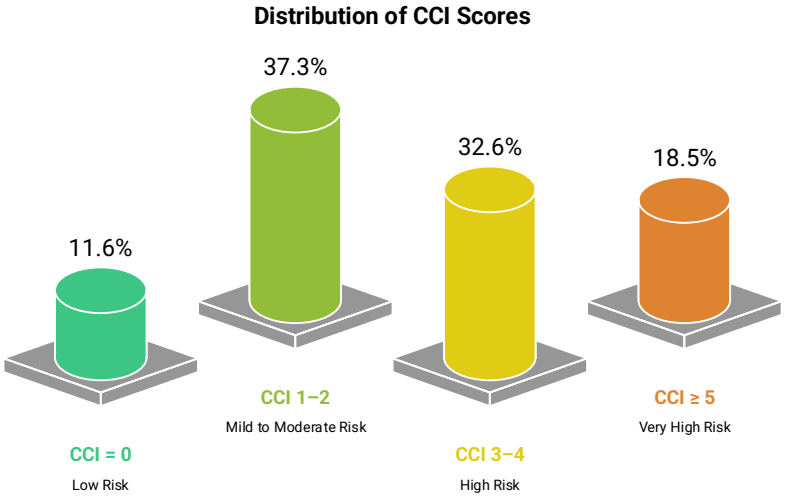



***Figure 11 Distribution of Charlson Comorbidity Index (CCI) categories in the study population.*** *CCI categories generally reflect increasing comorbidity burden and mortality risk as the score rises: CCI = 0 indicates no recorded comorbidity and therefore the lowest risk; CCI = 1–2 corresponds to a mild to moderate comorbidity burden and low-to-moderate risk; CCI = 3–4 indicates a high comorbidity burden with elevated risk; and CCI ≥ 5 reflects a very high comorbidity burden and the highest risk of adverse outcomes and mortality.*

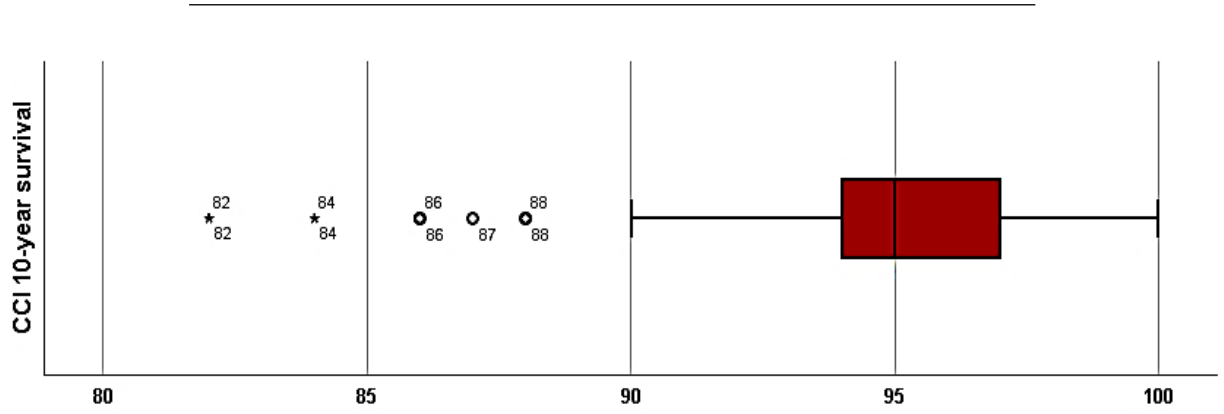



***Figure 12 Boxplot showing estimated 10-year survival derived from the Charlson Comorbidity Index***

Overall, the study displayed a predominantly **Mild-to-High comorbidity risk profile**, with a smaller subgroup presenting **Very high comorbidity burden** (CCI ≥ 5).

### I.3.2.Anemia:

The most prevalent comorbidity was anemia, which was distributed as follows:

- **159 patients (57.62%)** were classified as anemic,
- and **113 (40.94%)** were classified as not anemic.

While missing data accounted for **4 (1.44%)**. (see figure 13)

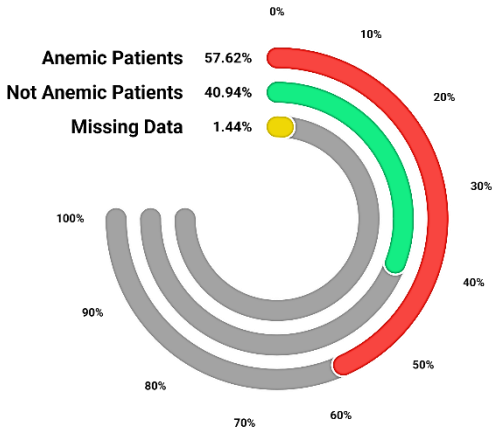



*Figure 13 Distribution of Anemia Status*

#### I.3.2.1. Hemoglobin levels by sex among the anemic subgroups

In the anemic population, mean hemoglobin (Hb) was comparable between sexes, with a slightly higher average in men.

Among women, the mean Hb was **9.30** and a standard deviation (SD) of **1.88**; values ranged from **3.70** to **11.90**. The median was 9.50 with IQR [7.90–11.00]

Among men, the mean Hb was **9.49** and SD of **2.24**; values ranged from **2.40** to **12.80**. The median was 9.50 [7.85—11.52].

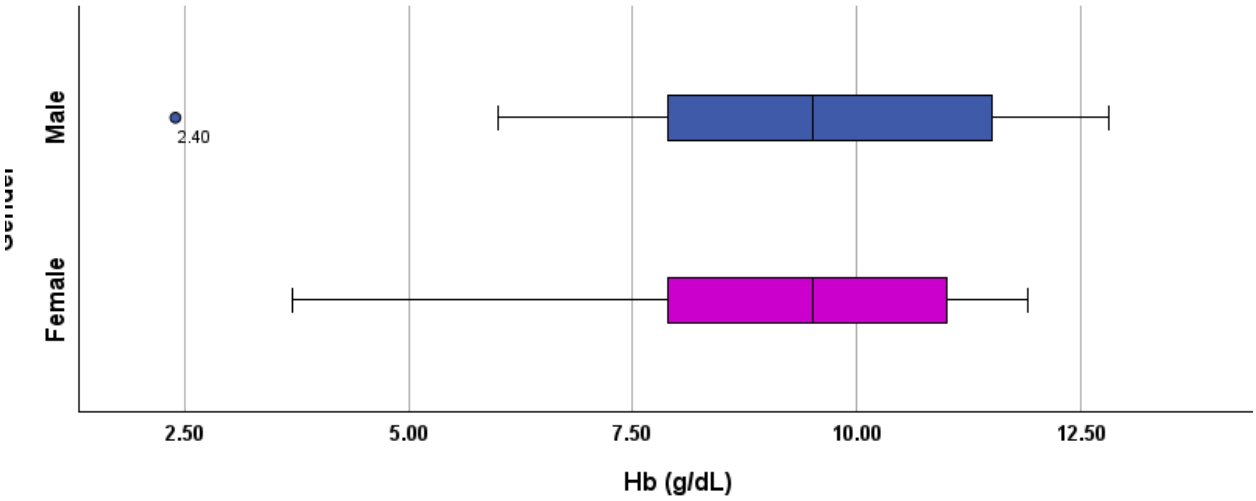



***Figure 14 Comparison of Hemoglobin Levels by Gender in Anemic Patients (Boxplot Analysis).*** *Both male and female groups demonstrate comparable median hemoglobin levels, clustered around approximately 9–10 g/dL, indicating a similar severity of anemia across genders. The interquartile ranges are also largely overlapping, suggesting that the central distribution of hemoglobin values is consistent between males and females when anemia is present.*

#### I.3.2.2. Hemoglobin levels by sex among the non-anemic subgroups

In the non-anemic population, hemoglobin (Hb) levels were higher in men than in women.

Among women, the mean Hb was **13.53** and an SD of **1.05**; values ranged from **12.00** to **15.90**. The median was 13.40 with IQR [12.60–14.25].

Among men, the mean Hb was **14.80** and an SD of **1.03**; values ranged from **13.20** to **17.90**. The median was 14.60 with IQR [14.00–15.47].

Distributional shape differed by sex, showing **mild positive skewness** in both groups (women: **0.44**; men: **0.77**), indicating a slight tail toward higher Hb values.

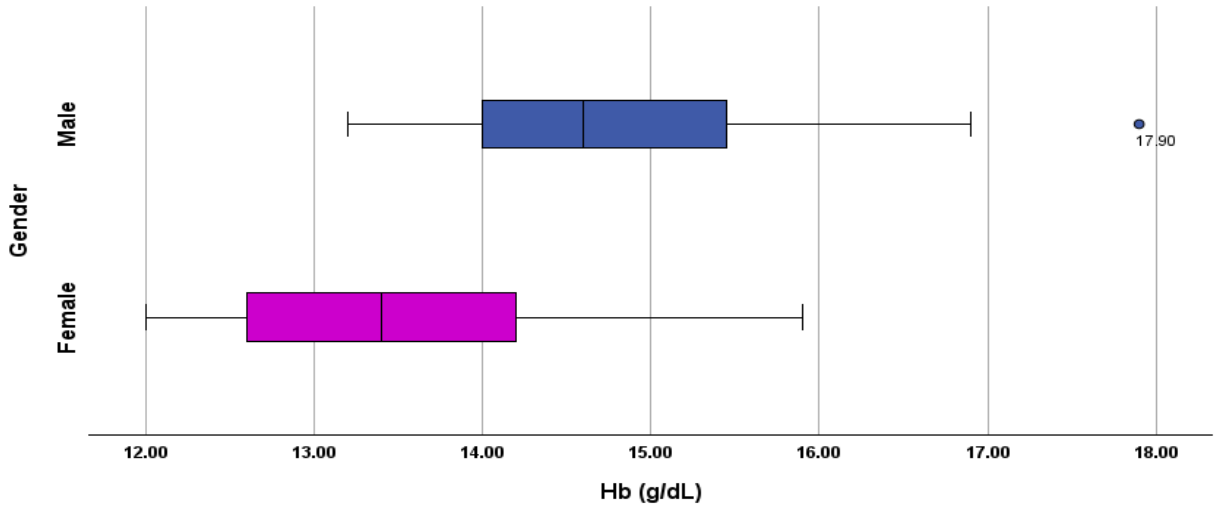



*Figure 15 Comparison of Hemoglobin Levels by Gender in Non-Anemic Patients (Boxplot Analysis). Male patients exhibit higher median hemoglobin levels compared to females, with values centered around approximately 14.5–15 g/dL, whereas females show lower median values around 13–13.5 g/dL. The interquartile ranges are moderately spread in both groups but remain clearly separated, indicating a consistent difference between genders.*

### I.3.3.Hypertension:

#### I.3.3.1. Distribution of hypertensive population:

The 2nd most prevalent comorbidity in the study population was hypertension.

In our sample, **138 patients (50.0%)** had **no hypertension**, whereas **117 patients (42.4%)** were **hypertensive**; hypertension status was **missing in 21 patients (7.6%)**. Considering only records with available data (**n = 276**), the prevalence of hypertension was **45.9%**. (see figure 16)

Overall, hypertension was a common comorbidity in this Study

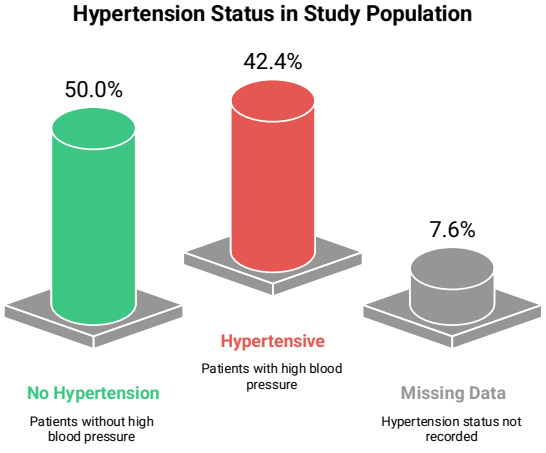



*Figure 16 Prevalence of Hypertensive patients*

### I.3.3.2. Distribution of Blood pressure within the population

The mean systolic blood pressure was **133.48 mmHg (SD 20.46)**, with a median of **130 mmHg**. The interquartile range (IQR) was **120–150 mmHg** and a range from **86 to 220 mmHg**. The distribution showed **moderate right skewness** (skewness = **0.781**), indicating that higher SBP values were present and slightly increased the mean relative to the median. (see figure17)

The mean diastolic blood pressure was **74.83 mmHg (SD 13.02)**, with a median of **71 mmHg**. The IQR was **67–80 mmHg**. The range was **36 to 150 mmHg**. The distribution was **right-skewed** (skewness = **1.113**), suggesting a greater spread toward higher DBP values, though the overall range remained clinically plausible. (see figure 17)

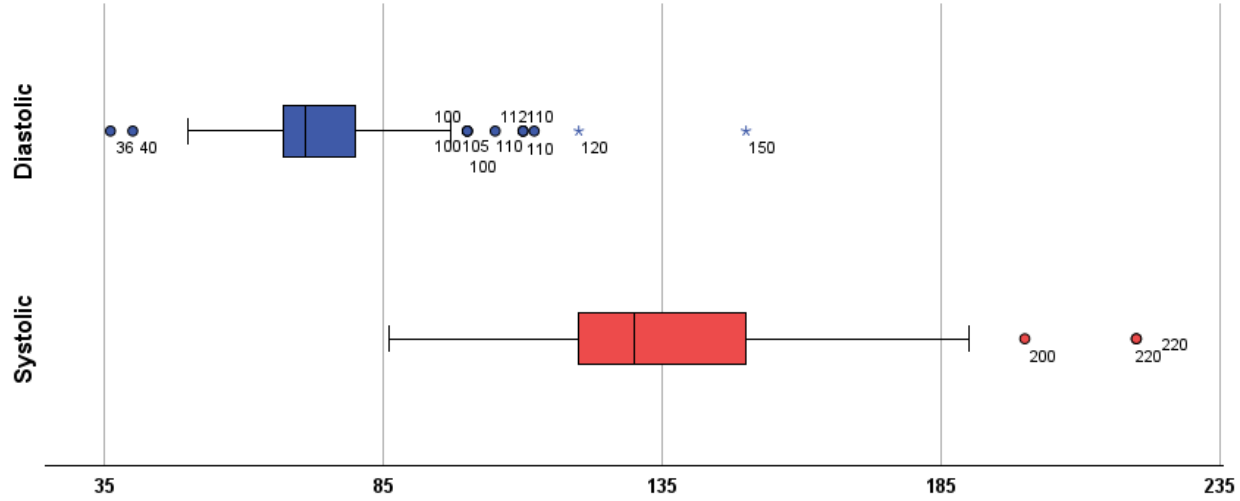



*Figure 17 Distribution of Systolic and Diastolic Blood Pressure with Identification of Extreme Values*

### I.3.3.3. Distribution of hypertension treatment

Regarding antihypertensive therapy, **50 of the 117 hypertensive patients** were recorded as receiving treatment. For the remaining **67 hypertensive patients**, the **type of antihypertensive treatment was undocumented**.

Among treated patients, **monotherapy predominated** (**42/50; 84.0%**), while **dual therapy** was used in **8/50 (16%)**.

Angiotensin-converting enzyme (ACE) inhibitors were the most frequently prescribed therapy, used in 45 patients (90.0%), indicating their predominant role in blood pressure management within the hypertensive. Calcium channel blockers were the second most common class, prescribed in 6 patients (12%), followed by angiotensin II receptor blockers (ARBs) in 2 patients (4.0%).

Other antihypertensive agents were less commonly used, including thiazide diuretics in 3 patients (6.0%), beta-blockers in 1 patient (2.0%), and methyldopa in 1 patient (2.0%). (see table 11)

*Table 11 Proportions of hypertension therapy in patients with hypertension*

| Hypertension treatment | n | Percentage (%) |
|---|---|---|
| Calcium-Inhibitors | 6 | 12 |
| Angiotensin 2 receptor blockers | 2 | 4 |
| Converting enzyme inhibitor | 45 | 90 |
| B-Blockers | 1 | 2 |
| Thiazide diuretics | 3 | 6 |
| Methyl-dopa | 1 | 2 |

### I.3.4.Diabetes:

In the study sample (n = 276), **91 participants were diabetic**, corresponding to a prevalence of **33.0%**, while **185 were non-diabetic** (**67.0%**). This indicates that one-third of the cohort had a documented diabetes. (see figure 18)

The mean fasting blood glucose level was **1.21 g/L** (SD = **0.77**), while the median was **0.95 g/L**, with an interquartile range ranging from **0.81 g/L** to **1.21 g/L**. Values extended from **0.43 g/L** to **5.50 g/L**..

HbA1c values showed a mean of **6.50%** (SD = **1.98**) and a median of **5.90%**, with the 25th and 75th percentiles at **5.40%** and **6.80%**, respectively. The observed range was **3.90% to 13.80%**.

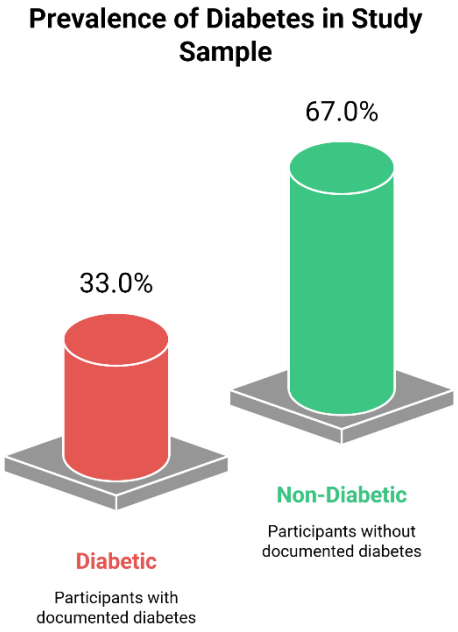



*Figure 18 Prevalence of Diabetics*

The plot below shows the distribution of both fasting glucose and HbA1as a half-violin plot. (see figure19)

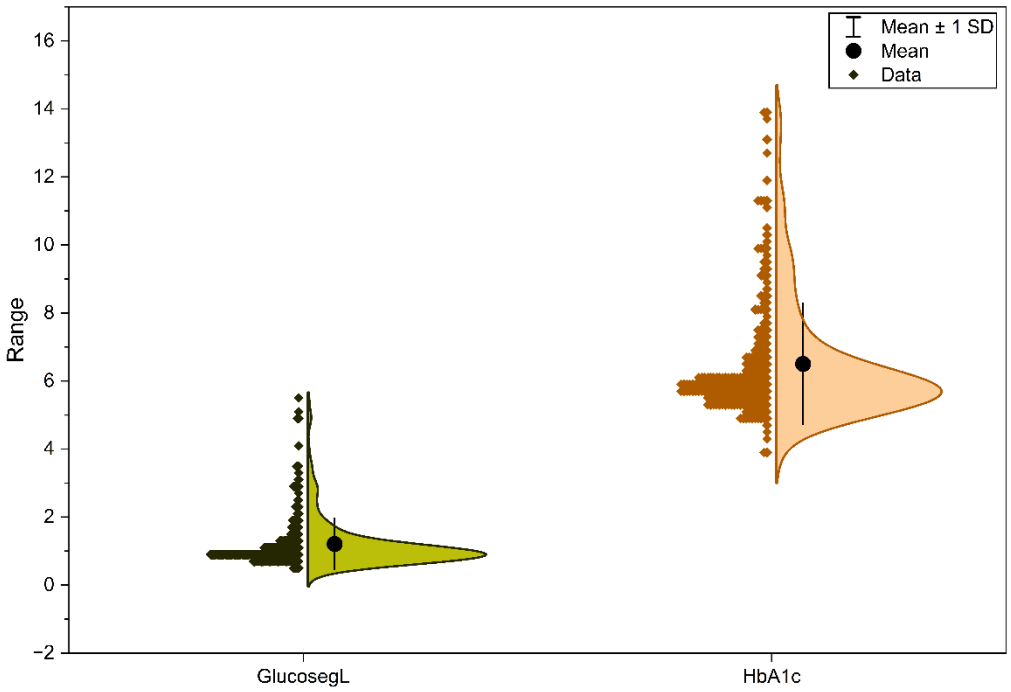



*Figure 19 Violin Plot for Glucose in g/L and HbA1c in % for the whole sample.*

### I.3.4.1. Glycemic biomarkers within diabetics

In the diabetic subgroup, Fasting plasma glucose mean ± SD was 1.69 ± 1.12. The median fasting plasma glucose level was 1.26 g/L, with an interquartile range of 0.84 to 2.26 g/L. Values ranged from 0.45 to 5.50 g/L.

While HbA1c mean ± SD was 8.12 ± 2.09. The median HbA1c was 7.50%, with an interquartile range of 6.62% to 9.35%. The values observed ranged from 4.80% to 13.80%.

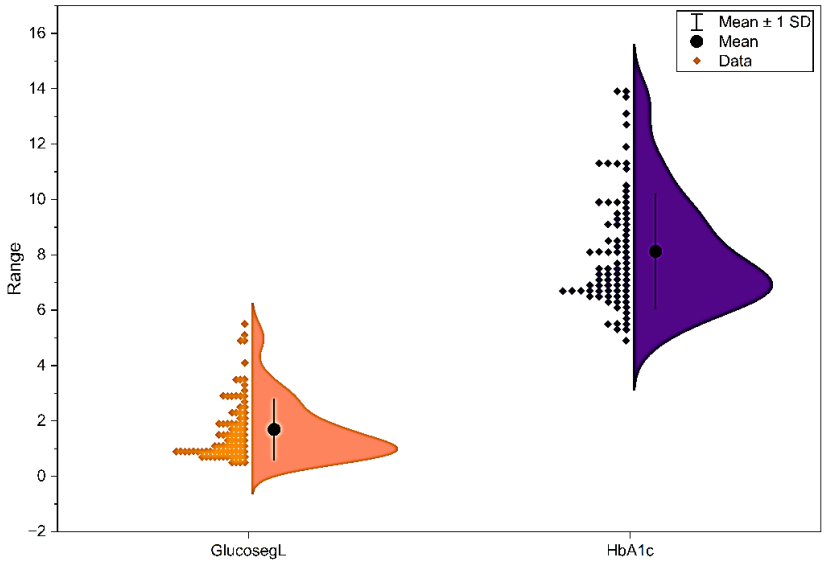



*Figure 20 Violin Plot for Glucose in g/L and HbA1c in % for the diabetic subgroup.*

### I.3.4.2. Glycemic biomarkers within non-diabetics

In the **non-diabetic** subgroup, Glucose mean ± SD was 0.95 ± 0.22. The **median was 0.91 g/L** (IQR **0.80-1.03**). Values ranged from **0.43 to 1.73 g/L**.

While HbA1c mean ± SD was 5.57 ± 0.45. The **median** was **5.60%** (IQR **5.30-5.90**). Values ranged from **3.90 to 6.40%**.

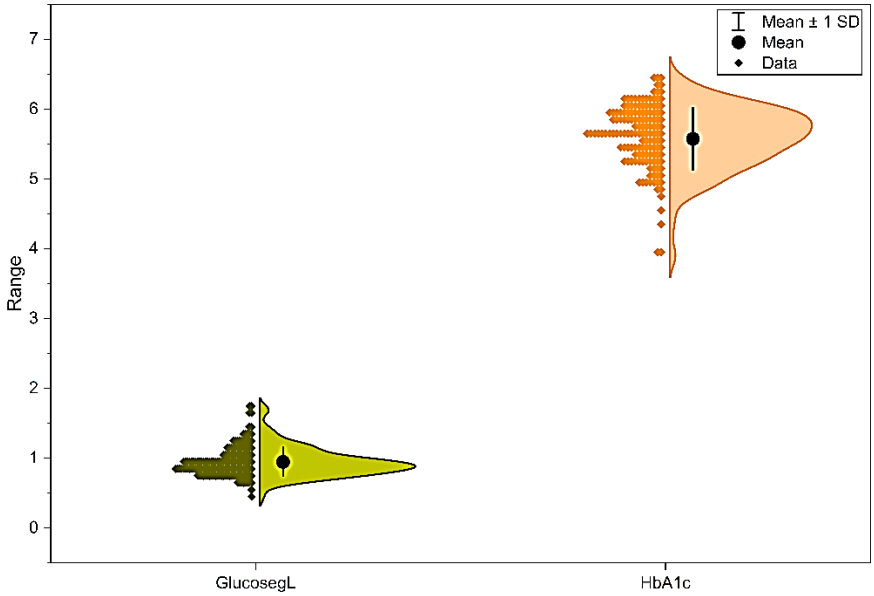



*Figure 21 Violin Plot for Glucose in g/L and HbA1c in % for the non-diabetic subgroup.*

### I.3.4.3. Diabetes severity:

According to the severity classification, **17 patients (18.08%)** had **diabetes without complications**, whereas **74 patients (78.72%)** had **diabetes with end-organ damage while 3 patients (3.20%) diabetic severity was unknown**. These findings indicate that diabetes with complicated forms being more common than uncomplicated diabetes.

## I.4. Renal Characteristics of the population:

### I.4.1. Distribution of Nephropathy types and Subtypes in the sample:

**The distribution of nephropathy types revealed marked etiological heterogeneity, with a predominance of undocumented or unspecified nephropathies (34.78%).** Among identified causes, systemic glomerular diseases were the leading category (31.88%), chiefly related to diabetes mellitus (22.1%), followed by lupus-associated nephropathy (7.20%). Primary glomerular diseases accounted for 13.76% of cases, with focal segmental glomerulosclerosis being the most frequent subtype (9.05%). Vascular nephropathies represented 13.04% of cases and were mainly driven by hypertensive nephrosclerosis (11.23%). In contrast, tubulointerstitial nephropathies and urinary tract obstruction remained uncommon, each accounting for only 1.44% of the cohort. (see table 12)

*Table 12 Spectrum of Nephropathy Types and Their Subcategories in the Study*

| *Nephropathy type and sub-types* | | n | Percentage (%) |
|---|---|---|---|
| *Vascular diseases* | | 36 | 13.04 |
| | Renal artery stenosis | 2 | 0.72 |
| | ANCA Vasculitis | 3 | 1.08 |
| | hypertensive nephrosclerosis | 31 | 11.23 |
| | renal vein thrombosis | 0 | 0 |
| *Primary glomerular diseases* | | 38 | 13.76 |
| | Membranous nephropathy | 5 | 1.81 |
| | Alport syndrome | 0 | 0 |
| | IgA nephropathy | 2 | 0.72 |
| | focal segmental glomerulosclerosis | 25 | 9.05 |
| | minimal change disease | 6 | 2.17 |
| *Tubulointerstitial diseases* | | 4 | 1.44 |
| | Drug-induced TIN (e.g., sulfonamides, allopurinol) | 1 | 0.36 |
| | infectious causes (viral/bacterial/parasitic) | 1 | 0.36 |
| | multiple myeloma | 1 | 0.36 |
| | polycystic kidneys | 0 | 0 |
| | Recurrent UTI | 1 | 0.36 |
| *Urinary tract obstruction* | | 4 | 1.44 |
| | Urolithiasis | 4 | 1.44 |
| *Systemic causes of glomerular disease* | | 88 | 31.88 |
| | Diabetes mellitus | 61 | 22.1 |
| | systemic lupus erythematosus | 20 | 7.20 |
| | rheumatoid arthritis | 3 | 1.08 |
| | mixed connective tissue disease | 3 | 1.08 |
| | amyloidosis | 2 | 0.72 |
| | Others | 2 | 0.72 |
| Undocumented/unknown | | 96 | 34.78 |

### I.4.2.Renal function in the population study:

The study included **276 chronic kidney patient**, with **complete data available for uremia, serum creatinine, and eGFR (CKD-EPI)**. Descriptive analysis showed marked variability in renal function-related parameters across the whole population.

Uremia had a **median of 0.65 g/L**, with values ranging from **0.08 to 23 g/L**. The interquartile range was **0.32-1.30 g/L**. (see table 13)

Serum creatinine had a **median of 17.00 mg/L**. Observed values ranged from **2.39 to 186.26 mg/L**, with the IQR at **7.50 mg/L** and **46.75 mg/L**, respectively. (see table 13)

The **eGFR (CKD-EPI) median of 39.95**. The observed range was **2.9 to 171.9 mL/min/1.73 m²**, while the interquartile range extended from **12.15 to 97.02 mL/min/1.73 m²**. Although the skewness was minimal (**0.043**), normality testing still indicated a statistically significant departure from a Gaussian distribution. (see table 13)

Normality was assessed using the **Shapiro-Wilk test**, which showed significant non-normality for all three variables: **uremia ($W = 0.370$, $p < 0.001$)**, **serum creatinine ($W = 0.750$, $p < 0.001$)**, and **eGFR CKD-EPI ($W = 0.887$, $p < 0.001$)**. The graphical distribution of eGFR also supported this finding, showing a Bimodal pattern rather than a perfectly normal curve. (see figure 22)

*Table 13 Summary of statistical results for renal function lab results*

| Variable | Median/Mean |
|---|---|
| **Serum urea (g/L)** | 0.65 [0.32-1.30] |
| **Serum creatinine (mg/L)** | 17 [7.49-46.75] |
| **eGFR (CKD-EPI) mL/min/1.73m²** | 39.95 [12.15-97.02] |

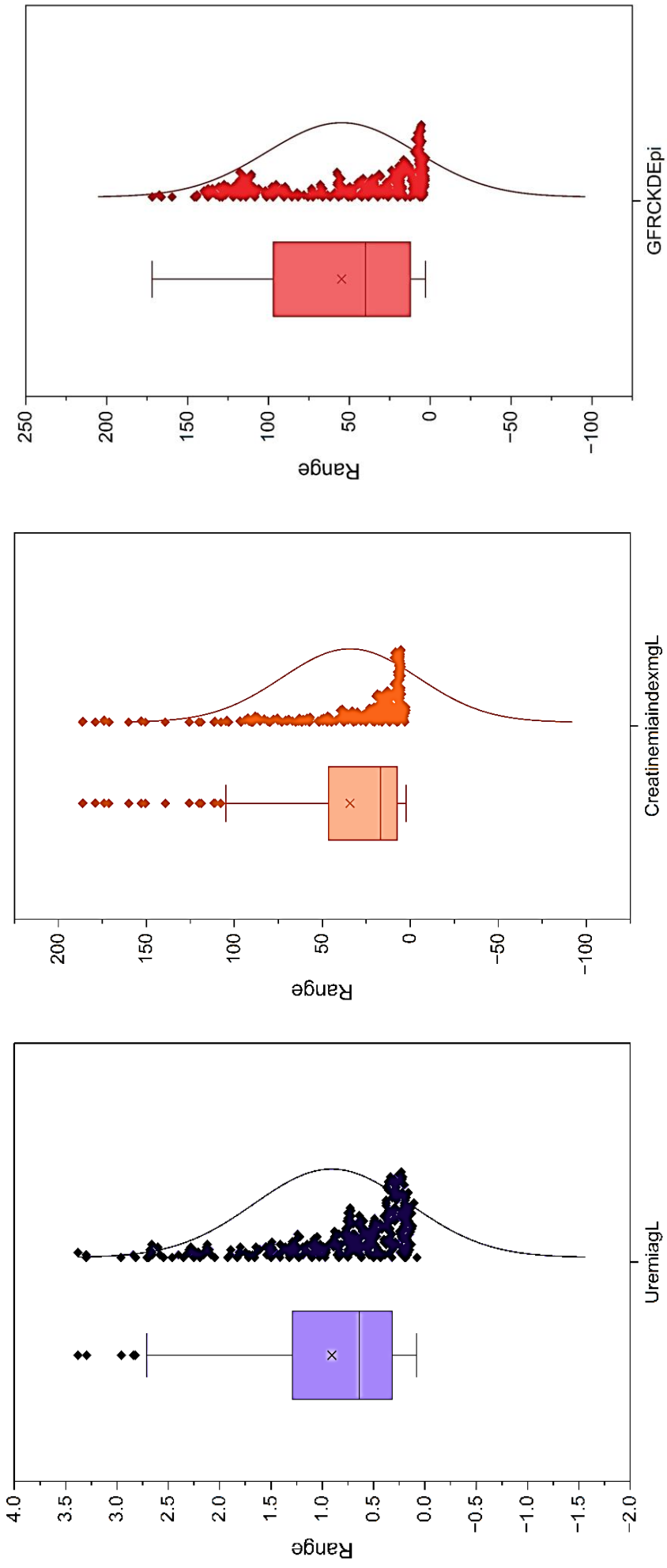



***Figure 22 Distribution of estimated glomerular filtration rate, serum creatinine, and blood urea in the study population.*** *This figure shows the distribution of three renal function parameters in the study population: estimated glomerular filtration rate calculated using the CKD–EPI equation (eGFR), serum creatinine, and blood urea. Each panel combines a density curve, individual data points, and a boxplot, allowing visualization of the overall distribution, central tendency, dispersion, and outliers. eGFR shows substantial variability, with most observations clustered in the low–to–intermediate range. Serum creatinine and blood urea display asymmetrical distributions with several high extreme values, reflecting the heterogeneity of renal impairment within the study population.*

### 1.4.3. Distribution of GFR Stages Within the Sample:

Among the 276 participants, the largest proportion was classified in **G1 (≥90 mL/min/1.73 m²)**, accounting for **78 patients (28.3%)**. This was followed by **G5 (<15 mL/min/1.73 m²)** in **74 patients (26.8%)**, **G4 (15–29 mL/min/1.73 m²)** in **42 patients (15.2%)**, **G3b (30–44 mL/min/1.73 m²)** in **32 patients (11.6%)**, **G2 (60–89 mL/min/1.73 m²)** in **25 patients (9.1%)**, and **G3a (45–59 mL/min/1.73 m²)** in **25 patients (9.1%)**. (see table 14 and figure 23))

Overall, **37.32%** of participants had an eGFR ≥60 mL/min/1.73 m² (G1–G2), whereas **62.68%** had an eGFR <60 mL/min/1.73 m² (G3a–G5).

*Table 14 Distribution of Chronic Kidney Disease Stages According to CKD-EPI eGFR Categories.*

| CKD-EPI eGFR category | Definition (mL/min/1.73 m²) | n | % | |
|---|---|---|---|---|
| **G1** | ≥90 | 78 | 28.26 | **37.32** |
| **G2** | 60–89 | 25 | 9.06 | |
| **G3a** | 45–59 | 25 | 9.06 | **62.68** |
| **G3b** | 30–44 | 32 | 11.60 | |
| **G4** | 15–29 | 42 | 15.21 | |
| **G5** | <15 | 74 | 26.81 | |

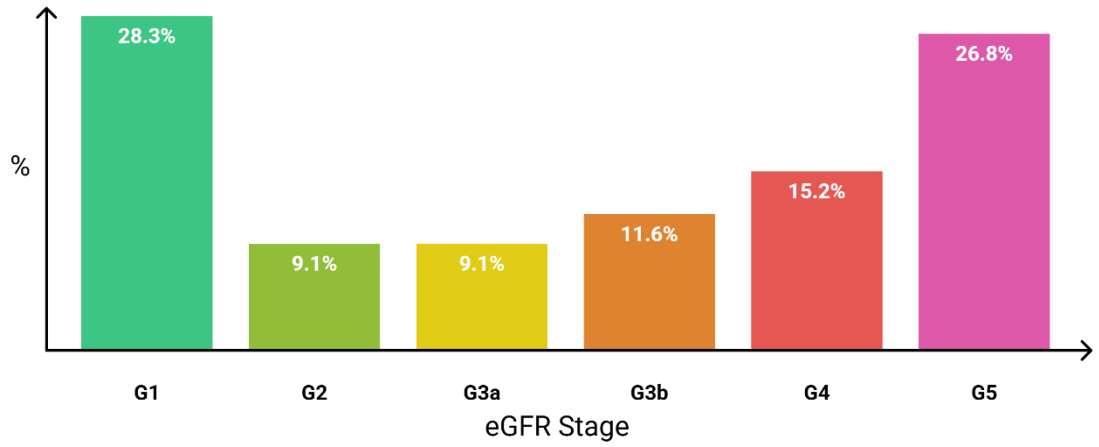



*Figure 23 Frequency Distribution of Chronic Kidney Disease Stages According to CKD-EPI eGFR Categories*

### 1.4.4. Kidney Damage Markers within the sample

In the overall study population (**n = 276**), albumin-to-creatininuria ratio (ACR) data were available for all participants, with **no missing values**. The **median ACR was 217.4 mg/g** with an **interquartile range (IQR) of 44.60 to 782.90 mg/g**. The **mean ACR was 735.10 ± 2053.54 mg/g**, with values ranging from **4.7 to 22951mg/g**. The large difference between the mean and median, together with the marked positive skewness (**9.0**), indicates a **highly right-skewed distribution**, reflecting the presence of very high ACR values in a subset of patients. (see figure 24)

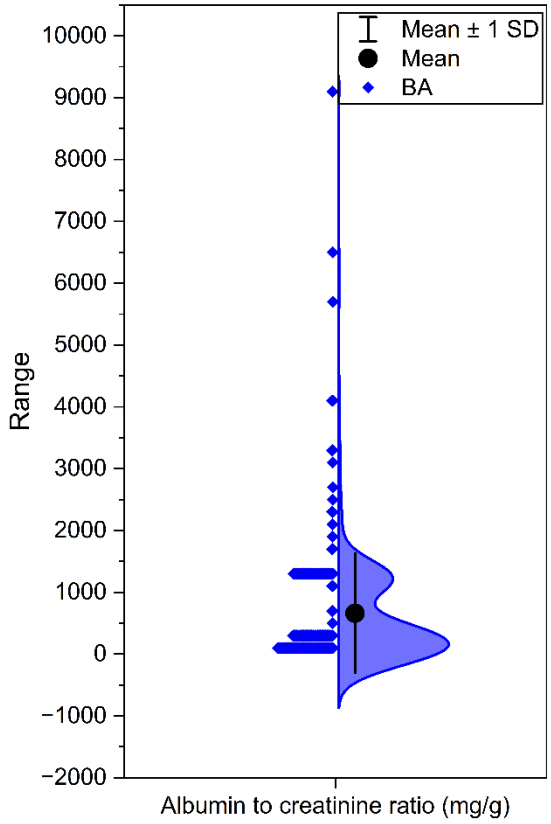



*Figure 24 Violin Plot of the Distribution of Albumin-to-Creatinine Ratio (mg/g) After Exclusion of Two Extreme Outliers to Improve Data Visualization*

According to KDIGO albuminuria categories, **49 patients (17.8%)** were classified as **A1**, **108 (39.1%)** as **A2**, and **119 (43.1%)** as **A3**. Thus, **82.4%** of the study population had **moderately to severely increased albuminuria (A2–A3)**, while **43.1%** had **severely increased albuminuria (A3)**. (See figure 25)

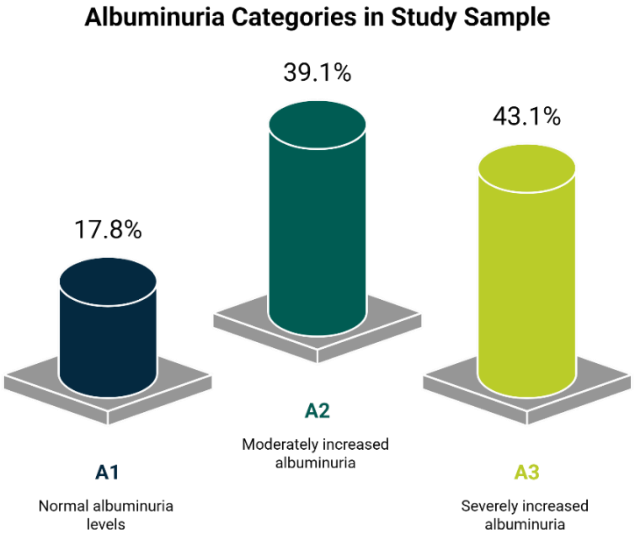



*Figure 25 Proportion of Patients Across ACR Categories (A1, A2, and A3)*

### 1.4.5. KDIGO renal risk stratification:

Renal risk stratification according to the KDIGO classification showed that the largest proportion of patients fell into the **very high-risk** category, accounting for **155 patients (56.2%)**. This was followed by the **high-risk** category, which included **56 patients (20.3%)**. The **moderate-risk** category comprised **38 patients (13.8%)**, whereas the **low-risk** category represented the smallest proportion, with **27 patients (9.8%)**. (see figure 26)

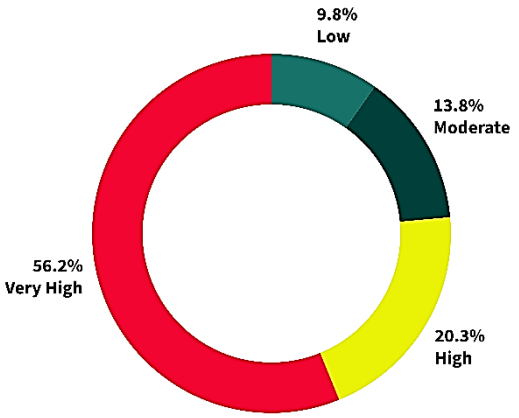



*Figure 26 Classification of Patients by KDIGO Chronic Kidney Disease Risk Categories*

Overall, these findings indicate that a substantial proportion of the study population was clustered within the more severe KDIGO prognostic strata, particularly the **very high-risk group**, suggesting a considerable burden of advanced renal risk within the cohort.

| KDIGO Prognosis of CKD by GFR and Albuminuria Categories | | | | A1 | A2 | A3 |
|---|---|---|---|---|---|---|
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30mg/g <3 mg/mmol | 30-300 mg/g 3-30 mg/mmol | >300 mg/g >30mg/mmol |
| GFR categories (ml/min/1.73m²) Description and range | G1 | Normal or high | >= 90 | 24 | 28 | 26 |
| | G2 | Mildly decreased | 60-89 | 3 | 6 | 16 |
| | G3a | Mildly to moderately decreased | 45-59 | 6 | 8 | 11 |
| | G3b | Moderately to severely decreased | 30-44 | 7 | 11 | 14 |
| | G4 | Severely decreased | 15-29 | 1 | 17 | 24 |
| | G5 | Kidney failure | <15 | 8 | 38 | 28 |

*Figure 27 Distribution of Patients Across KDIGO Prognostic Categories Defined by GFR and Albuminuria*

## 1.5. Dyslipidemia Burden in our sample with Cardiovascular risk assessment:

### 1.5.1. Distribution of Dyslipidemia within our population:

Dyslipidemia status was predominantly positive in the study population. Of the 276 patients analyzed, 203 (73.6%) were classified as having dyslipidemia, while 34 (12.3%) were classified as not dyslipidemic. A further 39 patients (14.1%) fell into undocumented/unknown category for dyslipidemia status in the database. Overall, these findings indicate a high burden of dyslipidemia in the study sample. (see figure 28)

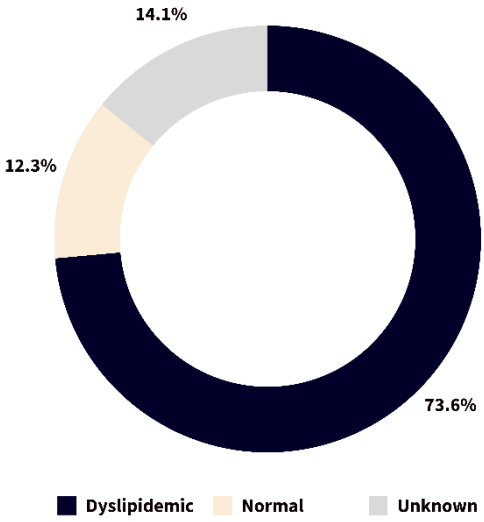



*Figure 28 Dyslipidemia Status in our population*

### 1.5.2. Dyslipidemia characteristics in the population

In the overall study population (**n = 276**), lipid abnormalities showed a heterogeneous distribution across the different fractions.

For **total cholesterol**, **124 patients (44.9%)** had **normal values**, whereas **44 (15.9%)** were classified as **borderline high**, **69 (25.0%)** as **high**, and **39 (14.1%)** with missing data.

For **HDL-cholesterol**, **low HDL** was observed in **140 patients (50.7%)**, making it the most frequent lipid abnormality in the cohort, while **97 patients (35.1%)** had **normal HDL levels** and **39 (14.1%)** had **no HDL data**.

Regarding **LDL-cholesterol**, **152 patients (55.1%)** had **normal levels**, **29 (10.5%)** were **borderline high**, **20 (7.2%)** were **high**, and **36 (13.0%)** were **very high**, whereas **39 (14.1%)** had **no LDL data**.

For **triglycerides**, **118 patients (42.8%)** had **normal values**, while **42 (15.2%)** were **borderline high**, **74 (26.8%)** were **high**, and **3 (1.1%)** were **very high**; similarly, **39 patients (14.1%)** had **no triglyceride data**.

*Table 15 Frequency of patients according to Total cholesterol, HDL, LDL, Triglycerides categories*

| Lipid parameter | Category | n | % of total sample |
|---|---|---|---|
| **Total cholesterol** | Normal | 124 | 44.9 |
| **Hypercholesterolemia 40.9%** | Borderline high | 44 | 15.9 |
| | High | 69 | 25.0 |
| | Very high | 0 | 0 |
| | Unknown | 39 | 14.1 |
| **HDL-cholesterol** | Normal | 97 | 35.1 |
| **Low HDL 50.7%** | Low HDL | 140 | 50.7 |
| | Unknown | 39 | 14.1 |
| **LDL-cholesterol** | Normal/optimal | 152 | 55.1 |
| **Hyperlipoproteinemia 30.7%** | Borderline high | 29 | 10.5 |
| | High | 20 | 7.2 |
| | Very high | 36 | 13.0 |
| | Unknown | 39 | 14.1 |
| **Triglycerides** | Normal | 118 | 42.8 |
| **Hypertriglyceridemia 43.1%** | Borderline high | 42 | 15.2 |
| | High | 74 | 26.8 |
| | Very high | 3 | 1.1 |
| | Unknown | 39 | 14.1 |

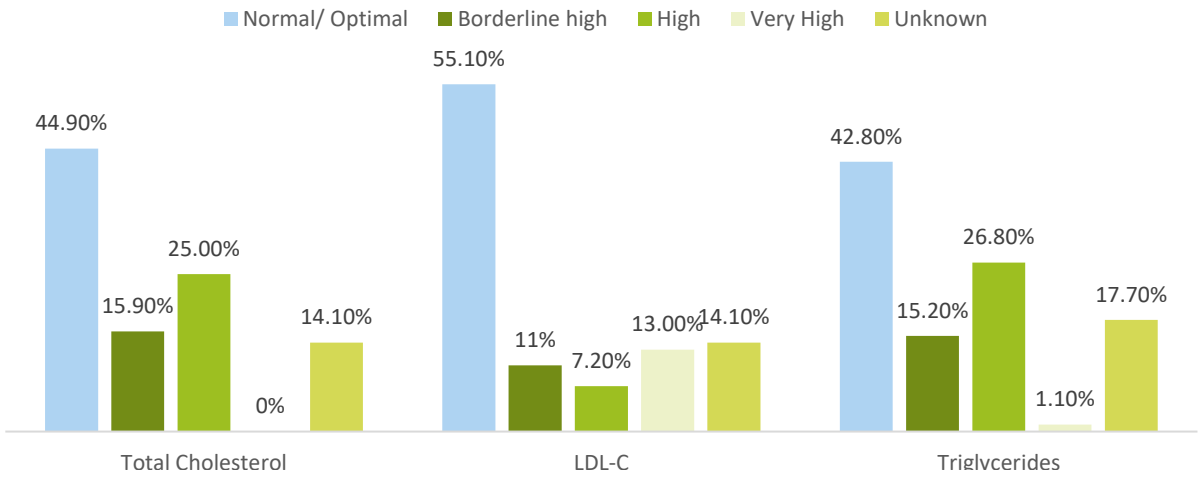



*Figure 29 summary of proportions of lipid profile according to NCEP ATA III*

### 1.5.3. Characteristics of Lipid Profile Lab results in the population:

In the overall study population, lipid profile measurements were available for 236 patients for total cholesterol, 234 for HDL-C, 235 for LDL-C, and 235 for triglycerides.

Median lipid values were 1.94 g/L for total cholesterol, 0.41 g/L for HDL-C, 1.15 g/L for LDL-C, and 1.51 g/L for triglycerides.

The corresponding interquartile ranges were 1.56–2.46 g/L, 0.33–0.53 g/L, 0.85–1.56 g/L, and 1.04–2.30 g/L, respectively.

Mean ± standard deviation values were

- 2.21 ± 1.07 g/L for total cholesterol,
- 0.45 ± 0.25 g/L for HDL-C,
- 1.38 ± 0.96 g/L for LDL-C,
- and 1.75 ± 1.02 g/L for triglycerides.

All lipid variables showed right-skewed distributions, as reflected by positive skewness coefficients, with the greatest asymmetry observed for HDL-C. In addition, the wide observed ranges for total cholesterol, LDL-C, and triglycerides indicate substantial inter-individual variability in lipid levels across the cohort.

*Table 16 Summary of descriptive statistics for the lipid lab results*

| Lipid parameter | n | Median (IQR), g/L |
|---|---|---|
| **Total cholesterol** | 236 | 1.94 [1.56–2.45] |
| **HDL-C** | 234 | 0.41 [0.33–0.53] |
| **LDL-C** | 235 | 1.15 [0.85–1.56] |
| **Triglycerides** | 235 | 1.51 [1.04–2.30] |

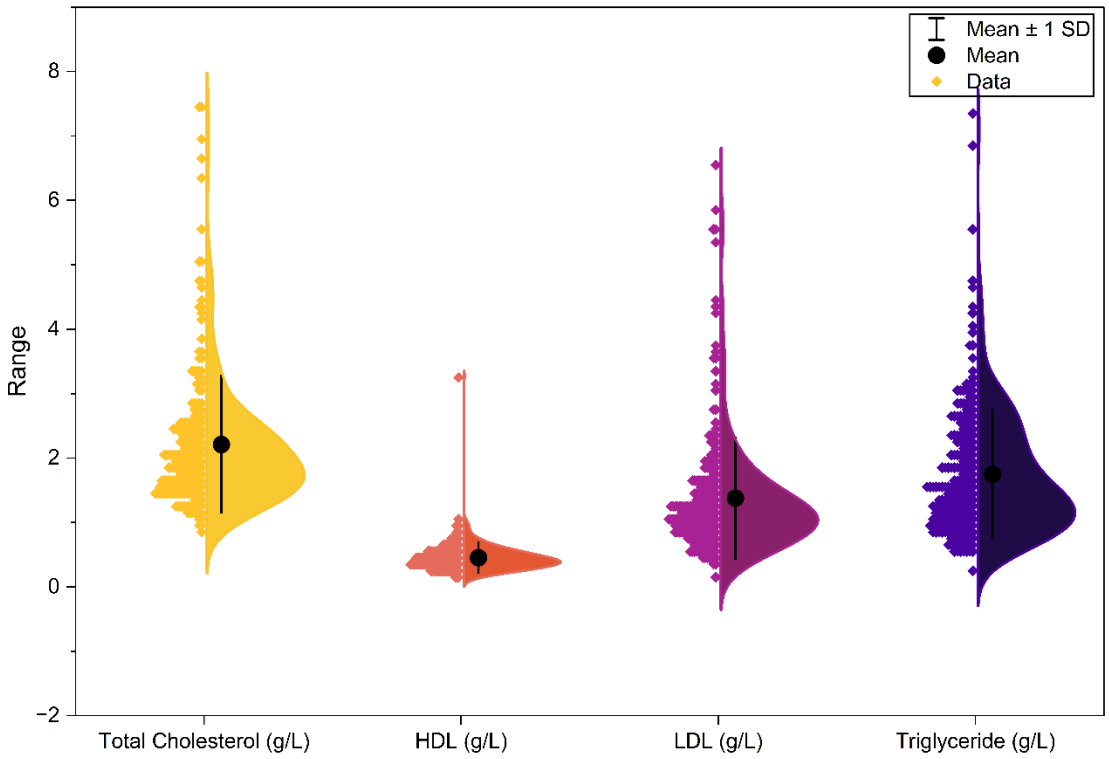



*Figure 30 Distributional Characteristics of Lipid Profile Components (Total Cholesterol, HDL, LDL, and Triglycerides) with Identification of Extreme Values*

### 1.5.4. Dyslipidemic Population Treatment Regimen characteristics

Among the **203 dyslipidemic patients** included in this analysis, **95 (46.8%)** were receiving lipid-lowering therapy, while **30 (14.8%)** were not on treatment. Treatment status was **unknown in 78 patients (38.3%)**. These findings indicate that, although a considerable proportion of the cohort was treated for dyslipidemia, therapeutic information was missing or unclear in nearly half of the study population. (see table 17)

*Table 17 Lipid-Lowering Treatment Status Profile of the Dyslipidemic sample*

| Lipid-lowering treatment status | n | % |
|---|---|---|
| **No** | 30 | 14.8 |
| **Yes** | 95 | 46.8 |
| **Unknown** | 78 | 38.3 |

### I.5.4.1. Type of treatment taken by the dyslipidemia population

Regarding the type of lipid-lowering management, **statins** were the most frequently documented therapeutic option, used by **84 patients (41.38%)**. Information on treatment type was **unknown in 84 patients (41.4%)**. In contrast, **30 patients (14.8%) were not receiving any lipid-lowering treatment** at the time of assessment. Less common treatment patterns included **statins combined with lifestyle or dietary regimen** in **6 patients (3%)**, **fibrates** in **2 patients (1%)**, and **lifestyle or dietary regimen alone** in **2 patients (1%)** while **omega-3 therapy** was recorded in only **1 patient (0.5%)**.

Overall, statins represented the predominant documented lipid-lowering therapy in the study population, although treatment information was unavailable for a substantial proportion of cases.

*Table 18 Lipid lowering treatment type distribution in the dyslipidemia population*

| Lipid-lowering treatment type | n | % |
|---|---|---|
| **Statins** | 84 | 41.38 |
| **Unknown** | 84 | 41.4 |
| **No Lipid Treatment** | 30 | 14.8 |
| **Regimen + statins** | 6 | 3 |
| **Fibrates** | 2 | 1 |
| **Regimen alone** | 2 | 1 |
| **Omega-3** | 1 | 0.5 |

### 1.5.4.2. Type of treatment molecules taken by the dyslipidemia population

When lipid-lowering therapy was examined according to the prescribed molecule and dose, **statins clearly represented the predominant documented therapeutic class** in the study population. However, it should be noted that the exact molecule and dose were **undocumented in 92 patients (45.3%)**, while **30 patients (14.8%) were not receiving any lipid-lowering treatment** at the time of assessment.

Within the **statin group**, **Atorvastatin** was the most frequently prescribed molecule. Specifically, **Atorvastatin 40 mg** was recorded in **33 patients (16.3%)**, making it the single most common documented statin regimen, followed by **Atorvastatin 20 mg** in **17 patients (8.4%)**.

**Simvastatin** also accounted for an important proportion of documented statin prescriptions. **Simvastatin 20 mg** was reported in **17 patients (8.4%)**, representing the second most frequent documented regimen overall after Atorvastatin 40 mg. Other simvastatin prescriptions included **simvastatin 40 mg** in 3 **patients (1.5%)**, **simvastatin 10 mg** in **2 patients (1%)**.

**Rosuvastatin** was less commonly prescribed in this population. **Rosuvastatin 10 mg** was documented in **3 patients (1.5%)**, whereas **rosuvastatin 40 mg** was recorded in only **1 patient (0.5%)**.

Among the **non-statin lipid-lowering therapies**, **Fenofibrate** were reported in **2 patients (1%)**, while **omega-3 therapy** was documented in **1 patient (0.5%)**. In addition, **lifestyle regimen alone** was recorded in **1 patient (0.5%)**.

Overall, these findings indicate that **statins, particularly atorvastatin and simvastatin at doses of 20 mg and 40 mg, constituted the principal documented lipid-lowering therapies** in the study population. Nevertheless, the substantial proportion of patients with **unknown therapeutic specification** limits a fully detailed interpretation of prescribing patterns.

*Table 19 lipid treatment molecule type distribution in the dyslipidemia population*

| Therapeutic category | Molecule and dose | n | % |
|---|---|---|---|
| No lipid-lowering treatment | Not receiving treatment | 30 | 14.8 |
| Statins | Atorvastatin 20 mg | 14 | 6.9 |
| | Atorvastatin 40 mg | 33 | 16.3 |
| | Rosuvastatin 10 mg | 3 | 1.5 |
| | Rosuvastatin 40 mg | 1 | 0.5 |
| | Simvastatin 10 mg | 2 | 1 |
| | Simvastatin 20 mg | 17 | 8.4 |
| | Simvastatin 40 mg | 3 | 1.5 |
| Fibrate | Fenofibrate | 2 | 1 |
| Substitute therapy | Omega-3 | 1 | 0.5 |
| Lifestyle management | Regimen | 1 | 0.5 |
| Unknown | Treatment unspecified | 92 | 45.3 |

### 1.5.5. Cardiovascular Risk assessment with ASCVD Risk

In the studied population (**n = 276**), the distribution of atherosclerotic cardiovascular disease (**ASCVD**) risk categories showed a predominance of lower-risk profiles. The **intermediate-risk** category was the most represented, accounting for **96 patients (34.8%)**, followed by the **low-risk** category with **92 patients (33.3%)**. Patients classified as **high risk** represented **66 cases (23.9%)**, while the **borderline-risk** category was the least frequent, comprising **22 patients (8.0%)**.

Overall, **114 patients (41.3%)** fell within the **low- and borderline-risk** categories, whereas **162 patients (58.7%)** were classified as **intermediate or high risk**.

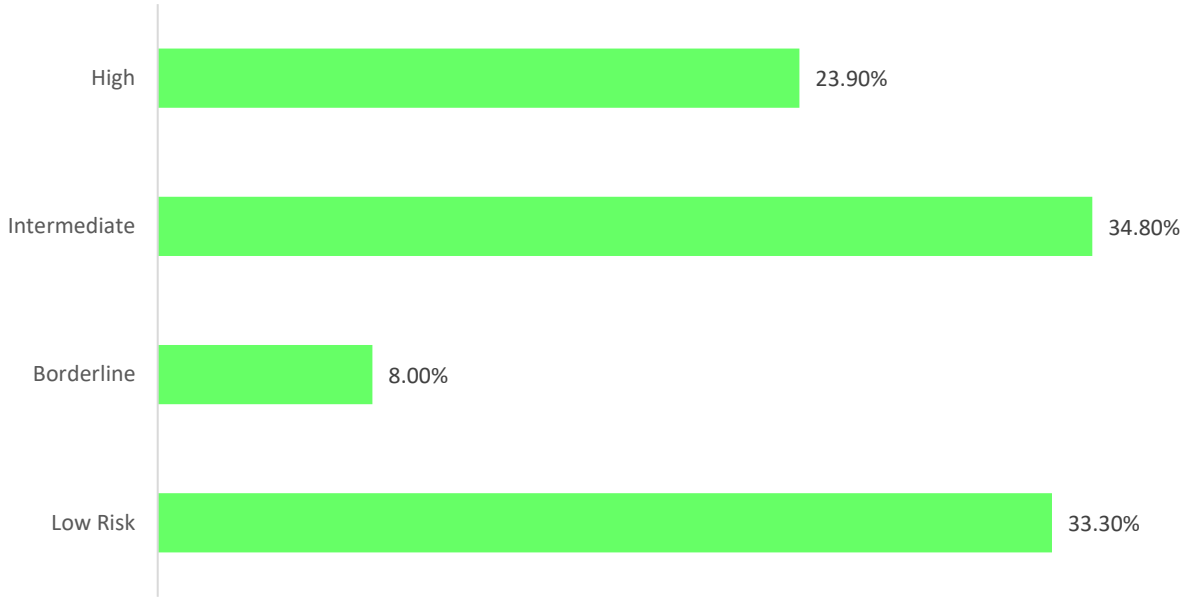



*Figure 31 Distribution of ASCVD Risk*

# 2. Analytical Statistics

## 2.1. Renal severity according to lipid abnormalities

### 2.1.1. Renal parameters according to dyslipidemia status

**Comparison according to dyslipidemia status showed few differences in demographic and anthropometric parameters, but several significant biological disparities.** Age-group distribution differed significantly between dyslipidemic and non-dyslipidemic patients ($p = 0.012$), with the 40-60 year age group being more represented among non-dyslipidemic patients. In contrast, sex, median age, weight, BMI, BMI categories, blood pressure, hypertension, glucose, HbA1c, and diabetes status did not differ significantly between the two groups ($p > 0.05$). Biologically, dyslipidemic patients had lower hemoglobin levels (11.20 vs 12.65 g/dl, $p = 0.023$), a higher prevalence of anemia (60.2% vs 41.2%, $p = 0.038$), lower proteinemia (63.00 vs 69.34 g/L, $p = 0.003$), and lower albuminemia (33.00 vs 39.45 g/L, $p < 0.001$). (see table 20)

*Table 20 Comparison according to dyslipidemia status*

| | | Dyslipidemic | Non-Dyslipidemic | p |
|---|---|---|---|---|
| **Gender** | | | | |
| | Male | 77 (37.9%) | 11 (32.4%) | 0.533 |
| | Female | 126 (62.1%) | 23 (67.6%) | |
| **Age Groups** | | | | |
| | ≤ 40 | 92 (45.3%) | 12 (35.3%) | **0.012** |
| | 40-60 | 63 (31.0%) | 19 (55.9%) | |
| | >60 | 48 (23.6%) | 3 (8.8%) | |
| **Age (years)** | | 44.00 (31.00-58.00) | 43.50 (30.75-55.00) | 0.786 |
| **Weight (Kg)** | | 70.00 (59.05-82.00) | 70.00 (59.75-75.00) | 0.649 |
| **BMI (Kg/m²)** | | 26.23 (21.59-31.22) | 28.95 (23.48-31.30) | 0.432 |
| **BMI Status** | | | | |
| | Underweight | 12 (8.2%) | 2 (12.5%) | 0.668 |
| | Normal | 49 (33.6%) | 3 (18.8%) | |
| | Overweight | 38 (26.0%) | 5 (31.3%) | |
| | Obese | 47 (32.2%) | 6 (37.5%) | |
| **BP-S** | | 130 (120-150) | 128 (120-150) | 0.503 |
| **BP-D** | | 75 (66-80) | 70 (70-80) | 0.583 |
| **Hypertensive** | | 89 (46.8%) | 13 (46.4%) | 0.967 |
| **Hb (g/dL)** | | 11.20 (8.90-13.40) | 12.65 (10.97-14.05) | **0.023** |
| **Anemia** | | 121 (60.2%) | 14 (41.2%) | **0.038** |
| **Glucose (g/L)** | | 0.94 (0.82-1.20) | 0.93 (0.8-1.12) | 0.478 |
| **HbA1C (%)** | | 5.9 (5.5-6.67) | 5.8 (5.4-6.10) | 0.384 |
| **Diabetes** | | 65 (32.0%) | 7 (20.6%) | 0.180 |
| **Proteinemia (g/L)** | | 63.00 (52.00-70.10) | 69.34 (64.77-74.77) | **0.003** |
| **Albuminemia (g/L)** | | 33.00 (25.00-40.00) | 39.45 (35.00-41.89) | **<0.001** |

**The comparison of renal markers according to dyslipidemia status did not show statistically significant differences in conventional indices of renal impairment.** Serum urea, creatinine, eGFR, albumin-to-creatinine ratio, eGFR categories, dichotomized renal function, albuminuria stages, and KDIGO renal risk distribution were similar between dyslipidemic and non-dyslipidemic patients. Although dyslipidemic patients tended to have higher albuminuria levels, this trend remained of borderline significance only ($p = 0.061$). By contrast, the ASCVD cardiovascular risk profile differed significantly between groups ($p = 0.023$), with dyslipidemic patients more frequently classified as high cardiovascular risk, supporting the close link between dyslipidemia and global cardio-renal risk burden. (see table 21)

*Table 21 Comparison according to dyslipidemia status (continued)*

| Renal markers | | Dyslipidemic | Non-Dyslipidemic | p |
|---|---|---|---|---|
| **Urea (g/L)** | | 0.70 (0.32-1.34) | 0.40 (0.29-1.32) | 0.339 |
| **Creatinine (mg/L)** | | 17.00 (8.46-47.00) | 14.72 (6.54-44.15) | 0.481 |
| **eGFR (mL/min/1.73m²)** | | 39.70 (12.30-94.90) | 45.30 (15.67-109.40) | 0.449 |
| **ACR (mg/g)** | | 285.50 (57.5-1009.4) | 208.8 (60.27-434.42) | 0.061 |
| **eGFR categories** | | | | |
| | G1 | 54 (26.6%) | 10 (29.4%) | 0.860 |
| | G2 | 20 (9.9%) | 5 (14.7%) | |
| | G3a | 20 (9.9%) | 2 (5.9%) | |
| | G3b | 23 (11.3%) | 5 (14.7%) | |
| | G4 | 32 (15.8%) | 4 (11.8%) | |
| | G5 | 54 (26.6%) | 8 (23.5%) | |
| **GFR** | | | | |
| | < 60 | 129 (63.5%) | 19 (55.9%) | 0.393 |
| | > 60 | 74 (36.5%) | 15 (44.1%) | |
| **Albuminuria categories** | | | | |
| | A1 | 28 (13.8%) | 5 (14.7%) | 0.372 |
| | A2 | 78 (38.4%) | 17 (50%) | |
| | A3 | 97 (47.8%) | 12 (35.3%) | |
| **ACR** | | | | |
| | > 30 | 175 (86.2%) | 29 (85.3%) | 0.887 |
| | < 30 | 28 (13.8%) | 5 (14.7%) | |
| **KDIGO risk category** | | | | |
| | Low | 16 (7.9%) | 2 (5.9%) | 0.226 |
| | Moderate | 26 (12.8%) | 9 (26.5%) | |
| | High | 43 (21.2%) | 6 (17.6%) | |
| | Very High | 118 (58.1%) | 17 (50%) | |
| **ASCVD Risk** | | | | |
| | Low | 60 (29.6%) | 17 (50%) | **0.023** |
| | Borderline | 16 (7.9%) | 3 (8.8%) | |
| | Intermediate | 70 (34.5%) | 12 (35.3%) | |
| | High | 57 (28.1%) | 2 (5.9%) | |

### 2.1.2. Renal parameters according to Hypercholesterolemia

**Patients with elevated total cholesterol differed from those with normal total cholesterol mainly by biological and hemodynamic parameters rather than by demographic or anthropometric characteristics.** No statistically significant differences were observed regarding sex, age, weight, BMI, BMI categories, systolic blood pressure, hypertension status, glucose, HbA1c, or diabetes prevalence. In contrast, the high total cholesterol group displayed significantly higher diastolic blood pressure, significantly lower frequencies of anemia, and substantially lower serum protein and albumin levels. These findings suggest that hypercholesterolemia in this cohort was associated with a distinct biological profile, particularly marked by hypoalbuminemia and hypoproteinemia. (see table 22)

*Table 22 Comparison according to total cholesterol status.*

| | | TC (Normal) | TC (High) | p |
|---|---|---|---|---|
| **Gender** | | | | |
| | Male | 45 (36.3%) | 43 (38.1%) | 0.779 |
| | Female | 79 (63.7%) | 70 (61.9%) | |
| **Age Groups** | | | | |
| | ≤ 40 | 56 (45.2%) | 48 (42.5%) | 0.178 |
| | 40-60 | 47 (37.9%) | 35 (31.0%) | |
| | >60 | 21 (16.9%) | 30 (26.5%) | |
| **Age (years)** | | 42.0 (31.0–55.0) | 46.0 (31.5–60.0) | 0.397 |
| **Weight (Kg)** | | 70.0 (61.5–85.0) | 70.0 (57.0–81.0) | 0.684 |
| **BMI (Kg/m²)** | | 26.53 (22.13–31.25) | 26.16 (21.63–31.22) | 0.600 |
| **BMI Status** | | | | |
| | Underweight | 8 (10.7%) | 6 (6.9%) | 0.856 |
| | Normal | 23 (30.7%) | 29 (33.3%) | |
| | Overweight | 20 (26.7%) | 23 (26.4%) | |
| | Obese | 24 (32.0%) | 29 (33.3%) | |
| **BP-S** | | 130.0 (120.0–149.5) | 130.0 (120.0–150.0) | 0.180 |
| **BP-D** | | 70.0 (65.0–80.0) | 80.0 (70.0–80.5) | 0.004 |
| **Hypertensive** | | 50 (44.6%) | 52 (49.1%) | 0.514 |
| **Hb (g/dL)** | | 11.45 (8.78–13.20) | 12.10 (9.35–14.00) | 0.067 |
| **Anemia** | | 78 (63.9%) | 57 (50.4%) | 0.037 |
| **Glucose (g/L)** | | 0.95 (0.83–1.24) | 0.94 (0.78–1.14) | 0.185 |
| **HbA1C (%)** | | 5.80 (5.40–6.73) | 5.90 (5.50–6.55) | 0.920 |
| **Diabetes** | | 37 (29.8%) | 35 (31.0%) | 0.850 |
| **Proteinemia (g/L)** | | 69.0 (60.0–72.65) | 57.0 (46.0–68.0) | <0.001 |
| **Albuminemia (g/L)** | | 37.9 (29.62–42.07) | 30.95 (18.93–38.0) | <0.001 |

Patients with high total cholesterol showed significantly greater renal severity in terms of albuminuria and renal risk stratification, despite similar overall renal function. Median ACR was significantly higher in the high total cholesterol group (368.1 vs 217.4 mg/g, $p = 0.002$). Likewise, albuminuria categories differed significantly between groups ($p = 0.006$), with a higher proportion of A3 albuminuria among patients with elevated total cholesterol (56.6% vs 36.3%). eGFR stage distribution also differed significantly ($p = 0.018$), as did KDIGO renal risk categories ($p = 0.025$). However, median urea, creatinine, eGFR, and the proportion of patients with eGFR <60 mL/min/1.73 m² were comparable between groups ($p > 0.05$). In addition, ASCVD risk distribution differed significantly ($p = 0.010$), with high cardiovascular risk being more frequent in patients with elevated total cholesterol (33.6% vs 16.9%). (see table 23)

*Table 23 Comparison according to total cholesterol. (continued)*

| Renal markers | | TC(Normal) | TC (High) | p |
|---|---|---|---|---|
| **Urea (g/L)** | | 0.75 (0.31–1.48) | 0.62 (0.34–1.22) | 0.392 |
| **Creatinine (mg/L)** | | 20.94 (6.76–68.73) | 15.54 (8.74–31.45) | 0.203 |
| **eGFR (mL/min/1.73m²)** | | 34.65 (7.53–102.20) | 47.50 (20.70–88.20) | 0.143 |
| **ACR (mg/g)** | | 217.4 (46.93–721.1) | 368.1 (81.9–1095.8) | **0.002** |
| **eGFR categories** | | | | |
| | G1 | 37 (29.8%) | 27 (23.9%) | **0.018** |
| | G2 | 9 (7.3%) | 16 (14.2%) | |
| | G3a | 8 (6.5%) | 14 (12.4%) | |
| | G3b | 13 (10.5%) | 15 (13.3%) | |
| | G4 | 15 (12.1%) | 21 (18.6%) | |
| | G5 | 42 (33.9%) | 20 (17.7%) | |
| **Albuminuria categories** | | | | |
| | A1 | 19 (15.3%) | 14 (12.4%) | **0.006** |
| | A2 | 60 (48.4%) | 35 (31.0%) | |
| | A3 | 45 (36.3%) | 64 (56.6%) | |
| **KDIGO risk category** | | | | |
| | Low | 12 (9.7%) | 6 (5.3%) | **0.025** |
| | Moderate | 22 (17.7%) | 13 (11.5%) | |
| | High | 17 (13.7%) | 32 (28.3%) | |
| | Very High | 73 (58.9%) | 62 (54.9%) | |
| **GFR** | | | | |
| | < 60 | 78 (62.9%) | 70 (61.9%) | 0.879 |
| | > 60 | 46 (37.1%) | 43 (38.1%) | |
| **ACR** | | | | |
| | > 30 | 105 (84.7%) | 99 (87.6%) | 0.515 |
| | < 30 | 19 (15.3%) | 14 (12.4%) | |
| **ASCVD Risk** | | | | |
| | Low | 45 (36.3%) | 32 (28.3%) | **0.010** |
| | Borderline | 14 (11.3%) | 5 (4.4%) | |
| | Intermediate | 44 (35.5%) | 38 (33.6%) | |
| | High | 21 (16.9%) | 38 (33.6%) | |

### 2.1.3. Renal parameters according to Hyperlipoproteinemia

**Compared with patients with normal LDL-C levels, those with high LDL-C showed significant biological differences but only limited differences in renal severity.** High LDL-C was associated with higher hemoglobin levels (12.40 vs 11.45 g/dL, $p = 0.022$), a lower prevalence of anemia (47.1% vs 63.3%, $p = 0.015$), and significantly lower proteinemia and albuminemia (57.0 vs 68.0 g/L and 30.60 vs 35.34 g/L, respectively; both $p < 0.001$). (see table 24)

Regarding renal markers, patients with high LDL-C had a higher median eGFR (54.10 vs 36.25 mL/min/1.73 m², $p = 0.048$), and the distribution of eGFR categories differed significantly between groups ($p = 0.011$). However, urea, creatinine, albuminuria categories, KDIGO risk categories, dichotomized eGFR and ACR groups, and ASCVD risk distribution were not significantly different ($p > 0.05$), although ACR and ASCVD risk both showed borderline trends. (see table 25)

*Table 24 Comparison according to LDL-C.*

| | LDL-C (Normal) | LDL-C (High) | p |
|---|---|---|---|
| **Gender** | | | |
| Male | 60 (39.5%) | 28 (32.9%) | 0.318 |
| Female | 92 (60.5%) | 57 (67.1%) | |
| **Age Groups** | | | |
| ≤ 40 | 66 (43.4%) | 38 (44.7%) | 0.083 |
| 40-60 | 59 (38.8%) | 23 (27.1%) | |
| >60 | 27 (17.8%) | 24 (28.2%) | |
| **Age (years)** | 42.00 (32.25-56.00) | 46.00 (31.00-60.50) | 0.749 |
| **Weight (Kg)** | 68.00 (58.50-80.50) | 73.00 (60.70-84.25) | 0.275 |
| **BMI (Kg/m²)** | 26.44 (21.68-30.71) | 26.44 (22.26-31.44) | 0.431 |
| **BMI Status** | | | |
| Underweight | 12 (12.4%) | 2 (3.1%) | 0.071 |
| Normal | 29 (29.9%) | 23 (35.4%) | |
| Overweight | 29 (29.9%) | 14 (21.5%) | |
| Obese | 27 (27.8%) | 26 (40.0%) | |
| **BP-S** | 130.00 (120.00-150.00) | 130.00 (120.00-150.00) | 0.876 |
| **BP-D** | 70.00 (67.00-80.00) | 76.00 (67.00-80.00) | 0.435 |
| **Hypertensive** | 65 (46.8%) | 37 (46.8%) | 0.992 |
| **Hb (g/dL)** | 11.45 (8.90-13.13) | 12.40 (9.50-14.15) | 0.022 |
| **Anemia** | 95 (63.3%) | 40 (47.1%) | 0.015 |
| **Glucose (g/L)** | 0.94 (0.81-1.20) | 0.94 (0.80-1.15) | 0.653 |
| **HbA1C (%)** | 5.80 (5.40-6.70) | 5.90 (5.50-6.45) | 0.985 |
| **Diabetes** | 48 (31.6%) | 24 (28.2%) | 0.591 |
| **Proteinemia (g/L)** | 68.00 (57.64-72.50) | 57.00 (44.70-66.00) | <0.001 |
| **Albuminemia (g/L)** | 35.34 (28.50-41.84) | 30.60 (18.18-38.98) | <0.001 |

*Table 25 Comparison according to LDL-C. (continued)*

| Renal markers | LDL-C (Normal) | LDL-C (High) | p |
|---|---|---|---|
| **Urea (g/L)** | 0.705 (0.340–1.425) | 0.600 (0.300–1.190) | 0.242 |
| **Creatinine (mg/L)** | 18.25 (8.21–60.57) | 15.26 (8.31–28.50) | 0.055 |
| **eGFR (mL/min/1.73m²)** | 36.25 (9.05–95.95) | 54.10 (21.80–95.90) | **0.048** |
| **ACR (mg/g)** | 230.90 (53.90–782.90) | 304.30 (84.20–1009.40) | 0.067 |
| **eGFR categories** | | | **0.011** |
| G1 | 40 (26.3%) | 24 (28.2%) | |
| G2 | 12 (7.9%) | 13 (15.3%) | |
| G3a | 14 (9.2%) | 8 (9.4%) | |
| G3b | 19 (12.5%) | 9 (10.6%) | |
| G4 | 17 (11.2%) | 19 (22.4%) | |
| G5 | 50 (32.9%) | 12 (14.1%) | |
| **Albuminuria categories** | | | 0.087 |
| A1 | 22 (14.5%) | 11 (12.9%) | |
| A2 | 68 (44.7%) | 27 (31.8%) | |
| A3 | 62 (40.8%) | 47 (55.3%) | |
| **KDIGO risk category** | | | 0.393 |
| Low | 12 (7.9%) | 6 (7.1%) | |
| Moderate | 21 (13.8%) | 14 (16.5%) | |
| High | 27 (17.8%) | 22 (25.9%) | |
| Very High | 92 (60.5%) | 43 (50.6%) | |
| **GFR** | | | 0.155 |
| < 60 | 100 (65.8%) | 48 (56.5%) | |
| > 60 | 52 (34.2%) | 37 (43.5%) | |
| **ACR** | | | 0.744 |
| > 30 | 130 (85.5%) | 74 (87.1%) | |
| < 30 | 22 (14.5%) | 11 (12.9%) | |
| **ASCVD Risk** | | | 0.070 |
| Low | 55 (36.2%) | 22 (25.9%) | |
| Borderline | 14 (9.2%) | 5 (5.9%) | |
| Intermediate | 53 (34.9%) | 29 (34.1%) | |
| High | 30 (19.7%) | 29 (34.1%) | |

### 2.1.4. Renal parameters according to Hypertriglyceridemia

**The comparison according to triglyceride status indicates that hypertriglyceridemia was associated with a more adverse cardio-renal and biological profile.** Patients with elevated TG were more frequently male and had significantly higher diastolic blood pressure. They also exhibited significantly lower serum protein and albumin concentrations, suggesting a less favorable nutritional and biological status. (see table 26)

From a renal perspective, hypertriglyceridemic patients had higher urea levels and substantially higher albuminuria, with a significant shift toward more severe albuminuria categories, particularly A3. Although serum creatinine, median eGFR, eGFR stage distribution, and dichotomized renal function did not differ significantly between groups, KDIGO renal risk was significantly worse among patients with high TG. Moreover, cardiovascular risk stratification by ASCVD score was also significantly less favorable in the hypertriglyceridemic group, supporting the strong association between elevated triglycerides, albuminuric burden, and global cardio-renal risk. (see table 27)

*Table 26 Comparison according to Triglyceride.*

| | | TG (Normal) | TG (High) | p |
|---|---|---|---|---|
| **Gender** | | | | |
| | Male | 34 (28.8%) | 54 (45.4%) | 0.008 |
| | Female | 84 (71.2%) | 65 (54.6%) | |
| **Age Groups** | | | | |
| | ≤ 40 | 52 (44.1%) | 52 (43.7%) | |
| | 40-60 | 43 (36.4%) | 39 (32.8%) | 0.711 |
| | >60 | 23 (19.5%) | 28 (23.5%) | |
| **Age (years)** | | 42.00 (31.75-56.00) | 44.00 (29.00-58.00) | 0.909 |
| **Weight (Kg)** | | 70.00 (61.75-80.25) | 69.00 (56.25-83.13) | 0.881 |
| **BMI (Kg/m²)** | | 26.77 (22.95-31.31) | 26.23 (21.37-30.79) | 0.574 |
| **BMI Status** | | | | |
| | Underweight | 9 (12.2%) | 5 (5.7%) | 0.378 |
| | Normal | 22 (29.7%) | 30 (34.1%) | |
| | Overweight | 17 (23.0%) | 26 (29.5%) | |
| | Obese | 26 (35.1%) | 27 (30.7%) | |
| **BP-S** | | 130.00 (120.00-150.00) | 131.00 (120.00-150.00) | 0.290 |
| **BP-D** | | 70.00 (63.00-80.00) | 80.00 (70.00-83.50) | 0.002 |
| **Hypertensive** | | 46 (43.4%) | 56 (50.0%) | 0.329 |
| **Hb (g/dL)** | | 12.00 (9.68-13.68) | 10.90 (8.60-13.40) | 0.080 |
| **Anemia** | | 63 (54.3%) | 72 (60.5%) | 0.337 |
| **Glucose (g/L)** | | 0.95 (0.81-1.20) | 0.93 (0.81-1.19) | 0.963 |
| **HbA1C (%)** | | 5.80 (5.40-6.50) | 5.90 (5.50-6.70) | 0.504 |
| **Diabetes** | | 36 (30.5%) | 36 (30.3%) | 0.966 |
| **Proteinemia (g/L)** | | 68.00 (58.04-72.45) | 59.00 (46.00-69.44) | <0.001 |
| **Albuminemia (g/L)** | | 36.45 (30.75-41.62) | 30.55 (19.00-39.90) | <0.001 |

*Table 27 Comparison according to Triglyceride. (continued)*

| Renal markers | | TG (Normal) | TG (High) | p |
|---|---|---|---|---|
| **Urea (g/L)** | | 0.50 (0.30-1.12) | 0.79 (0.35-1.49) | **0.029** |
| **Creatinine (mg/L)** | | 15.15 (6.69-42.20) | 18.18 (9.22-56.90) | 0.173 |
| **eGFR (mL/min/1.73m²)** | | 44.20 (17.20-102.00) | 34.70 (12.10-91.30) | 0.285 |
| **ACR (mg/g)** | | 217.40 (38.75-736.55) | 304.30 (81.90-1009.40) | **0.001** |
| **eGFR categories** | | | | |
| | G1 | 34 (28.8%) | 30 (25.2%) | 0.794 |
| | G2 | 14 (11.9%) | 11 (9.2%) | |
| | G3a | 10 (8.5%) | 12 (10.1%) | |
| | G3b | 16 (13.6%) | 12 (10.1%) | |
| | G4 | 16 (13.6%) | 20 (16.8%) | |
| | G5 | 28 (23.7%) | 34 (28.6%) | |
| **Albuminuria categories** | | | | |
| | A1 | 24 (20.3%) | 9 (7.6%) | **0.006** |
| | A2 | 49 (41.5%) | 46 (38.7%) | |
| | A3 | 45 (38.1%) | 64 (53.8%) | |
| **KDIGO risk category** | | | | |
| | Low | 15 (12.7%) | 3 (2.5%) | **0.020** |
| | Moderate | 19 (16.1%) | 16 (13.4%) | |
| | High | 21 (17.8%) | 28 (23.5%) | |
| | Very High | 63 (53.4%) | 72 (60.5%) | |
| **GFR** | | | | |
| | < 60 | 70 (59.3%) | 78 (65.5%) | 0.322 |
| | > 60 | 48 (40.7%) | 41 (34.5%) | |
| **ACR** | | | | |
| | > 30 | 94 (79.7%) | 110 (92.4%) | **0.005** |
| | < 30 | 24 (20.3%) | 9 (7.6%) | |
| **ASCVD Risk** | | | | |
| | Low | 50 (42.4%) | 27 (22.7%) | **0.003** |
| | Borderline | 11 (9.3%) | 8 (6.7%) | |
| | Intermediate | 37 (31.4%) | 45 (37.8%) | |
| | High | 20 (16.9%) | 39 (32.8%) | |

### 2.1.5. Renal parameters according to Low HDL-C

**The comparison according to HDL-C status suggests that low HDL-C was associated primarily with hematological alterations rather than with clear differences in renal severity.** Patients with low HDL-C were more frequently represented in the younger age group and exhibited significantly lower hemoglobin concentrations together with a substantially higher frequency of anemia. However, no significant differences were observed in anthropometric parameters, blood pressure, glycemic markers, serum proteins, or most renal indices. Although patients with low HDL-C tended to have lower eGFR values and a less favorable distribution of eGFR stages, these differences did not reach statistical significance. Overall, low HDL-C in this cohort appeared to be more strongly associated with anemia than with a distinct worsening of albuminuria, KDIGO renal risk, or cardiovascular risk profile. (see table 28-29)

*Table 28 Comparison according to HDL-C. (continued)*

| | | HDL-C (Normal) | HDL-C (High) | p |
|---|---|---|---|---|
| **Gender** | | | | |
| | Male | 41 (42.3%) | 47 (33.6%) | 0.173 |
| | Female | 56 (57.7%) | 93 (66.4%) | |
| **Age Groups** | | | | |
| | ≤ 40 | 32 (33.0%) | 72 (51.4%) | **0.018** |
| | 40-60 | 41 (42.3%) | 41 (29.3%) | |
| | >60 | 24 (24.7%) | 27 (19.3%) | |
| **Age (years)** | | 45.00 (35.00–59.50) | 40.00 (29.00–56.00) | 0.055 |
| **Weight (Kg)** | | 70.00 (59.00–82.00) | 70.00 (59.40–82.00) | 0.718 |
| **BMI (Kg/m²)** | | 26.30 (22.41–30.82) | 26.44 (21.88–31.25) | 0.966 |
| **BMI Status** | | | | |
| | Underweight | 7 (10.4%) | 7 (7.4%) | 0.784 |
| | Normal | 19 (28.4%) | 33 (34.7%) | |
| | Overweight | 19 (28.4%) | 24 (25.3%) | |
| | Obese | 22 (32.8%) | 31 (32.6%) | |
| **BP-S** | | 130.00 (120.00–150.00) | 130.00 (120.00–148.00) | 0.411 |
| **BP-D** | | 76.00 (70.00–80.00) | 70.00 (65.00–80.00) | 0.135 |
| **Hypertensive** | | 45 (51.7%) | 57 (43.5%) | 0.234 |
| **Hb (g/dL)** | | 12.60 (10.30–14.05) | 10.75 (8.60–13.03) | **<0.001** |
| **Anemia** | | 40 (41.2%) | 95 (68.8%) | **<0.001** |
| **Glucose (g/L)** | | 0.94 (0.80–1.13) | 0.94 (0.84–1.22) | 0.216 |
| **HbA1C (%)** | | 5.80 (5.50–6.50) | 5.90 (5.40–6.70) | 0.425 |
| **Diabetes** | | 27 (27.8%) | 45 (32.1%) | 0.478 |
| **Proteinemia (g/L)** | | 63.00 (52.05–70.21) | 66.00 (55.00–71.50) | 0.400 |
| **Albuminemia (g/L)** | | 34.70 (26.20–40.00) | 33.95 (25.60–40.33) | 0.840 |

*Table 29 Comparison according to HDL-C. (continued)*

| Renal markers | | HDL-C (Normal) | HDL-C (Low) | p |
|---|---|---|---|---|
| **Urea (g/L)** | | 0.49 (0.31–1.22) | 0.77 (0.34–1.40) | 0.147 |
| **Creatinine (mg/L)** | | 14.92 (8.10–36.20) | 19.60 (8.59–62.48) | 0.067 |
| **eGFR (mL/min/1.73m²)** | | 52.70 (19.65–91.50) | 34.20 (7.95–96.73) | 0.053 |
| **ACR (mg/g)** | | 304.30 (62.40–1009.40) | 271.65 (46.93–782.90) | 0.252 |
| **eGFR categories** | | | | 0.064 |
| | G1 | 25 (25.8%) | 39 (27.9%) | |
| | G2 | 16 (16.5%) | 9 (6.4%) | |
| | G3a | 10 (10.3%) | 12 (8.6%) | |
| | G3b | 14 (14.4%) | 14 (10.0%) | |
| | G4 | 14 (14.4%) | 22 (15.7%) | |
| | G5 | 18 (18.6%) | 44 (31.4%) | |
| **Albuminuria categories** | | | | 0.492 |
| | A1 | 13 (13.4%) | 20 (14.3%) | |
| | A2 | 35 (36.1%) | 60 (42.9%) | |
| | A3 | 49 (50.5%) | 60 (42.9%) | |
| **KDIGO risk category** | | | | 0.261 |
| | Low | 5 (5.2%) | 13 (9.3%) | |
| | Moderate | 17 (17.5%) | 18 (12.9%) | |
| | High | 24 (24.7%) | 25 (17.9%) | |
| | Very High | 51 (52.6%) | 84 (60.0%) | |
| **GFR** | | | | |
| | < 60 | 56 (57.7%) | 92 (65.7%) | 0.212 |
| | > 60 | 41 (42.3%) | 48 (34.3%) | |
| **ACR** | | | | |
| | > 30 | 84 (86.6%) | 120 (85.7%) | 0.847 |
| | < 30 | 13 (13.4%) | 20 (14.3%) | |
| **ASCVD Risk** | | | | |
| | Low | 39 (40.2%) | 38 (27.1%) | 0.138 |
| | Borderline | 5 (5.2%) | 14 (10.0%) | |
| | Intermediate | 32 (33.0%) | 50 (35.7%) | |
| | High | 21 (21.6%) | 38 (27.1%) | |

## 2.2. Lipid profile according to CKD severity and risk

### 2.2.1. According to CKD stages

**According to eGFR stage, significant differences were observed in several demographic, clinical, hematological, and lipid parameters.** Sex distribution varied significantly across renal stages ($p = 0.016$). Women predominated overall, particularly in G1 (78.2%), G3a (64.0%), G3b (68.8%), and G5 (60.8%), whereas men were relatively more represented in G2 (48.0%) and especially G4 (52.4%). Although age-group distribution did not differ significantly between stages ($p = 0.162$), median age showed a significant variation ($p = 0.003$), with younger patients in G1 (39.5 years) and G3a (41.0 years), and older patients in G2 (54.0 years) and G3b (53.0 years). Body weight showed only borderline variation ($p = 0.055$), whereas BMI differed significantly across stages ($p = 0.014$). Median BMI was highest in G1 (29.71 kg/m²) and lower in more advanced stages, particularly G3b (24.35 kg/m²) and G5 (24.62 kg/m²). Similarly, BMI categories differed significantly ($p < 0.001$): obesity was most frequent in G1 (47.5%), while normal BMI became more common in G3b (50.0%) and G5 (42.6%).

**Blood pressure and hypertension also varied significantly according to renal stage.** Median systolic blood pressure increased from 120 mmHg in G1 to 140 mmHg in G2, G3b, and G4, before remaining high in G5 at 135 mmHg ($p = 0.007$). Median diastolic blood pressure also differed significantly ($p = 0.021$), ranging from 70 mmHg in G1 and G3b to 80 mmHg in G2. The prevalence of hypertension increased overall with worsening renal stage ($p = 0.025$), from 31.1% in G1 to 58.1% in G3b, 52.5% in G4, and 52.3% in G5.

**A marked deterioration in hematological status was observed with advancing renal impairment.** Hemoglobin levels differed significantly across stages ($p < 0.001$), with the highest median value in G2 (14.0 g/dL) and progressively lower values in advanced CKD, reaching 10.9 g/dL in G4 and 9.3 g/dL in G5. In parallel, anemia prevalence increased significantly from 36.8% in G1 and 24.0% in G2 to 50.0% in G3a, 56.3% in G3b, 69.0% in G4, and 90.4% in G5 ($p < 0.001$). Diabetes status also differed significantly across stages ($p = 0.006$), with the highest frequency observed in G1 (46.2%), followed by G3b (40.6%) and G4 (38.1%), whereas lower proportions were seen in G2 (16.0%) and G5 (20.3%). In contrast, median glucose, HbA1c, proteinemia, and albuminemia did not differ significantly across renal stages ($p > 0.05$).

**The lipid profile showed significant heterogeneity across eGFR categories for total cholesterol, HDL-C, and LDL-C, but not for triglycerides.** Median total cholesterol varied significantly ($p = 0.002$), with relatively higher values in G3a (2.15 g/L) and G4 (2.18 g/L), and the lowest value in G5 (1.67 g/L). HDL-C also differed significantly ($p = 0.005$), with the highest median level in G2 (0.50 g/L) and lower values in advanced stages, especially G4 (0.40 g/L) and G5 (0.37 g/L). LDL-C followed a similar pattern ($p = 0.011$), peaking in G4 (1.39 g/L) and being lowest in G5 (0.96 g/L). By contrast, triglyceride levels did not vary significantly across stages ($p = 0.431$), although numerically higher medians were observed in G3a, G4, and G5.

**Cardiovascular risk increased significantly with worsening renal function.** ASCVD risk category distribution differed markedly across eGFR stages ($p < 0.001$). The low-risk category predominated in G1 (67.9%) and remained frequent in G3a (52.0%), but progressively declined in more advanced stages, reaching only 7.1% in G4 and 6.8% in G5. Conversely, intermediate and high cardiovascular risk categories became more frequent with declining renal function. Intermediate risk rose from 17.9% in G1 to 42.9% in G4 and 45.9% in G5, while high risk increased from 6.4% in G1 to

25.0% in G3b, 45.2% in G4, and 36.5% in G5. Overall, these findings indicate that worsening renal function was associated with a heavier burden of hypertension, anemia, and cardiovascular risk, together with significant changes in several lipid parameters.

*Table 30 Comparison according to GFR stages.*

| | G1 | G2 | G3a | G3b | G4 | G5 | p |
|---|---|---|---|---|---|---|---|
| **Gender** | | | | | | | |
| Male | 17 (21.8%) | 12 (48.0%) | 9 (36.0%) | 10 (31.3%) | 22 (52.4%) | 29 (39.2%) | **0.016** |
| Female | 61 (78.2%) | 13 (52.0%) | 16 (64.0%) | 22 (68.8%) | 20 (47.6%) | 45 (60.8%) | |
| **Age Groups** | | | | | | | |
| ≤ 40 | 42 (53.8%) | 7 (28.0%) | 11 (44.0%) | 9 (28.1%) | 18 (42.9%) | 32 (43.2%) | 0.162 |
| 40-60 | 27 (34.6%) | 10 (40.0%) | 9 (36.0%) | 13 (40.6%) | 11 (26.2%) | 24 (32.4%) | |
| >60 | 9 (11.5%) | 8 (32.0%) | 5 (20.0%) | 10 (31.3%) | 13 (31.0%) | 18 (24.3%) | |
| **Age (years)** | 39.5 (27.5–48.5) | 54.0 (36.0–66.0) | 41.0 (29.0–51.0) | 53.0 (38.0–63.0) | 44.5 (34.75–65.0) | 45.0 (31.75–59.25) | **0.003** |
| **Weight (Kg)** | 70.0 (61.0–91.0) | 74.0 (66.0–85.0) | 64.0 (56.75–76.7) | 66.0 (54.9–81.5) | 75.0 (64.0–80.0) | 63.0 (55.0–72.0) | 0.055 |
| **BMI (Kg/m²)** | 29.71 (23.81–36.33) | 27.55 (24.22–30.69) | 24.76 (18.91–29.11) | 24.35 (21.34–31.54) | 26.53 (22.66–30.82) | 24.62 (20.83–28.73) | **0.014** |
| **BMI Status** | | | | | | | |
| Underweight | 6 (10.2%) | 0 (0.0%) | 2 (11.1%) | 1 (5.0%) | 1 (3.7%) | 5 (10.6%) | **<0.001** |
| Normal | 12 (20.3%) | 4 (26.7%) | 7 (38.9%) | 10 (50.0%) | 8 (29.6%) | 20 (42.6%) | |
| Overweight | 13 (22.0%) | 6 (40.0%) | 6 (33.3%) | 3 (15.0%) | 9 (33.3%) | 14 (29.8%) | |
| Obese | 28 (47.5%) | 5 (33.3%) | 3 (16.7%) | 6 (30.0%) | 9 (33.3%) | 8 (17.0%) | |
| **BP-S** | 120.0 (114.75–140.0) | 140.0 (125.5–150.0) | 130.0 (120.0–150.0) | 140.0 (120.0–150.0) | 140.0 (120.0–150.0) | 135.0 (120.0–150.0) | **0.007** |
| **BP-D** | 70.0 (60.0–80.0) | 80.0 (69.25–85.75) | 71.0 (65.0–80.0) | 70.0 (70.0–80.0) | 77.5 (70.0–83.75) | 75.0 (70.0–81.0) | **0.021** |
| **Hypertensive** | 23 (31.1%) | 13 (59.1%) | 8 (34.8%) | 18 (58.1%) | 21 (52.5%) | 34 (52.3%) | **0.025** |
| **Hb (g/dL)** | 12.6 (11.05–14.0) | 14.0 (12.4–14.6) | 11.7 (8.39–13.35) | 11.75 (9.38–14.08) | 10.9 (9.28–13.4) | 9.3 (7.9–11.15) | **<0.001** |
| **Anemia** | 28 (36.8%) | 6 (24.0%) | 12 (50.0%) | 18 (56.3%) | 29 (69.0%) | 66 (90.4%) | **<0.001** |
| **Glucose (g/L)** | 0.97 (0.85–1.35) | 0.85 (0.81–1.06) | 0.99 0.88–1.17) | 1.04 (0.84–1.19) | 0.94 (0.78–1.14) | 0.93 (0.785–1.325) | 0.406 |
| **HbA1C (%)** | 6.0 (5.55–7.75) | 5.95 (5.42–6.85) | 6.1 (5.7–6.75) | 5.95 (5.4–6.825) | 5.9 (5.5–6.7) | 5.7 (5.25–6.15) | 0.263 |
| **Diabetes** | 36 (46.2%) | 4 (16.0%) | 7 (28.0%) | 13 (40.6%) | 16 (38.1%) | 15 (20.3%) | **0.006** |
| **Proteinemia (g/L)** | 65.10 (51.68–72.35) | 64.50 (53.00–75.00) | 64.02 (52.75–70.38) | 64.00 (51.40–69.97) | 59.00 (48.50–67.50) | 66.00 (55.50–72.65) | 0.203 |
| **Albuminemia (g/L)** | 34.22 (26.51–40.97) | 34.99 (24.00–42.50) | 34.50 (24.89–41.63) | 34.00 (24.88–39.93) | 31.60 (20.50–39.34) | 34.00 (28.10–40.13) | 0.712 |

*Table 31 Comparison according to GFR stages. (continued)*

| | G1 | G2 | G3a | G3b | G4 | G5 | p |
|---|---|---|---|---|---|---|---|
| **Total cholesterol (g/L)** | 1.84 (1.51–2.69) | 2.10 (1.57–3.09) | 2.15 (1.81–2.43) | 2.02 (1.61–2.49) | 2.18 (1.81–2.70) | 1.67 (1.43–2.15) | **0.002** |
| **HDL (g/L)** | 0.42 (0.35–0.56) | 0.50 (0.40–0.62) | 0.45 (0.26–0.55) | 0.42 (0.34–0.59) | 0.40 (0.34–0.45) | 0.37 (0.30–0.46) | **0.005** |
| **LDL-C (g/L)** | 1.01 (0.84–1.72) | 1.30 (0.85–1.945) | 1.26 (1.09–1.61) | 1.16 (0.87–1.41) | 1.39 (1.05–1.83) | 0.96 (0.76–1.24) | **0.011** |
| **Triglycerides (g/L)** | 1.33 (0.92–2.26) | 1.29 (0.95–2.29) | 1.63 (1.03–2.86) | 1.39 (0.91–2.01) | 1.56 (1.37–2.36) | 1.54 (1.10–2.12) | 0.431 |
| **ASCVD risk category** | | | | | | | |
| Low | 53 (67.9%) | 10 (40.0%) | 13 (52.0%) | 8 (25.0%) | 3 (7.1%) | 5 (6.8%) | **<0.001** |
| Borderline | 6 (7.7%) | 2 (8.0%) | 1 (4.0%) | 3 (9.4%) | 2 (4.8%) | 8 (10.8%) | |
| Intermediate | 14 (17.9%) | 7 (28.0%) | 10 (40.0%) | 13 (40.6%) | 18 (42.9%) | 34 (45.9%) | |
| High | 5 (6.4%) | 6 (24.0%) | 1 (4.0%) | 8 (25.0%) | 19 (45.2%) | 27 (36.5%) | |

### 2.2.2. According to ACR Categories

**According to albuminuria category, several demographic, clinical, biological, and lipid parameters differed significantly across groups.** Sex distribution varied significantly according to albuminuria stage ($p = 0.006$). Female patients predominated in all categories, but their proportion progressively decreased from A1 (79.6%) to A2 (67.6%) and A3 (54.6%), whereas the proportion of male patients increased from 20.4% in A1 to 45.4% in A3. Age-group distribution did not differ significantly between categories ($p = 0.079$), and neither median age ($p = 0.543$), body weight ($p = 0.896$), nor BMI ($p = 0.670$) showed significant variation. However, BMI categories differed significantly ($p = 0.031$). Obesity was more frequent in A1 (40.6%) and A2 (40.0%), whereas A3 was characterized by a higher proportion of patients with normal BMI (37.2%) and overweight status (35.1%).

**Blood pressure and hypertension increased significantly with worsening albuminuria.** Median systolic blood pressure rose progressively from 120 mmHg in A1 to 130 mmHg in A2 and 140 mmHg in A3 ($p < 0.001$). A similar pattern was observed for diastolic blood pressure, which increased from 70 mmHg in A1 and A2 to 80 mmHg in A3 ($p = 0.004$). Likewise, the prevalence of hypertension increased markedly across albuminuria stages, from 24.4% in A1 to 39.8% in A2 and 59.0% in A3 ($p < 0.001$). By contrast, hemoglobin levels and anemia prevalence did not differ significantly across categories ($p = 0.313$ and $p = 0.263$, respectively), although median hemoglobin tended to be lower in A3.

**Regarding metabolic variables, diabetes status differed significantly according to albuminuria category ($p = 0.045$), whereas glucose and HbA1c did not.** Diabetes was reported in 42.9% of patients in A1, 37.0% in A2, and 25.2% in A3. Median glucose and HbA1c values were comparable across groups, with no statistically significant differences. In contrast, serum protein and albumin concentrations decreased significantly with increasing albuminuria severity. Median proteinemia was 67.5 g/L in A1, 68.0 g/L in A2, and only 57.64 g/L in A3 ($p < 0.001$). Similarly, median albuminemia declined from 36.46 g/L in A1 and 36.20 g/L in A2 to 30.65 g/L in A3 ($p < 0.001$), indicating a more marked biological and nutritional impairment in patients with severe albuminuria.

**The lipid profile also showed significant variation across albuminuria stages.** Median total cholesterol increased significantly from 1.76 g/L in A1 to 1.82 g/L in A2 and 2.10 g/L in A3 ($p = 0.006$). Triglyceride levels also rose significantly with albuminuria severity, from 1.13 g/L in A1 to 1.49 g/L in A2 and 1.75 g/L in A3 ($p = 0.003$). By contrast, HDL-C levels remained stable across the three categories ($p = 0.726$), and LDL-C showed only a non-significant upward trend, increasing from 1.07 g/L in A1 to 1.21 g/L in A3 ($p = 0.085$).

**Cardiovascular risk worsened markedly with increasing albuminuria.** ASCVD risk distribution differed highly significantly across albuminuria categories ($p < 0.001$). The low-risk category predominated in A1, accounting for 67.3% of patients, but its frequency declined sharply in A2 (27.8%) and A3 (24.4%). Conversely, the proportion of patients at high cardiovascular risk increased substantially with worsening albuminuria, from 0% in A1 to 19.4% in A2 and 37.8% in A3. Intermediate-risk profiles were also frequent, particularly in A2 (44.4%) and A3 (30.3%). Overall, these findings indicate that increasing albuminuria severity was associated with higher blood pressure, a greater prevalence of hypertension, lower proteinemia and albuminemia, higher total cholesterol and triglyceride levels, and a markedly less favorable cardiovascular risk profile.

*Table 32 Comparison according to ACR categories.*

| | | A1 | A2 | A3 | p |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| | Male | 10 (20.4%) | 35 (32.4%) | 54 (45.4%) | **0.006** |
| | Female | 39 (79.6%) | 73 (67.6%) | 65 (54.6%) | |
| **Age Groups** | | | | | |
| | ≤ 40 | 22 (44.9%) | 39 (36.1%) | 58 (48.7%) | 0.079 |
| | 40-60 | 18 (36.7%) | 46 (42.6%) | 30 (25.2%) | |
| | >60 | 9 (18.4%) | 23 (21.3%) | 31 (26.1%) | |
| **Age (years)** | | 43.0 (30.5–55.5) | 45.0 (35.0–57.75) | 41.0 (30.0–60.0) | 0.543 |
| **Weight (Kg)** | | 73.5 (56.75–80.75) | 70.0 (56.0–85.0) | 68.0 (60.95–80.0) | 0.896 |
| **BMI (Kg/m²)** | | 27.31 (21.80–31.95) | 26.56 (21.38–31.25) | 25.96 (22.57–29.76) | 0.670 |
| **BMI Status** | | | | | |
| | Underweight | 3 (9.4%) | 8 (13.3%) | 4 (4.3%) | **0.031** |
| | Normal | 8 (25.0%) | 18 (30.0%) | 35 (37.2%) | |
| | Overweight | 8 (25.0%) | 10 (16.7%) | 33 (35.1%) | |
| | Obese | 13 (40.6%) | 24 (40.0%) | 22 (23.4%) | |
| **BP-S** | | 120.0 (112.0–140.0) | 130.0 (120.0–143.0) | 140.0 (120.0–150.0) | **<0.001** |
| **BP-D** | | 70.0 (63.0–80.0) | 70.0 (65.0–80.0) | 80.0 (70.0–85.0) | **0.004** |
| **Hypertensive** | | 11 (24.4%) | 37 (39.8%) | 69 (59.0%) | **<0.001** |
| **Hb (g/dL)** | | 12.25 (9.50–13.83) | 11.50 (9.40–13.15) | 10.90 (8.40–13.90) | 0.313 |
| **Anemia** | | 23 (47.9%) | 64 (61.0%) | 72 (60.5%) | 0.263 |
| **Glucose (g/L)** | | 1.02 (0.86–1.48) | 0.96 (0.82–1.29) | 0.91 (0.80–1.17) | 0.158 |
| **HbA1C (%)** | | 5.80 (5.35–7.50) | 5.95 (5.60–7.28) | 5.80 (5.40–6.33) | 0.200 |
| **Diabetes** | | 21 (42.9%) | 40 (37.0%) | 30 (25.2%) | **0.045** |
| **Proteinemia (g/L)** | | 67.50 (59.34–74.30) | 68.00 (57.00–72.50) | 57.64 (45.67–67.00) | **<0.001** |
| **Albuminemia (g/L)** | | 36.46 (31.14–42.38) | 36.20 (27.19–40.30) | 30.65 (23.00–39.00) | **<0.001** |

*Table 33 Comparison according to ACR categories. (continued)*

| | | A1 | A2 | A3 | p |
|---|---|---|---|---|---|
| **Total cholesterol (g/L)** | | 1.76 (1.48–2.28) | 1.82 (1.55–2.29) | 2.10 (1.65–2.77) | **0.006** |
| **HDL (g/L)** | | 0.42 (0.37–0.54) | 0.40 (0.32–0.54) | 0.42 (0.31–0.53) | 0.726 |
| **LDL-C (g/L)** | | 1.07 (0.84–1.39) | 1.09 (0.81–1.38) | 1.21 (0.89–1.85) | 0.085 |
| **Triglycerides (g/L)** | | 1.13 (0.97–1.64) | 1.49 (1.04–1.99) | 1.75 (1.15–2.62) | **0.003** |
| **ASCVD risk category** | | | | | |
| | Low | 33 (67.3%) | 30 (27.8%) | 29 (24.4%) | **<0.001** |
| | Borderline | 4 (8.2%) | 9 (8.3%) | 9 (7.6%) | |
| | Intermediate | 12 (24.5%) | 48 (44.4%) | 36 (30.3%) | |
| | High | 0 (0.0%) | 21 (19.4%) | 45 (37.8%) | |

# 3. Multivariable Analysis of association between Dyslipidemia and renal severity

## 3.1. Model 1: Unadjusted and adjusted binary logistic regression analysis of Lipid Abnormalities associated with impaired renal function

In binary logistic regression analysis, no significant association was found between lipid abnormalities and impaired renal function (G3a–G5 vs G1–G2). In both unadjusted and adjusted models, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, low HDL-C, and dyslipidemia status were not significantly associated with reduced renal function, with all p-values exceeding 0.05. After adjustment for age, sex, hypertension, and diabetes, these associations remained non-significant, suggesting that lipid abnormalities were not independent predictors of impaired renal function in this cohort.

*Table 34 Unadjusted and adjusted binary logistic regression analysis of factors associated with impaired renal function (G3a–G5 vs G1–G2).*

| Variable | Unadjusted OR (95% CI) | p-value | Adjusted[1] OR (95% CI) | p-value |
|---|---|---|---|---|
| **Hypercholesterolemia** | 0.960 (0.567-1.625) | 0.879 | 0.890 (0.510-1.554) | 0.682 |
| **hyperlipoproteinemia** | 0.675 (0.391-1.162) | 0.156 | 0.634 (0.356-1.129) | 0.122 |
| **Hypertriglyceridemia** | 1.305 (0.770-2.210) | 0.323 | 1.079 (0.614-1.895) | 0.791 |
| **Low HDL-C** | 1.403 (0.824-2.391) | 0.213 | 1.364 (0.766-2.427) | 0.292 |
| **Dyslipidemia Status** | 1.376 (0.660-2.870) | 0.394 | 0.922 (0.399-2.131) | 0.849 |

Adjusted[1]: age, gender, hypertension, diabetes

## 3.2. Model 2: Unadjusted and adjusted binary logistic regression analysis of factors associated with albuminuria

Binary logistic regression analysis was performed to identify factors associated with elevated albuminuria. In the unadjusted analysis, most lipid parameters were not significantly associated with elevated albuminuria. High total cholesterol was not significantly associated with the outcome (OR = 1.280; 95% CI: 0.609–2.690; p = 0.515), nor were high LDL-C (OR = 1.138; 95% CI: 0.523–2.479; p = 0.744), low HDL-C (OR = 0.929; 95% CI: 0.438–1.969; p = 0.847), or overall dyslipidemia status (OR = 1.078; 95% CI: 0.385–3.017; p = 0.887). In contrast, high triglycerides were significantly associated with elevated albuminuria in the crude analysis, with patients presenting hypertriglyceridemia having approximately threefold higher odds of elevated albuminuria compared with those with normal triglyceride levels (OR = 3.121; 95% CI: 1.383–7.043; p = 0.006).

After adjustment for age, sex, hypertension, and diabetes, the association between hypertriglyceridemia and elevated albuminuria was attenuated and no longer reached statistical significance, although a trend persisted (adjusted OR = 2.193; 95% CI: 0.918–5.241; p = 0.077). Likewise, no significant association was observed for high total cholesterol (adjusted OR = 1.368; 95% CI: 0.596–3.142; p = 0.460), high LDL-C (adjusted OR = 1.440; 95% CI: 0.593–3.495; p = 0.421), low HDL-C (adjusted OR = 0.767; 95% CI: 0.316–1.861; p = 0.558), or dyslipidemia status (adjusted OR = 0.736; 95% CI: 0.196–2.760; p = 0.649).

Overall, these results suggest that hypertriglyceridemia was associated with elevated albuminuria in the unadjusted analysis, but this association was not independent after adjustment for major clinical confounders.

*Table 35: Unadjusted and adjusted binary logistic regression analysis of factors associated with elevated albuminuria*

| Variable | Crude OR (95% CI) | p-value | Adjusted[1] OR (95% CI) | p-value |
|---|---|---|---|---|
| High total cholesterol | 1.280 (0.609-2.690) | 0.515 | 1.368(0.596-3.142) | 0.460 |
| High LDL-C | 1.138 (0.523-2.479) | 0.744 | 1.440 (0.593-3.495) | 0.421 |
| High triglycerides | 3.121 (1.383-7.043) | **0.006** | 2.193 (0.918-5.241) | 0.077 |
| Low HDL-C | 0.929 (0.438-1.969) | 0.847 | 0.767 (0.316-1.861) | 0.558 |
| Dyslipidemia Status | 1.078(0.385-3.017) | 0.887 | 0.736 (0.196-2.760) | 0.649 |

Adjusted[1]: age, gender, hypertension, diabetes

## 3.3. Model 3: Unadjusted and adjusted binary logistic regression analysis of factors associated with hypertriglyceridemia

Binary logistic regression analysis was performed to identify renal factors associated with hypertriglyceridemia. In the unadjusted analysis, impaired renal function defined by G3a–G5 was not significantly associated with hypertriglyceridemia (OR = 1.305; 95% CI: 0.770–2.210; p = 0.323). In contrast, elevated albuminuria (A2–A3) was significantly associated with hypertriglyceridemia, with affected patients showing more than threefold higher odds of hypertriglyceridemia compared with those in category A1 (OR = 3.121; 95% CI: 1.383–7.043; p = 0.006). Likewise, high KDIGO renal risk was significantly associated with hypertriglyceridemia in the crude model (OR = 5.631; 95% CI: 1.585–20.005; p = 0.008).

After adjustment for age, sex, hypertension, and diabetes, the association between impaired renal function (G3a–G5) and hypertriglyceridemia remained non-significant (adjusted OR = 1.080; 95% CI: 0.615–1.896; p = 0.789). The association with elevated albuminuria was attenuated and no longer reached statistical significance, although a borderline trend persisted (adjusted OR = 2.209; 95% CI: 0.928–5.260; p = 0.073). By contrast, high KDIGO renal risk remained independently and significantly associated with hypertriglyceridemia after adjustment, with an approximately fourfold increase in odds (adjusted OR = 4.066; 95% CI: 1.098–15.061; p = 0.036).

Overall, these findings suggest that hypertriglyceridemia was independently associated with high KDIGO renal risk, whereas its associations with reduced eGFR and elevated albuminuria were not statistically significant after multivariable adjustment.

*Table 35 Unadjusted and adjusted binary logistic regression analysis of factors associated with hypertriglyceridemia.*

| Variable | Unadjusted OR (95% CI) | p-value | Adjusted[1] OR (95% CI) | p-value |
|---|---|---|---|---|
| G3a–G5 | 1.305 (0.770–2.210) | 0.323 | 1.080 (0.615–1.896) | 0.789 |
| A2–A3 | 3.121 (1.383–7.043) | **0.006** | 2.209 (0.928–5.260) | 0.073 |
| High KDIGO risk | 5.631 (1.585–20.005) | **0.008** | 4.066 (1.098–15.061) | **0.036** |

Adjusted[1]: age, gender, hypertension, diabetes

### 3.4. Model 4: Unadjusted and adjusted binary logistic regression analysis of factors associated with low HDL-C

Binary logistic regression analysis was performed to assess the association between renal parameters and low HDL-C. In the unadjusted analysis, impaired renal function defined by G3a-G5 was not significantly associated with low HDL-C (OR = 1.403; 95% CI: 0.824-2.391; p = 0.213). Similarly, elevated albuminuria (A2-A3) was not significantly associated with low HDL-C (OR = 0.929; 95% CI: 0.438-1.969; p = 0.847), and high KDIGO renal risk was likewise not significantly associated with the outcome (OR = 0.531; 95% CI: 0.183-1.541; p = 0.241).

After adjustment for age, sex, hypertension, and diabetes, these associations remained non-significant. The adjusted odds ratio was 1.360 (95% CI: 0.763-2.423; p = 0.297) for G3a-G5, 0.765 (95% CI: 0.317-1.844; p = 0.551) for A2-A3, and 0.382 (95% CI: 0.102-1.436; p = 0.154) for high KDIGO renal risk.

Overall, no significant association was identified between reduced renal function, increased albuminuria, or high KDIGO renal risk and low HDL-C, either before or after adjustment for potential confounding factors.

*Table 36 Unadjusted and adjusted binary logistic regression analysis of factors associated with Low HDL.*

| Variable | Crude OR (95% CI) | p-value | Adjusted[1] OR (95% CI) | p-value |
|---|---|---|---|---|
| **G3a–G5** | 1.403 (0.824–2.391) | 0.213 | 1.360 (0.763-2.423)) | 0.297 |
| **A2–A3** | 0.929 (0.438–1.969) | 0.847 | 0.765 (0.317-1.844) | 0.551 |
| **High KDIGO Risk** | 0.531 (0.183-1.541) | **0.241** | 0.382 (0.102-1.436) | **0.154** |

Adjusted[1]: age, gender, hypertension, diabetes

### 3.5. Model 5: Unadjusted and adjusted binary logistic regression analysis of factors associated with high LDL-C

Binary logistic regression analysis was performed to evaluate the association between renal parameters and high LDL-C. In the unadjusted analysis, impaired renal function defined by G3a-G5 was not significantly associated with high LDL-C (OR = 0.675; 95% CI: 0.391-1.162; p = 0.156). Likewise, elevated albuminuria (A2-A3) showed no significant association with high LDL-C (OR = 1.138; 95% CI: 0.523-2.479; p = 0.744), and high KDIGO renal risk was also not significantly associated with the outcome (OR = 1.129; 95% CI: 0.408-3.124; p = 0.816).

After adjustment for age, sex, hypertension, and diabetes, the associations remained non-significant. The adjusted odds ratio was 0.638 (95% CI: 0.358-1.136; p = 0.127) for G3a-G5, 1.513 (95% CI: 0.628-3.645; p = 0.356) for A2-A3, and 1.484 (95% CI: 0.478-4.614; p = 0.495) for high KDIGO renal risk.

Overall, these findings indicate that none of the renal severity markers studied were significantly associated with high LDL-C, either in the crude analysis or after multivariable adjustment.

*Table 37 Unadjusted and adjusted binary logistic regression analysis of factors associated with high LDL-C*

| Variable | Crude OR (95% CI) | p-value | Adjusted[1] OR (95% CI) | p-value |
|---|---|---|---|---|
| **G3a–G5** | 0.675 (0.391–1.162) | 0.156 | 0.638 (0.358-1.136) | 0.127 |
| **A2–A3** | 1.138 (0.523–2.479) | 0.744 | 1.513 (0.628-3.645) | 0.356 |
| **High KDIGO Risk** | 1.129 (0.408-3.124) | **0.816** | 1.484 (0.478-4.614) | 0.495 |

Adjusted[1]: age, gender, hypertension, diabetes

## 3.6. Model 6: Unadjusted and adjusted binary logistic regression analysis of factors associated with hypercholesterolemia

Binary logistic regression analysis was performed to assess the association between renal parameters and high total cholesterol. In the unadjusted analysis, impaired renal function defined by G3a–G5 was not significantly associated with high total cholesterol (OR = 0.960; 95% CI: 0.567–1.625; p = 0.879). Similarly, elevated albuminuria (A2–A3) was not significantly associated with the outcome (OR = 1.280; 95% CI: 0.609–2.690; p = 0.515). High KDIGO renal risk also showed no significant association with high total cholesterol in the crude model (OR = 1.911; 95% CI: 0.692–5.273; p = 0.211).

After adjustment for age, sex, hypertension, and diabetes, the associations remained non-significant. The adjusted odds ratio was 0.892 (95% CI: 0.511–1.557; p = 0.687) for G3a–G5, 1.386 (95% CI: 0.607–3.164; p = 0.438) for A2–A3, and 2.235 (95% CI: 0.726–6.877; p = 0.161) for high KDIGO renal risk.

Overall, these results indicate that high total cholesterol was not significantly associated with impaired renal function, elevated albuminuria, or high KDIGO renal risk, either before or after multivariable adjustment.

*Table 38 Unadjusted and adjusted binary logistic regression analysis of factors associated with high cholesterol*

| Variable | Crude OR (95% CI) | p-value | Adjusted[1] OR (95% CI) | p-value |
|---|---|---|---|---|
| **G3a–G5** | 0.960 (0.567–1.625) | 0.879 | 0.892 (0.511-1.557) | 0.687 |
| **A2–A3** | 1.280 (0.609–2.690) | 0.515 | 1.386 (0.607-3.164) | 0.438 |
| **High KDIGO Risk** | 1.911 (0.692-5.273) | **0.211** | 2.235 (0.726-6.877) | 0.161 |

Adjusted[1]: age, gender, hypertension, diabetes

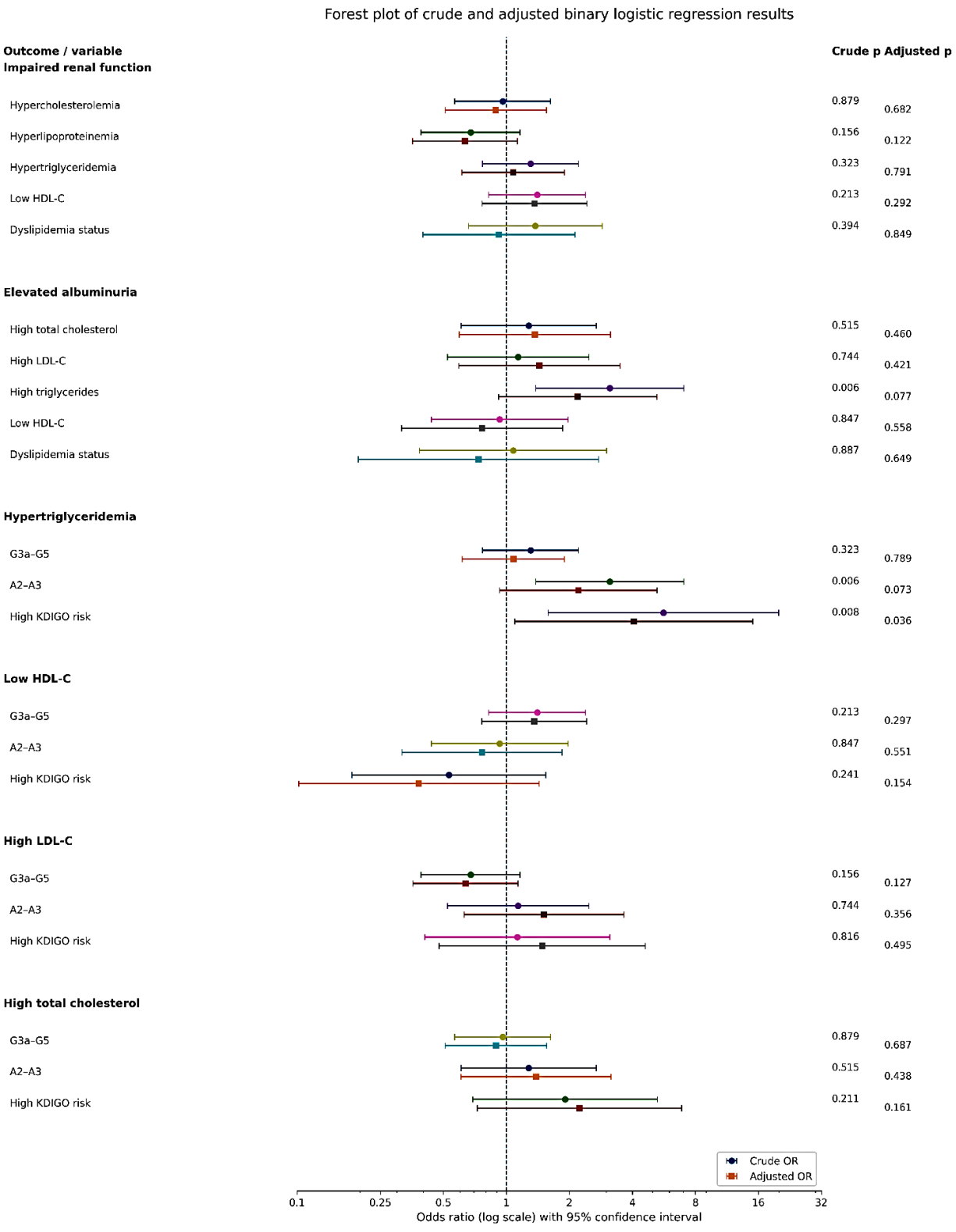



*Figure 32 Summary of Associations*


Discussion

# I. Literature Overview

## 1. Renal Disease Foundations

### 1.1. Definition of CKD and concept of chronicity

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or kidney function that are present for more than 3 months and have implications for health (1).

In practice, CKD is diagnosed when either (i) glomerular filtration rate (GFR) is persistently reduced to <60 mL/min/1.73 m², corresponding to KDIGO G3a–G5 categories, and/or (ii) there is evidence of kidney damage, even when GFR is preserved (2).

In this context, Markers of kidney damage include a broad set of measurable abnormalities that deepens the definition.

(i) Albuminuria, the most widely used biomarker, is typically quantified using the urine albumin-to-creatinine ratio (ACR); where an ACR ≥30 mg/g (≥3 mg/mmol) is considered clinically significant and contributes to CKD classification and risk stratification. When an elevated ACR is detected on a random sample, confirmation using a first-morning void is recommended to reduce biological variability and improve diagnostic accuracy (12).

Importantly, (ii) persistent albuminuria/proteinuria either by spot urine test or a 24h collection method may support a diagnosis of CKD even in the presence of a normal GFR, reflecting kidney damage and carrying independent prognostic significance.

Additional evidence of kidney damage may be provided by (iii) abnormalities of urine sediment (e.g., hematuria), (iv) tubular disorders manifesting as electrolyte/acid–base disturbances, (v) histopathologic lesions on kidney biopsy (e.g., glomerulosclerosis, interstitial fibrosis), and (vi) structural abnormalities on imaging. Imaging, particularly ultrasound, computed tomography, or magnetic resonance imaging may identify conditions such as polycystic kidneys, dysplasia, obstructive uropathy with hydronephrosis, cortical scarring, infiltrative disease, renal artery stenosis, or small echogenic kidneys in advanced stages, thereby providing morphological correlates of chronic kidney injury.

Without forgetting, (vii) a kidney transplant history that must be explicitly documented and considered when defining and classifying CKD. Transplant recipients are conventionally denoted using the “T” suffix appended to the GFR category (e.g., G3aT), reflecting that kidney function and prognosis after transplantation are interpreted within a distinct clinical context. In epidemiologic and clinical research, transplant history is therefore critical because it (i) identifies a population with altered renal anatomy and physiology (allograft), (ii) introduces major determinants of kidney outcomes (immunosuppression exposure, rejection episodes, recurrent primary disease), and (iii) can modify the meaning of standard CKD markers such as albuminuria and eGFR trajectories.

Across all the kidney damage markers described above (and eGFR reduction), the key unifying requirement is persistence for ≥3 months to confirm chronicity—with prior kidney transplantation considered evidence of CKD regardless of duration. The requirement for chronicity (≥3 months) is central, as it distinguishes CKD from acute kidney disorders—particularly acute kidney disease (AKD) and acute kidney injury (AKI) in which abnormalities are transient or of shorter

duration. This temporal criterion separates progressive chronic processes from reversible functional changes and therefore informs prognosis, surveillance intensity, and long-term management.


*Figure 33 Summary of markers of kidney damage*

*Table 39 Criteria of Chronic kidney disease according to KDIGO Guideline of 2024 (1)*

| | |
|---|---|
| Markers of kidney damage (1 or more) | • Albuminuria (ACR >30 mg/g [>3 mg/mmol])<br>• Urine sediment abnormalities<br>• Persistent hematuria<br>• Electrolyte and other abnormalities due to tubular disorders<br>• Abnormalities detected by histology<br>• Structural abnormalities detected by imaging History of kidney transplantation |
| Decreased GFR | GFR <60 ml/min per 1.73 m2 (GFR categories G3a–G5) |

## 1.2. CKD classification:

Once CKD is established, the subsequent step is **staging**, ideally using the **KDIGO CGA classification**, which integrates **Cause (C)**, **GFR category (G1–G5)**, and **Albuminuria category (A1–A3)** to define disease phenotype and stratify prognosis and complication risk. Although the *diagnosis* of CKD may be supported by a wide range of structural, functional, and urinary abnormalities persisting for ≥3 months, KDIGO's *risk stratification* relies chiefly on the two prognostically dominant dimensions—**eGFR and albuminuria**—because these measures robustly predict clinically important outcomes, including kidney failure, cardiovascular events, and mortality across diverse populations (1,13).

This distinction between the **diagnostic criteria** for CKD and the parameters used to **stage** CKD severity and risk is clinically consequential and is frequently misunderstood in routine practice. Such confusion can lead to incomplete risk appraisal—particularly when other markers of kidney damage are not measured or are underweighted. Accordingly, healthcare providers and trainees should remain vigilant to avoid underdiagnosis or misclassification of CKD due to misinterpretation of the diagnostic framework (1).

The KDIGO CGA system stratifies kidney function by eGFR into five categories (G1–G5): G1 (≥90 mL/min/1.73 m²; normal or high), G2 (60–89; mildly decreased), G3a (45–59; mildly to moderately decreased), G3b (30–44; moderately to severely decreased), G4 (15–29; severely decreased), and G5 (<15; kidney failure). When applicable, **suffixes** may be appended to the G category to clarify kidney replacement therapy status: **"D"** denotes **dialysis dependence** (e.g., **G5D**), and **"T"** denotes **kidney transplant recipient status** (e.g., **G1T–G5T**, **G5T**). This convention preserves explicit functional staging while transparently indicating treatment context (1,14). (see figure 41)

Albuminuria is similarly grouped into A1 (<30 mg/g, normal to mildly increased), A2 (30–300 mg/g, moderately increased), and A3 (>300 mg/g, severely increased) (1). (see figure 42)

This dual-axis classification, often referred to as CGA for cause, GFR, albuminuria, recognizes that the degree of renal filtration impairment and the extent of protein leakage carry independent yet interacting prognostic weights. Combining these categories creates a risk matrix or "heat map" where color-coded zones represent escalating probabilities of adverse outcomes such as kidney failure, cardiovascular events, and mortality (1,13).

One central feature of this classification is its capacity for longitudinal monitoring. Patients can shift zones over time as either eGFR declines or albuminuria changes. Large population meta-analyses confirm incremental increases in risk both downward through the GFR scale and horizontally across albuminuria categories [50]. Importantly, these patterns appear consistently across diverse geographies, including North America, Europe, and Asia, indicating broad applicability (13,15).

*Table 40 CKD Stratification with GFR following KDIGO 2024 Guidelines (1)*

| GFR category | GFR (ml/min/1.73 m²) | Terms |
|---|---|---|
| G1 | >90 | Normal or high |
| G2 | 60–89 | Mildly decreased |
| G3a | 45–59 | Mildly to moderately decreased |
| G3b | 30–44 | Moderately to severely decreased |
| G4 | 15–29 | Severely decreased |
| G5 | <15 | Kidney failure |

*Table 41 Albuminuria to creatinuria ration (ACR) stratification following KDIGO 2024 guidelines (1)*

| Category | ACR | | Terms |
|---|---|---|---|
| | mg/mmol | mg/g | |
| A1 | <3 | <30 | Normal to mildly increased |
| A2 | 3-30 | 30-300 | Moderately increased |
| A3 | >300 | >300 | Severely Increased |

| KDIGO: Prognosis of CKD by GFR and albuminuria categories | | | | A1 | A2 | A3 |
|---|---|---|---|---|---|---|
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30mg/g <3 mg/mmol | 30-300 mg/g 3-30 mg/mmol | >300 mg/g >30mg/mmol |
| GFR categories (ml/min/1.73 m2) Description and range | G1 | Normal or high | >= 90 | | | |
| | G2 | Mildly decreased | 60-89 | | | |
| | G3a | Mildly to moderately decreased | 45-59 | | | |
| | G3b | Moderately to severely decreased | 30-44 | | | |
| | G4 | Severely decreased | 15-29 | | | |
| | G5 | Kidney failure | <15 | | | |

***Figure 34 KDIGO CGA Risk Stratification** (1,14). Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate. CKD=chronic kidney disease. GFR=glomerular filtration rate; ACR=albumin creatinine ratio.*

## 1.3. Etiology of chronic kidney disease

Many chronic diseases can cause end-stage renal disease. In many developed and developing countries, diabetes mellitus is the leading cause.

Other causes include the following (16): (see figure 35)

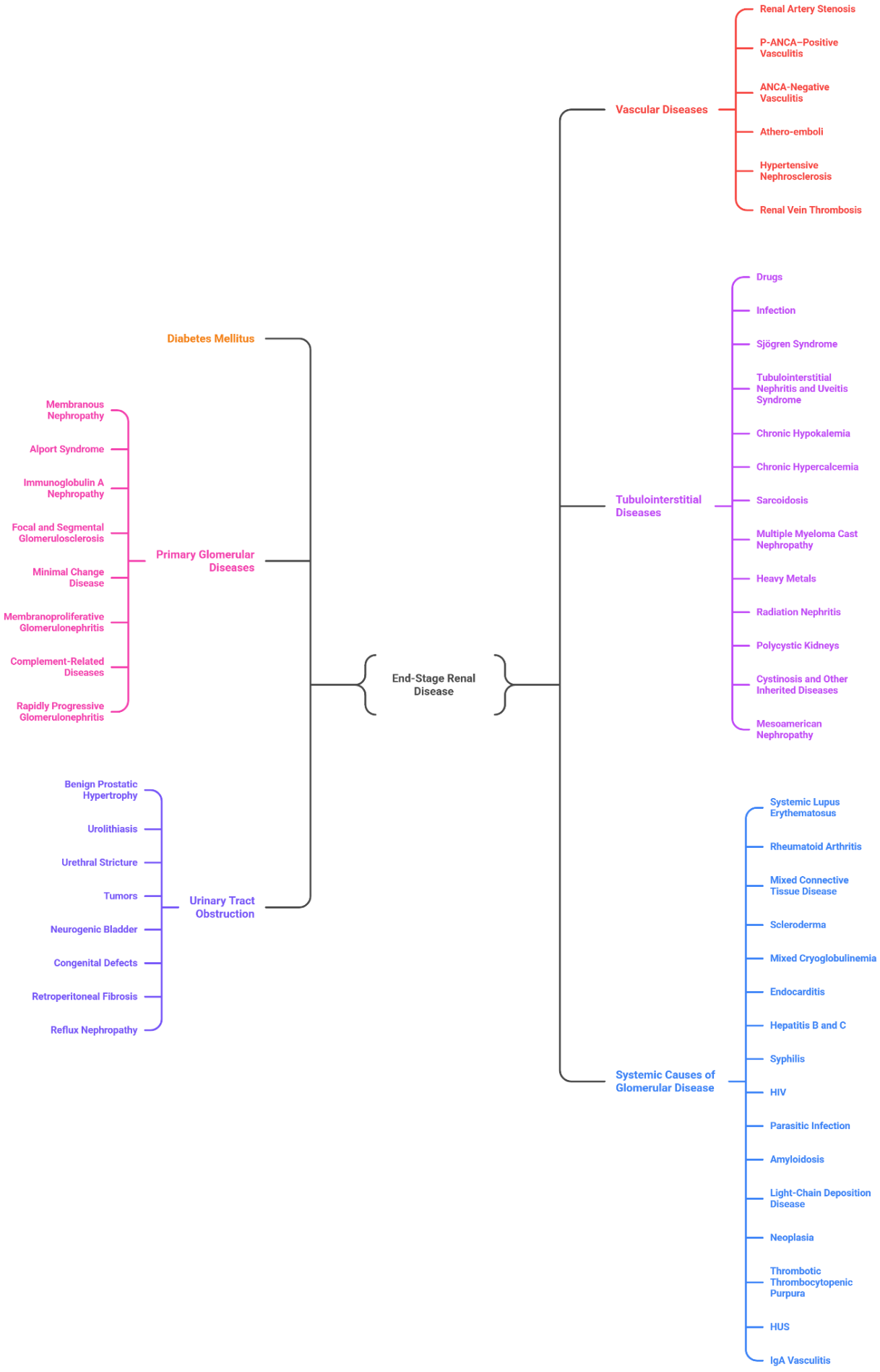



*Figure 35 Causes of chronic renal disease*

Conceptual framework: prerenal, intrinsic renal, and postrenal processes

For clinical reasoning, CKD etiologies can be organized into **three broads anatomic–functional categories** (16):

- **Prerenal disease**

Chronic prerenal states are typically seen in conditions such as **chronic heart failure** or **cirrhosis**, in which persistently reduced effective arterial blood volume lowers renal perfusion. Prolonged hypoperfusion increases susceptibility to intrinsic kidney injury (e.g., ischemic tubular damage), and—when sustained—may contribute to **progressive, irreversible decline in kidney function** over time.

- **Intrinsic renal disease**
  - **Renovascular (intrinsic vascular) disease**

The most frequent chronic renovascular process is **nephrosclerosis**, characterized by ongoing injury to small renal vessels with secondary involvement of **glomeruli** and the **tubulointerstitial**. Other causes include **renal artery stenosis**, most commonly due to **atherosclerosis** or **fibromuscular dysplasia**. Over months to years, reduced blood flow may lead to **ischemic nephropathy**, typically associated with **glomerulosclerosis** and **tubulointerstitial fibrosis**.

  - **Glomerular disease (nephritic vs nephrotic patterns)**

A **nephritic** pattern is suggested by an "active" urine sediment—classically **dysmorphic red blood cells** and **RBC casts** (with possible leukocyturia)—with variable degrees of proteinuria. Common etiologies include **post-infectious glomerulonephritis**, **infective endocarditis–associated GN**, **IgA nephropathy**, **lupus nephritis**, **anti-GBM (Goodpasture) disease**, and **vasculitis**.

A **nephrotic** pattern is defined by **heavy proteinuria** (typically **>3.5 g/24 h**), often with a relatively "bland" urine sediment (few cells or casts). Frequent causes include **minimal change disease**, **focal segmental glomerulosclerosis**, **membranous nephropathy**, **diabetic nephropathy**, and **amyloidosis**.

  - **Tubulointerstitial disease**

Among chronic tubulointerstitial disorders, **polycystic kidney disease (PKD)** is a leading etiology. Other causes include **nephrocalcinosis** (often related to hypercalcemia/hypercalciuria), **sarcoidosis**, **Sjögren syndrome**, and **reflux nephropathy**, particularly in children and young adults. In addition, CKD of **uncertain etiology** has been increasingly described in specific regions, especially among agricultural workers in parts of Central America and Southeast Asia, often referred to as **Mesoamerican nephropathy** or **chronic interstitial nephritis in agricultural communities**.

- **Postrenal (obstructive) nephropathy**

Chronic urinary tract obstruction may result from **prostatic disease**, **nephrolithiasis**, or **abdominal/pelvic tumors** compressing the ureter(s). **Congenital** obstructive lesions at the ureteropelvic or ureterovesical junctions are also common. Less frequent causes include **retroperitoneal fibrosis** and **neurogenic bladder**. Persistent obstruction can produce progressive renal damage if not relieved.

## 1.4. Chronic Kidney Disease Pathophysiology: The AKI to CKD Continuum

The progression from Acute Kidney Injury (AKI) to chronic kidney disease (CKD) is increasingly understood as a **continuum** in which severe, prolonged, or repetitive acute insults shift renal healing from adaptive regeneration to **maladaptive repair**, producing persistent inflammation, microvascular loss, metabolic failure, and ultimately irreversible fibrosis with progressive nephron dropout (17). Clinically, CKD is defined by **structural and/or functional kidney abnormalities persisting for ≥3 months**, reinforcing that "chronicity" reflects durable remodeling rather than delayed normalization of serum creatinine (1).

The process is initiated when ischemia–reperfusion injury, sepsis-associated tubular stress, or nephrotoxins trigger **tubular epithelial cell (TEC) death and sublethal injury** (17). As they represent the primary target of renal injury, they also represent the hallmark of maladaptive repair process through the development of interstitial fibrosis and, consequently, in the progression to chronic damage by their ability to transdifferentiate in myofibroblasts with a subsequent extracellular matrix deposition at the end (18–20).

As TECs undergo necrosis or apoptosis after an acute insult, they release intracellular danger-signal molecules—**damage-associated molecular patterns (DAMPs)**—into the extracellular space. These DAMPs engage **pattern-recognition receptors (PRRs)**, particularly **Toll-like receptors (TLRs)**, thereby activating innate immune signaling and driving the production of **proinflammatory cytokines, chemokines, and reactive oxygen species (ROS)**, which can amplify tubular injury and propagate further cell death and tissue damage (21,22) . In parallel, severe and/or prolonged cellular stress induces **DNA damage** in TECs and activates the **DNA-damage response (DDR)**, which triggers protective cell-cycle checkpoints; however, when sustained, these programs may contribute to maladaptive repair and chronic pathological remodeling (23).

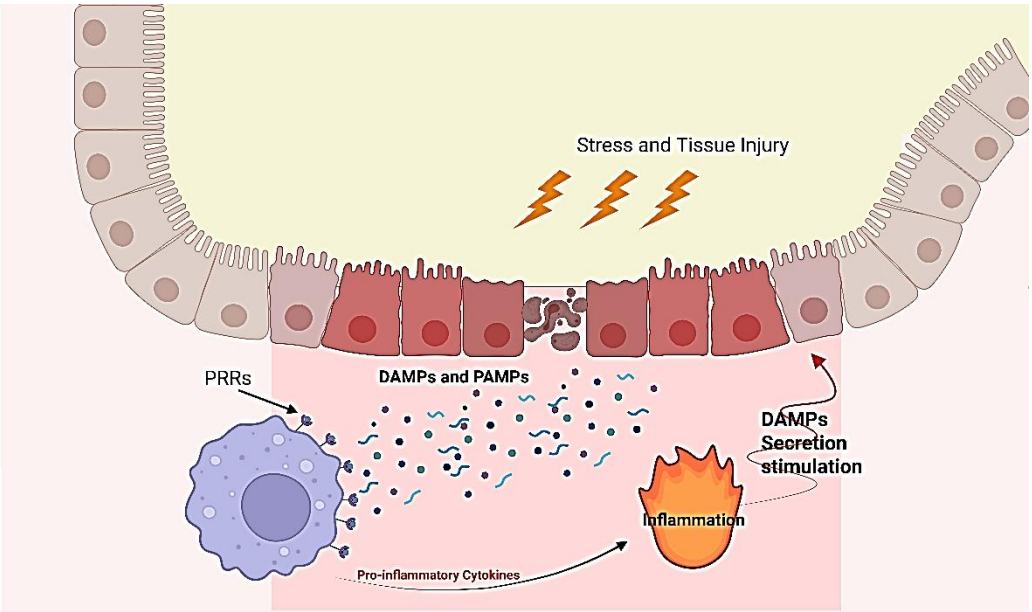



*Figure 36 Epithelial Injury–Induced Release of DAMPs and Activation of Inflammatory Signaling. Made in Biorender*

Several intracellular mediators released from necrotic TECs—such as **high mobility group box 1 (HMGB1), histones, heat kinin, and fibronectin**—further intensify inflammatory cascades once they enter the extracellular compartment (24). Over time, persistent inflammation becomes coupled to fibrosis: the continued release of inflammation-associated profibrotic cytokines, notably **transforming growth factor-β (TGF-β)** and **interleukin-13 (IL-13)**, can promote **epithelial-mesenchymal transition (EMT)** and other profibrotic responses, ultimately favoring **renal interstitial fibrosis** and progression toward chronic renal insufficiency (25).

Another mechanistic hallmark of maladaptive repair is **prolonged TEC cell-cycle arrest**, particularly **G2/M arrest**. While initially protective to prevent replication of damaged DNA, persistent G2/M arrest, unlike the G1/0 arrest in normal conditions, drives a senescence-like secretory phenotype characterized by increased release of **profibrotic mediators** including TGF-β-related signaling and connective tissue growth programs, which activate interstitial cells and amplify extracellular matrix (ECM) deposition (26,27). Interestingly, the number of cells with G2/M arrest significantly correlates with kidney fibrosis and pharmacological intervention that reverse G2/M arrest block AKI-to-CKD progression.

In parallel, AKI injures the renal endothelium and destabilizes peritubular capillaries, causing **microvascular rarefaction**—a durable reduction in capillary density—which reduces oxygen delivery and establishes **chronic tissue hypoxia** (28). This hypoxic microenvironment promotes oxidative stress and fibrogenic remodeling and becomes a self-reinforcing driver of progressive kidney dysfunction (29). Although the recovery ability of renal tubules is outstanding, the recovery of blood vessels is very different (30). Given the kidney's high metabolic demand and dependence on tightly regulated oxygen delivery, AKI-related microcirculatory dysfunction disrupts oxygen transport and tissue homeostasis; increased vascular permeability and interstitial edema further exacerbate hypoxia and oxidative stress, creating a permissive milieu for maladaptive repair and subsequent renal fibrosis after AKI (31).

The kidney has an exceptionally high metabolic rate—second only to the heart in oxygen consumption and mitochondrial content—because tubular transport work is continuously powered by mitochondrial ATP, particularly to sustain basolateral $Na^+/K^+$-ATPase–dependent ion gradients (31,32). Proximal tubular epithelial cells (TECs) are therefore "energy-intensive" and disproportionately vulnerable in AKI, where microvascular injury and edema reduce perfusion and impose tissue hypoxia (33). In the healthy proximal tubule, ATP generation relies predominantly on mitochondrial oxidative phosphorylation fueled largely by fatty acid β-oxidation (FAO); however, FAO is oxygen-dependent and is rapidly suppressed in hypoxic or post-injury states, with downregulation of FAO programs and reduced metabolic flexibility (34). The resulting shift toward glycolysis may transiently support survival but is energetically insufficient to sustain high transport demands (35); ATP depletion then destabilizes the actin cytoskeleton and epithelial polarity, contributing to brush-border loss, junctional disruption, barrier failure, and ultimately TEC detachment and death—events that set the stage for maladaptive repair and fibrotic remodeling (36,37).

Concurrently, AKI disturbs mitochondrial quality control. Under stress, mitochondrial fusion is suppressed while Drp1-driven fission becomes excessive, producing fragmented mitochondria that are primed for outer-membrane permeabilization (including Bax translocation) and apoptosis (38). Fragmentation and hypoxia impair electron transport, increasing mitochondrial ROS generation; ROS further damages mitochondria and amplifies inflammatory signaling, creating a self-reinforcing cycle that blocks adaptive tubular recovery. Finally, the recovery program that should replenish mitochondrial mass—mitochondrial biogenesis regulated by PGC-1α—is often blunted during the AKI-to-CKD transition; experimental activation of the SIRT1/PGC-1α axis has been shown to restore mitochondrial proteins/respiration and accelerate proximal tubular repolarization after ischemia–reperfusion injury, supporting the concept that rebuilding mitochondrial capacity is mechanistically linked to functional repair (38).

Meanwhile, the inflammatory response that is essential for debris clearance after AKI may fail to resolve, resulting in **persistent innate and adaptive immune activation**. Macrophages can remain in pro-inflammatory states or adopt "repair-associated" phenotypes that, in chronic injury contexts, paradoxically support fibrosis through profibrotic cytokine production and crosstalk with stromal cells; complement activation and T-cell cytokine signaling can further sustain inflammation and tissue remodeling (25).

With aging and/or repeated injury, chronic inflammation can also promote formation of **tertiary lymphoid structures/tissues (TLS/TLTs)** within the kidney—organized ectopic immune microenvironments that perpetuate local immune activation and hinder normal repair—helping explain why older individuals and those with recurrent insults often exhibit higher progression risk (25).

At the molecular level, these converging stresses—cell-cycle arrest/senescence, hypoxia-driven signaling, mitochondrial/FAO failure, and unresolved inflammation—activate core fibrogenic pathways, most prominently **TGF-β–dependent transcriptional programs** alongside other developmental and mechano-transduction networks. These signals culminate in expansion and activation of **myofibroblasts** (from resident fibroblasts, pericyte detachment, and other stromal sources), which deposit excessive ECM (e.g., collagen, fibronectin), producing **interstitial fibrosis and tubular atrophy**.

As functional parenchyma is replaced by scar tissue, surviving nephrons initially compensate through **hyperfiltration**, but this adaptation increases intraglomerular stress and accelerates structural failure. The net effect is a **feed-forward cycle**: acute injury begets maladaptive repair, which begets fibrosis and microvascular loss, which sustains hypoxia, metabolic dysfunction, and inflammation—thereby driving ongoing nephron dropout and the irreversible transition to CKD(39).

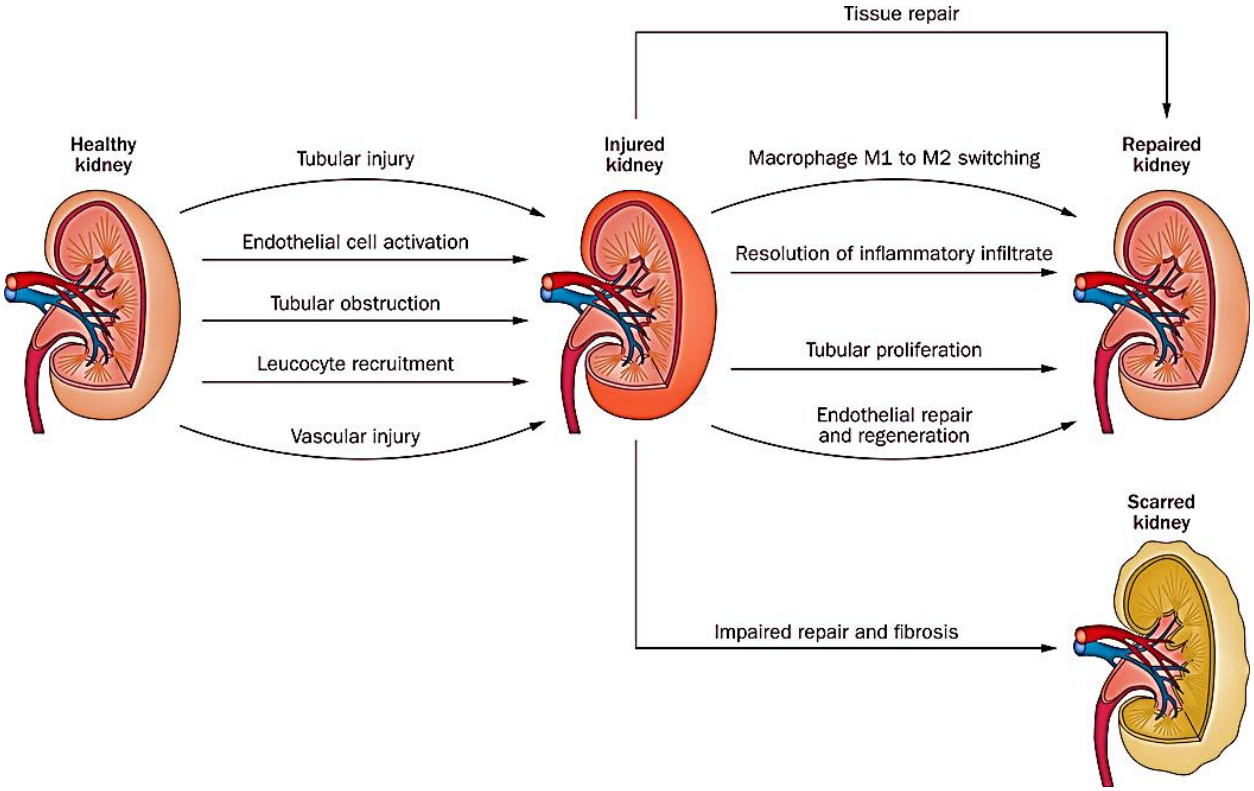



*Figure 37 A summary of some of the mechanisms involved in initial tissue injury and subsequent repair of the kidney after acute kidney injury. Maladaptive and incomplete repair lead to the development of fibrosis and, ultimately, chronic kidney disease (39)*

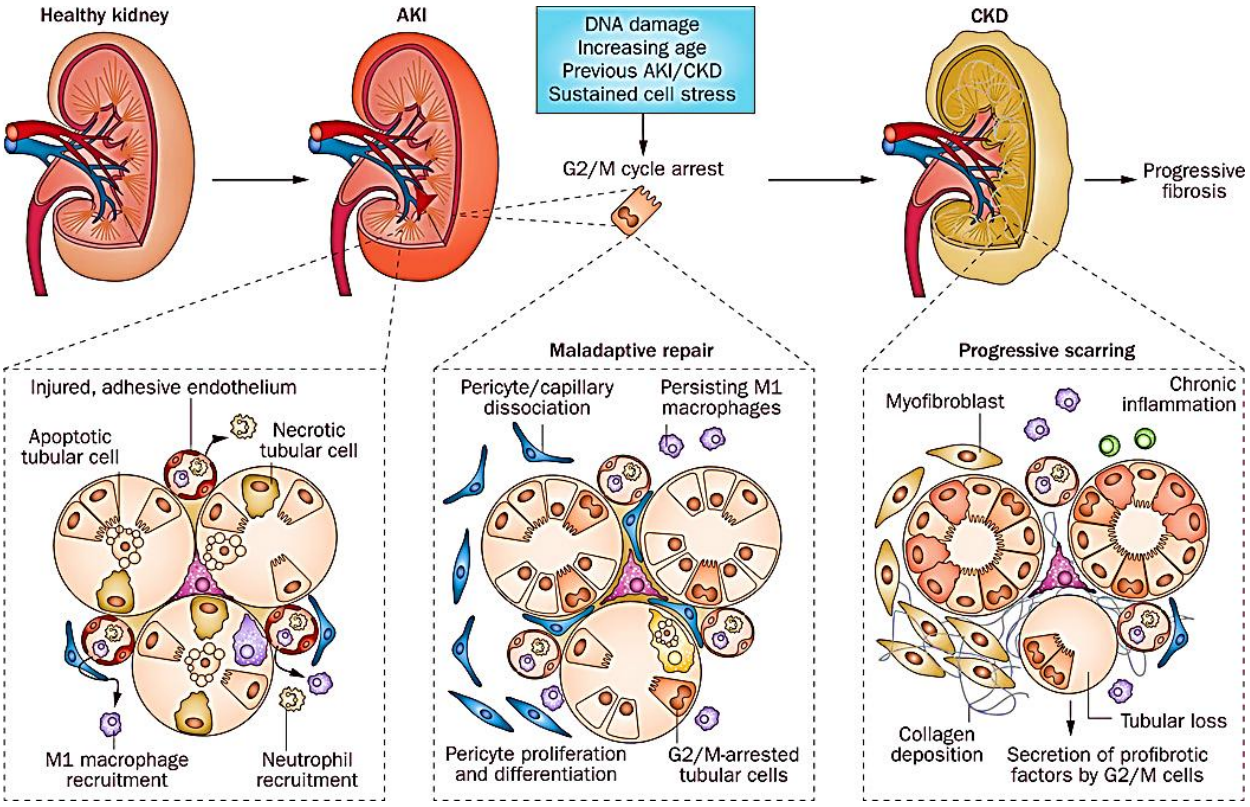



***Figure 38 Maladaptive repair of AKI leads to CKD*** *(39)**. Studies have highlighted the importance of G2/M cell-cycle arrest in response to severe, repeated and genotoxic renal insults. In the initial repair phase after injury, cells may become arrested in G2/M phase and release cytokines and growth factors that promote inflammatory cell retention within the kidney and ongoing inflammation. Injury and pro-inflammatory stimuli lead to pericyte dissociation from the endothelium, resulting in microvascular rarefaction and the progressive deposition of collagen I by myofibroblasts arising from activated pericytes. Ageing sensitizes tubular cells to G2/M arrest in response to cell stress and DNA damage, providing a potential explanation for the increased risk of CKD progression after AKI in the elderly. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease.*

# 2. Dyslipidemia Foundations

## 2.1. The Physiological Lifecycle of Lipids: From Dietary Intake to Cellular Utilization and Metabolic Regulation

**Lipids** are a broad class of hydrophobic organic molecules that are insoluble in water but soluble in nonpolar organic solvents (40). In human physiology, they are indispensable to multiple biological functions. They serve as a major long-term energy reserve, contribute to thermal insulation and mechanical protection, participate in cell signaling, and form essential structural components of biological membranes (41). The physiological handling of lipids is not a single event, but rather a dynamic and tightly regulated cycle that integrates intestinal absorption, plasma transport, hepatic synthesis and redistribution, cellular uptake and storage, oxidative degradation, and cholesterol recycling. This coordinated network ensures that lipid availability remains matched to the body's metabolic and structural needs while preventing toxic accumulation. In this thesis, lipid metabolism was presented according to the classical division into exogenous and endogenous pathways described by Kenneth R. Feingold, as this approach offers a clear and coherent framework for understanding the successive mechanisms of lipid lifecycle.

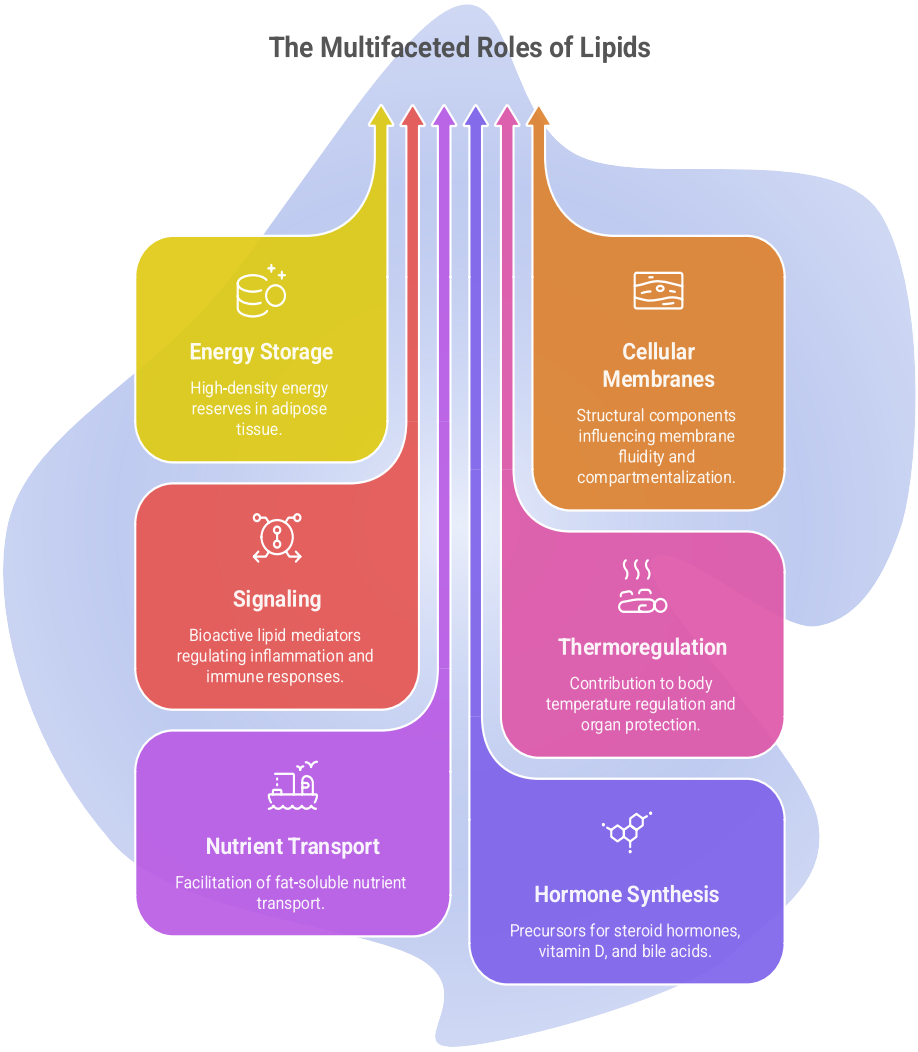



*Figure 39 The multifaceted roles of lipids in the body*

## The Exogenous Pathway: Intestinal Digestion, Absorption, and Transport of Dietary Lipids

The lipid cycle begins with the **exogenous pathway**, which involves the digestion and absorption of dietary lipids. Nutritional fats are mainly ingested as **triglycerides**, but also include cholesterol, phospholipids, and fat-soluble vitamins -The A-D-E-K Quatro (41). Because lipids are hydrophobic, dietary lipids undergo emulsification by bile acids secreted into the intestinal lumen. This step is essential because it increases the surface area available for enzymatic action. Pancreatic lipase then hydrolyzes triacylglycerols mainly into 2-monoacylglycerol and free fatty acids, while cholesterol esterase act on cholesterol esters to release free cholesterol and fatty acids (42). The resulting lipid products are incorporated into micelles, which facilitate their movement across the unstirred water layer to the brush border of enterocytes (43).

At the level of the intestinal epithelium, lipid uptake occurs through both passive diffusion and transporter-mediated mechanisms. Fatty acids may diffuse directly across the membrane, but protein-mediated uptake also plays a major role, particularly through CD36 (44), while intracellular trafficking is supported by fatty acid-binding proteins such as FABP1 and FABP2 (45,46). Cholesterol absorption is mediated predominantly by Niemann-Pick C1-like 1 protein (NPC1L1), the enterocyte target of ezetimibe, which internalizes cholesterol through an endocytic mechanism. An additional route of cholesterol uptake has also been proposed through scavenger receptor class B type I (SR-BI); however, the extent of its contribution to intestinal cholesterol absorption remains uncertain and appears to be less clearly established than that of NPC1L1 (47,48). At the same time, intestinal cells regulate sterol balance through the efflux transporters ABCG5 and ABCG8, which pump excess cholesterol and plant sterols back into the intestinal lumen, thereby limiting overabsorption (49).

Once inside the enterocyte, the absorbed lipids are transported to the endoplasmic reticulum, where they are re-esterified into more complex molecules. Triacylglycerol (Triglyceride) synthesis occurs primarily through the monoacylglycerol (MAG) pathway, in which monoacylglycerol acyltransferase (MAGT) and diacylglycerol acyltransferase (DAGT) sequentially convert 2-monoacylglycerol into triacylglycerol (50). Free cholesterol is esterified by ACAT2 to form cholesterol esters (CE), and phospholipid remodeling also takes place to generate structural components required for lipoprotein assembly (51). These intracellular processes restore the lipids to a form suitable for packaging and secretion.

The newly synthesized lipids are then incorporated into chylomicrons through a tightly regulated assembly process. Initially, a lipid-poor particle is formed around apolipoprotein B-48, with microsomal triglyceride transfer protein (MTTP) playing a central role in apoB-48 folding and early lipidation (52,53). This precursor particle subsequently acquires a larger triacylglycerol load to become a pre-chylomicron. The transport of these particles from the endoplasmic reticulum to the Golgi apparatus occurs via pre-chylomicron transport vesicles (PCTV) and represents a critical regulatory step in intestinal lipid export (54). Proteins such as SAR1B are required for this trafficking process, and their deficiency leads to impaired chylomicron secretion and intracellular lipid retention. Within the Golgi, additional maturation steps occur, including glycosylation of apoB-48 and the addition of apolipoprotein A-I, producing fully mature chylomicrons ready for secretion (52).

After maturation, chylomicrons are secreted across the basolateral membrane of enterocytes into the intercellular space and enter the lymphatic circulation through the central lacteals (55). They subsequently reach the bloodstream via the thoracic duct (48). In circulation, chylomicrons interact with lipoprotein lipase located on the capillary endothelium of adipose tissue and muscle. This enzyme hydrolyzes the triacylglycerols contained in chylomicrons, releasing free fatty acids that can either be oxidized for energy or stored in tissues. This process is facilitated by cofactors such as apolipoprotein C-II and apolipoprotein A-V (56). As chylomicrons progressively lose their triglyceride content, they are transformed into cholesterol-rich chylomicron remnants, which are then rapidly removed from the circulation by the liver through receptor-mediated uptake, notably involving LDL receptor-related protein 1 (LDLR1). In this way, the exogenous pathway ensures the efficient handling of dietary lipids from intestinal absorption to peripheral utilization and final hepatic clearance (57).

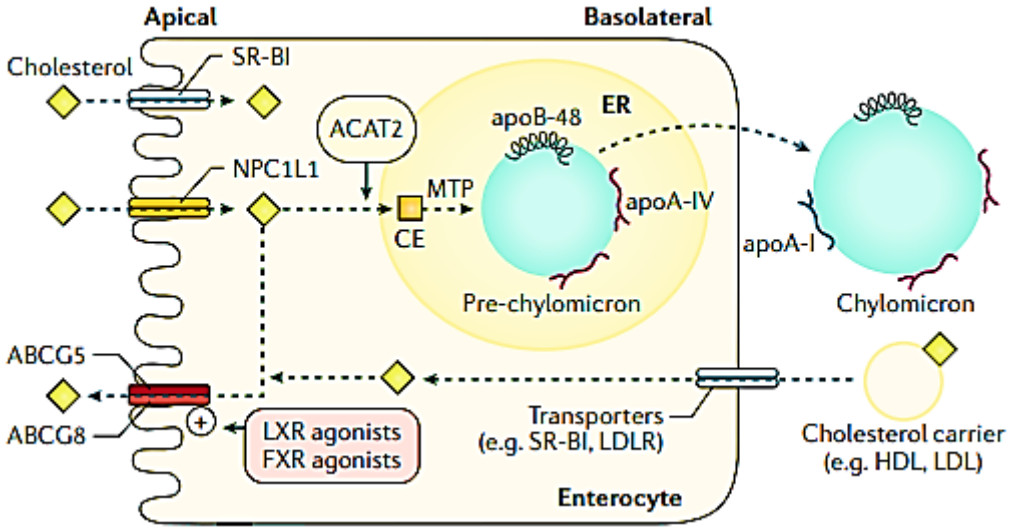



***Figure 40 Summary of intestinal cholesterol uptake and transport across the enterocyte*** *(58). Cholesterol present in the intestinal lumen is absorbed at the apical membrane of enterocytes primarily through NPC1L1, with possible contribution from SR-BI. Once internalized, part of the free cholesterol is esterified by acyl-CoA:cholesterol acyltransferase 2 (ACAT2) to form cholesteryl esters (CE) in the endoplasmic reticulum. These lipids are then assembled with apolipoprotein B-48 (apoB-48) through the action of microsomal triglyceride transfer protein (MTP), leading to the formation of pre-chylomicrons, which subsequently mature into chylomicrons and are secreted from the basolateral side into the circulation. In addition to absorption, cholesterol can also undergo intestinal excretion. The transporters* ***ABCG5*** *and* ***ABCG8*** *promote sterol efflux and contribute to* ***transintestinal cholesterol excretion (TICE)****, a pathway through which cholesterol derived from the plasma is taken up at the basolateral membrane and secreted back into the intestinal lumen. This process can be stimulated by* ***liver X receptor (LXR)*** *and* ***farnesoid X receptor (FXR)*** *agonists. Overall, the small intestine has a dual role in cholesterol homeostasis, participating in both cholesterol absorption and cholesterol elimination.*

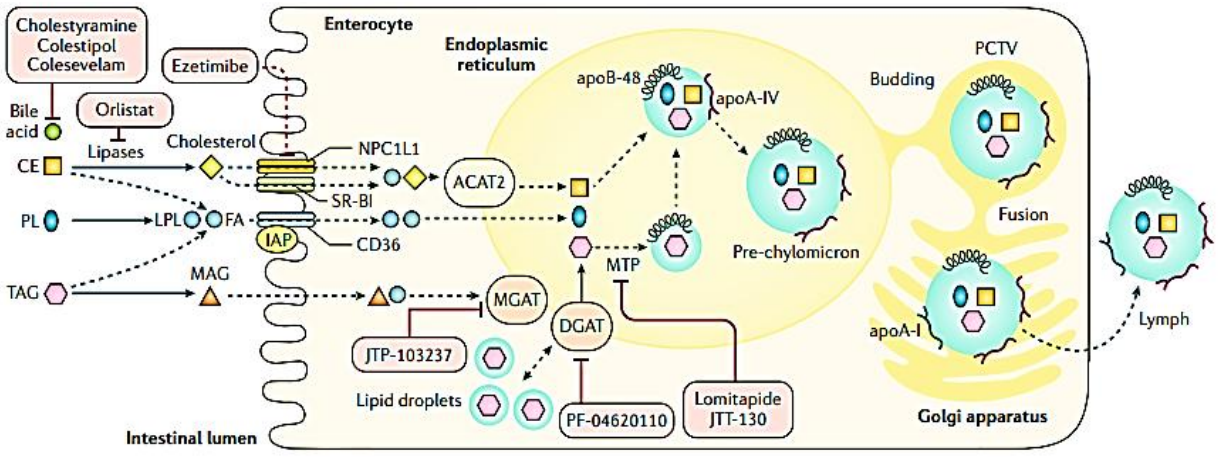



***Figure 41 Intestinal lipid uptake, intracellular processing, and chylomicron assembly in enterocytes*** *(58).* *Dietary lipids, including triacylglycerols (TAGs), cholesteryl esters (CE), and phospholipids (PL), together with biliary lipids, are hydrolyzed within the intestinal lumen by digestive enzymes into fatty acids (FA), monoacylglycerols (MAG), cholesterol, and lysophospholipids. Cholesterol is taken up predominantly through Niemann-Pick C1-like 1 (NPC1L1), whereas fatty acid uptake is facilitated in part by transporters such as CD36 and SR-BI. Within the enterocyte, absorbed lipids are re-esterified by key enzymes including* ***acyl-CoA:cholesterol acyltransferase 2 (ACAT2)****,* ***monoacylglycerol acyltransferase (MGAT)****, and* ***diacylglycerol acyltransferase (DGAT)*** *to regenerate cholesteryl esters and triacylglycerols. These lipids are then combined with* ***apolipoprotein B-48 (apoB-48)*** *through the action of* ***microsomal triglyceride transfer protein (MTP)*** *to form* ***pre-chylomicrons*** *in the endoplasmic reticulum. A fraction of intracellular lipids may also be temporarily stored in* ***cytoplasmic lipid droplets****. Pre-chylomicrons are subsequently transported to the Golgi apparatus by* ***pre-chylomicron transport vesicles (PCTV)****, where they undergo maturation before being secreted from the basolateral membrane as mature* ***chylomicrons****. These lipoprotein particles then enter the* ***lymphatic circulation****, which constitutes the principal route for the transport of dietary lipids from the intestine to the systemic circulation. The figure also highlights several pharmacological inhibitors that target intestinal lipid absorption and chylomicron formation.*

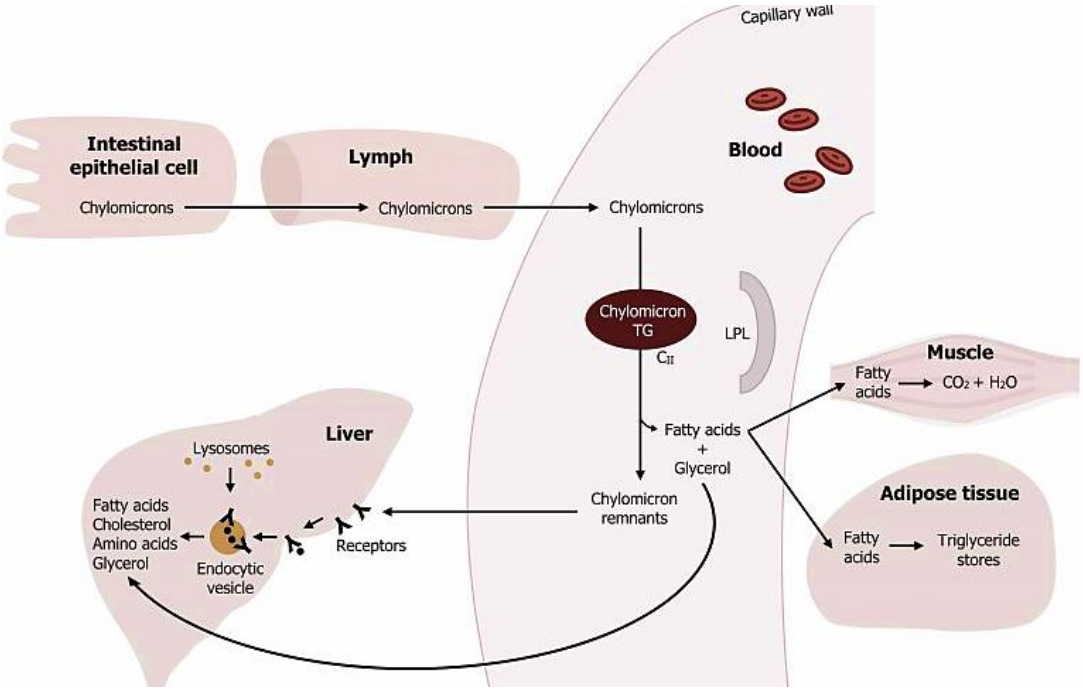



***Figure 42 Overview of the Exogenous Lipid Pathway*** *(59).* *Adapted from LeClair RJ. Lipoprotein metabolism and cholesterol synthesis. In: Cell Biology, Genetics, and Biochemistry for Pre-Clinical Students. Virginia Tech; 2021.*

The Endogenous Pathway: Hepatic Lipid Synthesis and Redistribution

In contrast to the exogenous pathway, which handles dietary lipids through **chylomicrons**, the endogenous pathway primarily relies on **very-low-density lipoproteins (VLDL)** to distribute liver-derived triglycerides and cholesterol throughout the body (60,61).

This process begins in the liver, the principal site of endogenous lipid synthesis, where hepatocytes produce both **cholesterol** and **triglycerides**. Approximately **80% of** circulating cholesterol originates from endogenous hepatic synthesis, in which the statins target, **3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase, HMGCR)** catalyzes the rate-limiting step (62,63). At the same time, triglycerides are synthesized from free fatty acids and glycerol within hepatocytes (61).

These newly formed lipids are then packaged into nascent **VLDL particles**, which serve as the principal form of transport for endogenous triglycerides (60,61). This assembly depends on **microsomal triglyceride transfer protein (MTTP)**, which facilitates the incorporation of triglycerides and cholesterol esters into the lipoprotein particle (64). Each VLDL particle contains a single molecule of **apolipoprotein B-100**, which provides structural stability and later serves as a ligand for receptor-mediated interactions (65).

Once secreted into the bloodstream, VLDL particles circulate toward peripheral tissues, particularly **skeletal muscle**, **cardiac muscle**, and **adipose tissue**. As they pass through the capillary bed, they encounter **lipoprotein lipase (LPL)**, an enzyme anchored to the endothelial surface. They get secured to the endothelial surface by GPIHBPI, this action initiates hydrolyzation of triglycerides contained within the VLDL core and releases **free fatty acids** and glycerol (66). These free fatty acids are then taken up by peripheral tissues according to their metabolic requirements. In muscle, they are primarily oxidized to generate energy, whereas in adipose tissue they are re-esterified and stored as triglycerides (66).

As VLDL progressively loses its triglyceride content, the particle becomes smaller and denser, transforming into **intermediate-density lipoprotein (IDL)**, which contains intermediate proportions of triglycerides and cholesterol. This remodeling continues in the circulation, where **hepatic lipase (HL)** further hydrolyzes the remaining triglycerides, while **cholesteryl ester transfer protein (CETP)** mediates lipid exchange between lipoproteins. Through this process, IDL acquires **cholesteryl esters** from **high-density lipoproteins (HDL)** in exchange for triglycerides, leading to progressive enrichment of the particles in cholesterol. As a result of these combined modifications, IDL is converted into **low-density lipoprotein (LDL)**, which is relatively poor in triglycerides but rich in cholesterol esters and therefore serves as the principal lipoprotein responsible for delivering cholesterol to peripheral tissues (67).

The final major stage of the endogenous pathway involves the clearance of circulating LDL particles, particularly by the liver. LDL binds to **LDL receptors (LDLRs)** expressed on the surface of hepatocytes through recognition of **apo B-100**, initiating receptor-mediated endocytosis and cellular uptake of the lipoprotein. Approximately 70% of LDL is removed from the circulation through this hepatic pathway (67). Once internalized, the particle is delivered to lysosomes, where **lysosomal**

**acid lipase (LAL)** hydrolyzes cholesterol esters to release **free cholesterol** for cellular use (68). Under normal conditions, LDL receptors are then recycled back to the plasma membrane to continue clearing LDL from the bloodstream. However, this recycling process can be disrupted by **PCSK9**, a protein that promotes LDL receptor degradation and thereby reduces hepatic LDL clearance (69,70).

The endogenous pathway is also subject to precise intracellular and hormonal regulation to maintain lipid homeostasis. One key regulatory molecule is **malonyl-CoA**, an intermediate of fatty acid synthesis that inhibits **carnitine palmitoyl transferase I (CPT1)**, thereby preventing the newly synthesized fatty acids from entering mitochondria for β-oxidation. This ensures that lipid synthesis and lipid degradation do not occur simultaneously (71). In addition, **insulin** acts as a major stimulator of hepatic lipogenesis, promoting the synthesis, storage, and export of endogenous lipids during the fed state, when energy availability is high. In this way, the endogenous pathway constitutes a coordinated system through which the liver synthesizes, packages, distributes, and regulates lipids in accordance with the metabolic needs of the organism.

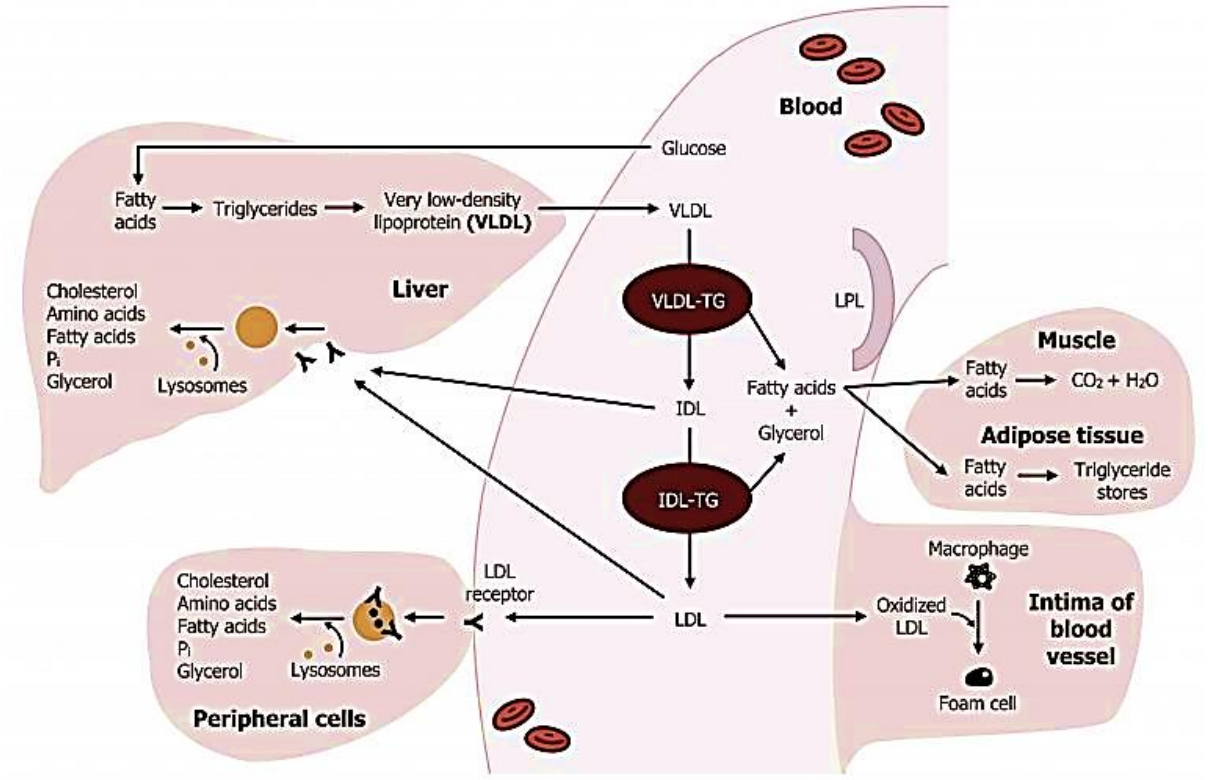



***Figure 43 Overview of the endogenous pathway*** *(59). Adapted from LeClair RJ. Lipoprotein metabolism and cholesterol synthesis. In: Cell Biology, Genetics, and Biochemistry for Pre-Clinical Students. Virginia Tech; 2021.*

## Lipid Catabolism: Mitochondrial Beta-Oxidation and ATP Production

Lipid catabolism within the cell is a tightly coordinated process that enables the generation of energy, mainly in the form of ATP, from two principal sources: lipids taken up from the extracellular environment and neutral lipids stored within cytosolic lipid droplets (CLDs) (72–74). These pathways converge toward the production of fatty acid–derived substrates that can be oxidized to meet cellular energy demands.

Extracellular lipids enter the cell through two major mechanisms. The first involves the uptake of intact lipoprotein particles, particularly low-density lipoproteins (LDL), which are internalized via the LDL receptor through receptor-mediated endocytosis (75,76). Once inside the cell, these particles are delivered to lysosomes, where lysosomal acid hydrolase (LAH), including lysosomal acid lipase (LAL), degrade their components. Cholesteryl esters (CE) are thereby hydrolyzed into free cholesterol, which can subsequently be redistributed to intracellular compartments such as the endoplasmic reticulum for the regulation of cellular sterol homeostasis (69). The second mechanism involves the uptake of free fatty acids released in the circulation following intravascular lipolysis (75,76). In capillary beds, lipoprotein lipase hydrolyzes triglycerides contained in chylomicrons (CM) and very-low-density lipoproteins (VLDL), liberating free fatty acids (FFA) that are then taken up by parenchymal cells through transport proteins such as CD36 and fatty acid transport proteins (53,58). Once internalized, these fatty acids are activated into acyl-CoA derivatives and are either directed toward oxidative pathways or re-esterified for storage.

Intracellular lipid stores are mainly contained within cytosolic lipid droplets, which consist of a neutral lipid core rich in triacylglycerols and cholesteryl esters, surrounded by a phospholipid monolayer (58,75). When cellular energy demand increases, these reserves are mobilized through two complementary pathways. The first is neutral lipolysis, a stepwise cytosolic process initiated by adipose triglyceride lipase and its co-activator CGI-58, which hydrolyze triacylglycerols into diacylglycerols and free fatty acids (58,77). This degradation is subsequently completed by hormone-sensitive lipase and monoacylglycerol lipase, resulting in the release of glycerol and additional fatty acids (58). The second pathway is lipophagy, a form of autophagy in which portions of lipid droplets are sequestered into autophagosomes and delivered to lysosomes. Within the autolysosome, lysosomal acid lipase hydrolyzes stored lipids into free fatty acids and unesterified cholesterol, which may then enter cellular metabolic pathways (78).

Regardless of their origin, fatty acids destined for energy production must undergo beta-oxidation. Long-chain fatty acids are first activated in the cytosol and then transported into the mitochondrial matrix through the carnitine shuttle, in which carnitine palmitoyl transferase 1 (CPT1) plays a central role by converting fatty acyl-CoA into fatty acylcarnitine. This step constitutes a major regulatory point in lipid catabolism. Once inside the mitochondria, fatty acids undergo successive four-step cycle of beta-oxidation, each consisting of dehydrogenation, hydration, a second dehydrogenation, and thiolytic cleavage (79). These reactions generate acetyl-CoA, NADH, and FADH2 (64). Acetyl-CoA enters the tricarboxylic acid cycle, while NADH and FADH2 provide electrons to the respiratory chain in the inner mitochondrial membrane, thereby supporting oxidative phosphorylation and ATP synthesis (40).

The balance between lipid storage and lipid oxidation is under strict metabolic regulation. Malonyl-CoA, an intermediate of fatty acid synthesis, acts as a potent inhibitor of carnitine palmitoyl transferase 1 and therefore prevents mitochondrial fatty acid entry when energy supply is sufficient and lipogenesis is active (71). Conversely, under conditions of low cellular energy, AMP-activated protein kinase is activated and reduces malonyl-CoA levels, thereby relieving the inhibition of carnitine palmitoyl transferase 1 and promoting lipid catabolism.

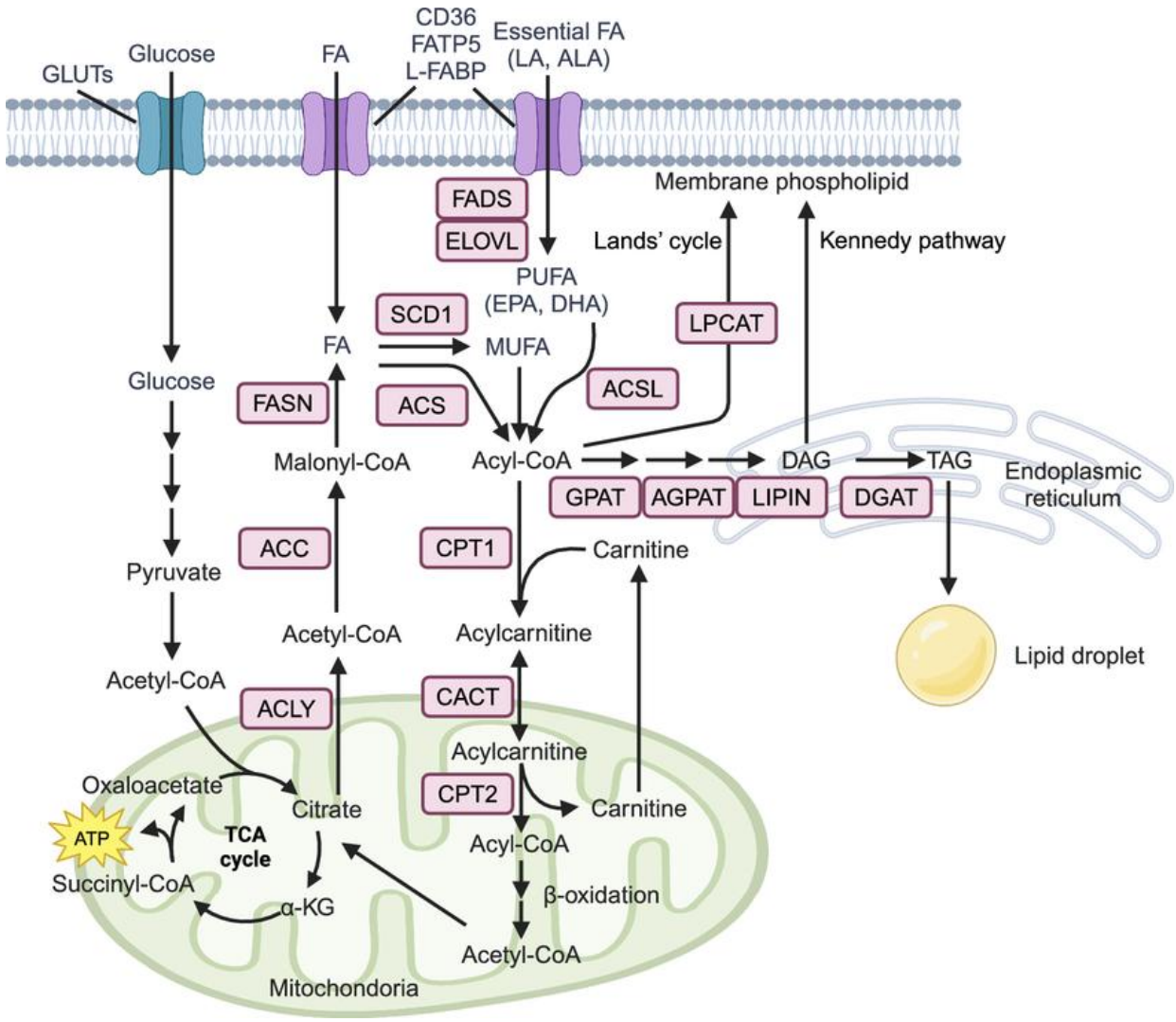



***Figure 44 Integrated intracellular fatty acid metabolism: uptake, synthesis, desaturation, storage, membrane remodeling, and mitochondrial β-oxidation*** *(80).*

*FA, fatty acid; GLUT, glucose transporter; L-FABP, liver fatty acid-binding protein; ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; ACS, acyl-CoA synthetase; CPT1A, carnitine palmitoyl transferase 1A; CPT2, carnitine palmitoyl transferase 2; CACT, carnitine acylcarnitine translocase; SCD1, stearoyl-CoA desaturase 1; FADS, fatty acid desaturases; ELOVL, elongation of very long-chain fatty acids; LPCAT, lysophosphatidylcholine acyltransferase; GPAT, glycerol-3-phosphate acyltransferase; AGPAT, acylglycerol phosphate acyltransferase; MUFA, monounsaturated fatty acid; DGAT, diacylglycerol acyltransferase; DAG, diacylglycerol; TAG, triacylglycerol.*

## Reverse Cholesterol Transport: HDL and Cholesterol Clearance

Reverse cholesterol transport (RCT) is a coordinated pathway through which excess cholesterol is removed from peripheral tissues, particularly from macrophage-derived foam cells within the arterial wall, and returned to the liver for metabolism and eventual excretion. This mechanism is regarded as anti-atherogenic because it limits cholesterol accumulation within the vasculature (67).

The process begins with the synthesis and secretion of apolipoprotein A-I (ApoA-I) by the liver and small intestine, the structural protein of HDL. Newly secreted ApoA-I is initially lipid-poor, commonly referred to as pre-β HDL, and the first lipids it accepts are from cholesterol and phospholipids efflux from hepatocytes and enterocytes (81). Once HDL particles, gains circulation and through interaction with the membrane transporter ABCA1 and ABCG1presented in the peripheral cells, free cholesterol and phospholipids are transferred also to ApoA-I, leading to the formation of nascent discoidal HDL particles (ND-HDL).

As these nascent HDL particles circulate, they undergo maturation through the action of lecithin-cholesterol acyltransferase (LCAT), an enzyme activated by ApoA-I. LCAT esterifies free cholesterol present on the HDL surface into cholesteryl esters, which, because of their hydrophobic nature, migrate into the core of the particle. This remodeling converts discoidal HDL into mature spherical HDL. These mature particles can then acquire additional cholesterol from peripheral cells through several mechanisms, including ABCG1-mediated transport, scavenger receptor class B type I (SR-BI), and passive diffusion (67).

Once loaded with cholesteryl esters, HDL delivers cholesterol to the liver through two main routes. In the direct pathway, HDL binds to hepatic SR-BI, allowing selective uptake of cholesteryl esters into hepatocytes without degradation of the entire HDL particle. In the indirect pathway, cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoproteins, mainly VLDL and LDL, in exchange for triglycerides. These cholesterol-enriched lipoproteins are subsequently cleared by the liver via the LDL receptor and subsequently metabolized by lipases when necessary.

The final stage of RCT is cholesterol elimination. Because the sterol nucleus cannot be degraded by human cells, hepatic cholesterol must be excreted either after conversion into bile acids or by direct secretion into bile as free cholesterol through the ABCG5/ABCG8 transporter complex (67). The cholesterol delivered into bile ultimately reaches the intestine and is excreted in the feces. In addition to this classical biliary route, transintestinal cholesterol excretion (TICE) has emerged as an important non-biliary pathway, whereby cholesterol derived from plasma lipoproteins is taken up by enterocytes and directly secreted into the intestinal lumen. This pathway appears to be regulated, at least in part, by nuclear receptors such as LXR and FXR (82).

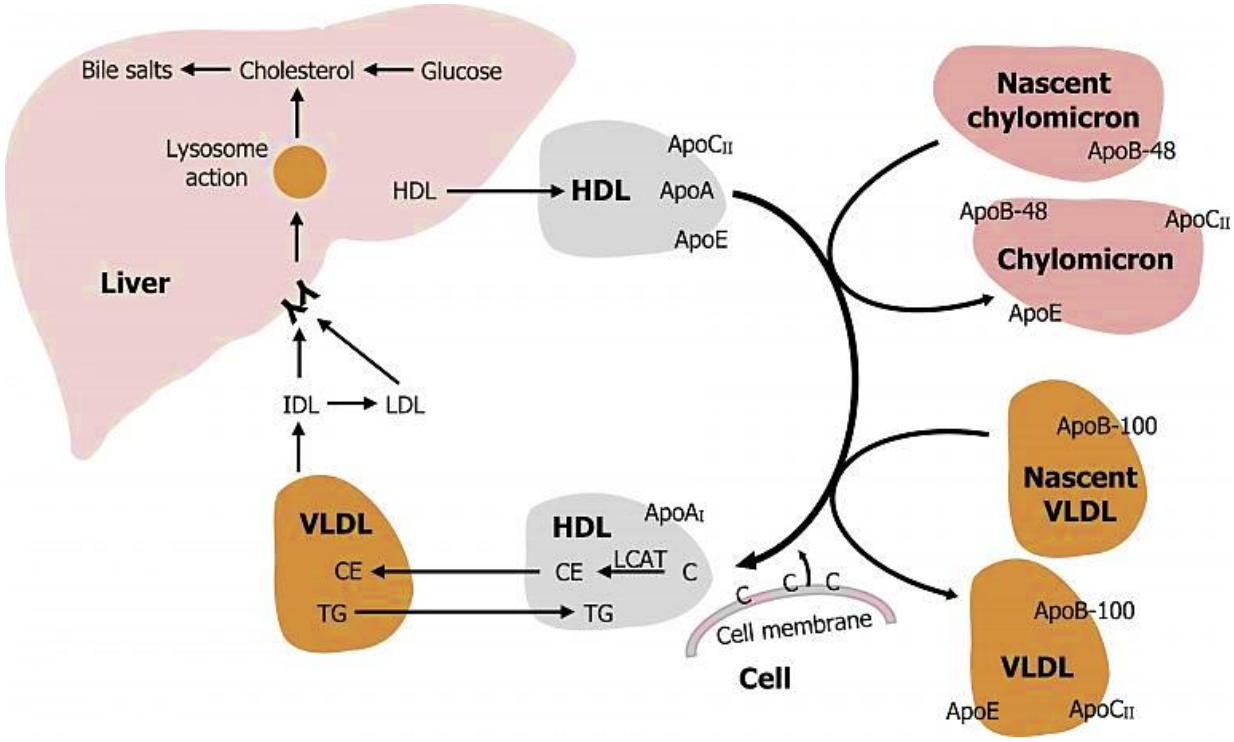



***Figure 45 Overview of HDL Metabolism and Reverse Cholesterol Transport*** *(59)**. Adapted from LeClair RJ. Lipoprotein metabolism and cholesterol synthesis. In: Cell Biology, Genetics, and Biochemistry for Pre-Clinical Students. Virginia Tech; 2021.*

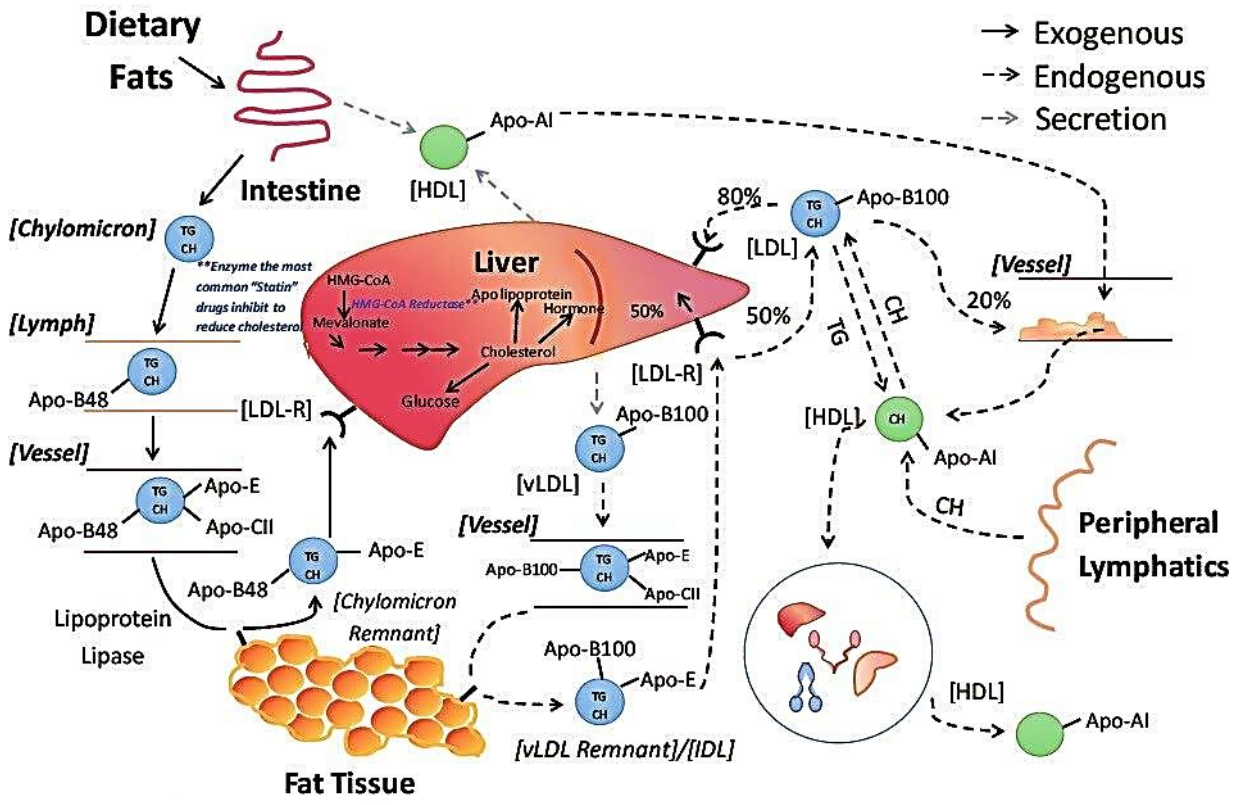



***Figure 46 Overview of Lipid Metabolism: Exogenous and Endogenous Lipoprotein Transport Pathways*** *(83).*
*This figure summarizes the major pathways of lipid metabolism by illustrating both the exogenous and endogenous routes of lipoprotein transport. The exogenous pathway begins in the intestine, where dietary lipids are packaged into chylomicrons containing apolipoprotein B48 (Apo-B48). These particles enter the lymphatic circulation and then the bloodstream, where triglycerides are hydrolyzed by lipoprotein lipase, allowing fatty acid delivery to adipose tissue. The resulting chylomicron remnants are subsequently taken up by the liver. The endogenous pathway is centered in the liver, where cholesterol is synthesized through the mevalonate pathway under the control of HMG-CoA reductase and incorporated, together with triglycerides, into very-low-density lipoproteins (VLDL) containing apolipoprotein B100 (Apo-B100). As VLDL particles circulate, they progressively lose triglycerides and are converted into intermediate-density lipoproteins (IDL) and then low-density lipoproteins (LDL), which are relatively rich in cholesterol. LDL delivers cholesterol to peripheral tissues, while a substantial proportion is also cleared by hepatic LDL receptors. Excess LDL cholesterol may contribute to lipid deposition within the vascular wall.*

## 2.2. Overview of Dyslipidemia

### Definition of dyslipidemia and clinical importance:

Dyslipidemia refers to a heterogeneous group of disorders characterized by abnormal concentrations of circulating lipids and lipoproteins in the blood (10).

These abnormalities may present as elevated total cholesterol (TC), increased low-density lipoprotein cholesterol (LDL-C), elevated triglycerides (TG), reduced high-density lipoprotein cholesterol (HDL-C), or various combinations of these alterations (84).

Its recognition and management are of major clinical importance because dyslipidemia constitutes one of the principal modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD) (10).

In particular, a large body of evidence has demonstrated that cholesterol transported by apolipoprotein B-containing lipoproteins, especially LDL-C, plays a causal role in atherogenesis by promoting arterial wall inflammation and plaque formation, which underlie most major cardiovascular events (85). As the atherosclerotic process often begins early in life and progresses silently over many years, dyslipidemia remains a central target of preventive strategies aimed at reducing long-term cardiovascular morbidity and mortality (86).

### Dyslipidemia Classification

Dyslipidemia is clinically classified into two primary categories based on its underlying etiology: primary and secondary forms(3).

**Primary dyslipidemia** is fundamentally **inherited** and arises from specific **genetic mutations** that disrupt the synthesis, transport, or clearance of lipoproteins, as seen in conditions such as familial hypercholesterolemia or familial chylomicronemia syndrome.

In contrast, **secondary dyslipidemia** is defined as an **acquired** condition resulting from modifiable lifestyle factors or underlying medical conditions that perturb lipid metabolism. Identifying these secondary causes is critical, as correcting the underlying factor can often markedly improve or even resolve the lipid abnormality. Common medical conditions known to induce secondary dyslipidemia include **diabetes mellitus**, **obesity**, **hypothyroidism**, and **liver disease** (including obstructive or cholestatic forms). Furthermore, renal-specific pathologies such as **chronic kidney disease** and **nephrotic syndrome** are significant contributors to acquired derangements, often manifesting as impaired clearance of triglyceride-rich lipoproteins or elevated low-density lipoprotein cholesterol. Behavioral factors, including a **sedentary lifestyle** (physical inactivity) and excessive **alcohol use**, along with the administration of **certain medications**—such as glucocorticoids, thiazide diuretics, oral estrogens, and immunosuppressive agents like cyclosporine—further exacerbate these metabolic disturbances.

## Lipid threshold

In clinical practice and epidemiological research, lipid abnormalities are commonly classified using standardized biochemical thresholds, particularly those established by the **National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)**. These cutoffs provide a consistent framework for categorizing lipid parameters according to their clinical significance and cardiovascular risk. Total cholesterol is considered desirable at <200 mg/dL, LDL-C ranges from optimal (<100 mg/dL) to very high (≥190 mg/dL), HDL-C is defined as low at <40 mg/dL, and triglycerides are classified from normal (<150 mg/dL) to very high (≥500 mg/dL). Although these thresholds are essential for descriptive classification in research, current guidelines recommend that treatment decisions should be based on the patient's overall ASCVD risk rather than on lipid concentrations alone.

*Table 42 Classification of Lipid Levels (mg/dL) According to NCEP ATP III*

| Lipid Parameter | Category | Threshold (mg/dL) |
|---|---|---|
| **LDL Cholesterol** | Optimal | <100 |
| | Near or above optimal | 100–129 |
| | Borderline high | 130–159 |
| | High | 160–189 |
| | Very high | ≥190 |
| **Total Cholesterol** | Desirable | <200 |
| | Borderline high | 200–239 |
| | High | ≥240 |
| **HDL Cholesterol** | Low | <40 |
| | High | ≥60 |
| **Triglycerides** | Normal | <150 |
| | Borderline high | 150–199 |
| | High | 200–499 |
| | Very high | ≥500 |

# 3. Epidemiology and Burden

## 3.1. Burden of CKD

❖ **Worldwide**

Chronic kidney disease (CKD) has emerged as a major global public health challenge because of its high prevalence, increasing mortality, and substantial contribution to disability-adjusted life years (DALYs) (87–90). It is defined by persistent abnormalities of kidney structure or function lasting at least 90 days, and it often remains asymptomatic until the disease has reached advanced stages (87).

The global burden of CKD continues to rise in terms of both premature mortality and long-term disability. According to the Global Burden of Disease study, CKD was responsible for nearly 1.2 million deaths worldwide in 2017, ranking as the 12th leading cause of death globally; by 2019, this number had increased to approximately 1.4 million deaths, making CKD the 11th leading cause of mortality (88,90). In parallel, the burden measured in DALYs also increased markedly, from 35.8 million in 2017 to 41.5 million in 2019 (88,90). Projections further suggest that CKD may become the fifth leading cause of years of life lost worldwide by 2040 (87).

In terms of prevalence, CKD affects more than 10% of the global population and is estimated to involve more than 800 million individuals worldwide (87,89). Global estimates for 2017 reported approximately 697.5 million cases, corresponding to a prevalence of 9.1% (89). However, prevalence estimates vary according to study methodology, diagnostic criteria, and the inclusion of early disease stages. A large systematic review and meta-analysis by Hill NR, et al reported a pooled global prevalence of 13.4% for CKD stages 1–5 and 10.6% for stages 3–5 (89). Across disease stages, prevalence has been estimated at approximately 3.5% for stage 1, 3.9% for stage 2, 7.6% for stage 3, 0.4% for stage 4, and 0.1% for stage 5, with stage 3 representing the largest proportion of cases (89). Marked geographic disparities have also been described, with a higher prevalence often observed in low- and middle-income countries, where healthcare systems are frequently less equipped to manage the disease burden and its complications (87,89,90).

Important demographic disparities are also observed in CKD epidemiology. Prevalence increases steadily with age and is particularly high among older adults. It has been estimated that approximately 34.3% of individuals over 70 years of age are affected by CKD at any stage (87,89). In several regions, the majority of CKD incidence and DALYs are concentrated in the 55–74-year age group (90). Sex-related differences are similarly well documented. Most epidemiological studies indicate that CKD is more prevalent in women than in men, with age-standardized prevalence estimates of 9.5% in females compared with 7.3% in males. Nevertheless, men tend to have higher mortality rates and faster progression to end-stage kidney disease (ESKD), a discrepancy that may be explained by biological factors, including possible protective effects of estrogen, as well as by differences in lifestyle, health-seeking behavior, and access to care (87,88).

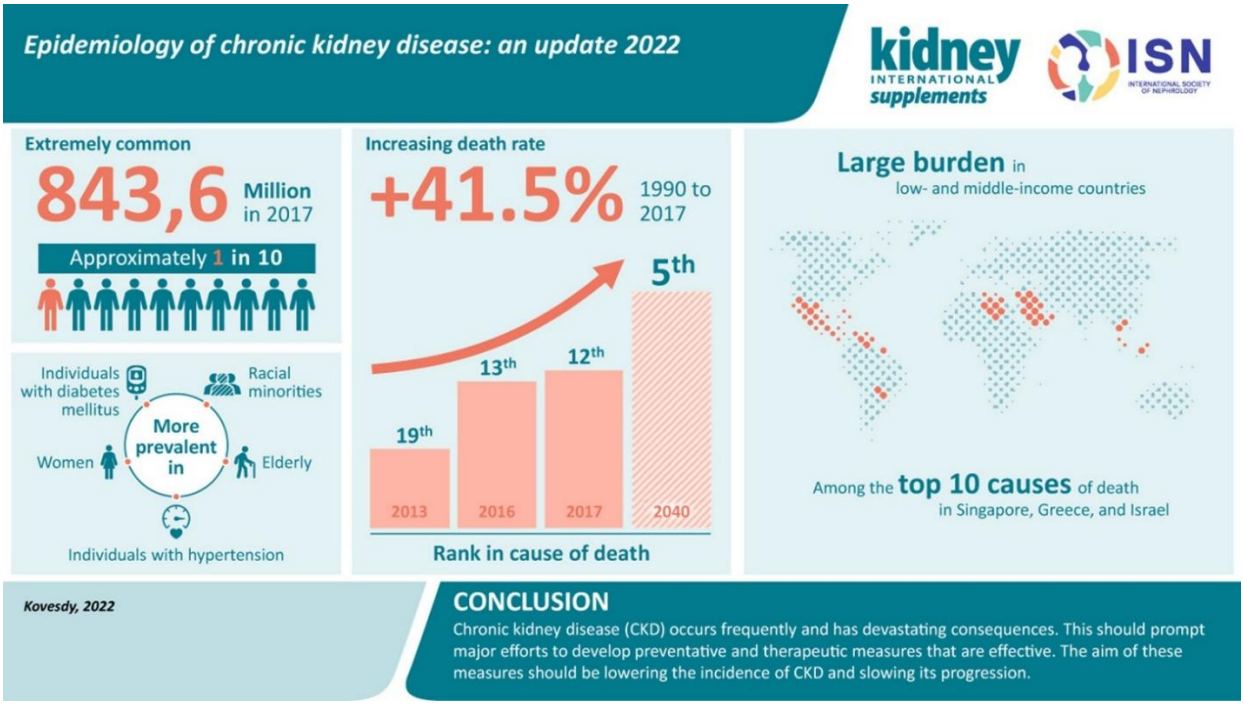



*Figure 47 prevalence of chronic kidney disease, with its mortality index and ranking (87).*

❖ **Continental and regional Comparisons**

The epidemiology of chronic kidney disease (CKD) varies considerably across continents, reflecting differences in socioeconomic development, healthcare infrastructure, access to screening and renal replacement therapy, and the distribution of major risk factors such as diabetes, hypertension, obesity, and infectious diseases (87,88,90).

In Africa, CKD represents a major and heterogeneous public health challenge. According to Hill NR, et al study, it estimated the overall prevalence of CKD on the continent at 15.8% for all stages and 4.6% for stages 3–5, with marked regional disparities between sub-Saharan Africa (17.7%) and North Africa (6.1%) (91). This contrast may be explained by differences in demographic structure, epidemiological transition, detection practices, and methodological variability between studies. Despite the comparatively lower prevalence observed in North Africa, the broader North Africa and Middle East region (NAME region) has been reported to have a particularly high age-standardized incidence of CKD recorded at 447.48 per 100,000 population in 2019, predominantly caused by metabolic and vascular risk factors in this area (90). In sub-Saharan Africa, CKD-related mortality remains disproportionately high, in large part because limited access to dialysis and kidney transplantation is associated with poor survival among patients with kidney failure (91).

In Asia, the burden of CKD is magnified by the very large populations of China and India, which together account for nearly one-third of global CKD cases (87,88). Regional estimates suggest a prevalence of approximately 13.18% for CKD stages 1–5 in East Asia and 13.74% in high-income Asia-Pacific countries such as Japan and South Korea (89). The increase in diabetes, hypertension, population ageing, and urbanization has contributed substantially to the growing CKD burden across Asian populations.

In North America, CKD prevalence is also high, particularly in the setting of widespread cardiometabolic risk factors. High-income North America has been reported to have an age-

standardized incidence rate of 310.44 per 100,000 population, while the prevalence of CKD stages 1–5 in the United States and Canada has been estimated at 15.45% (89,90). In the United States specifically, prevalence increased from 11.8% in the early 1990s to 14.2% by 2016, illustrating the sustained rise in CKD burden over time (87).

In Europe, some meta-analytic estimates suggest one of the highest reported prevalences of CKD stages 1–5, reaching 18.38%, while the prevalence of stages 3–5 is estimated at 11.86% (89). Nevertheless, Western Europe continues to exhibit relatively low age-standardized mortality and disability-adjusted life year (DALY) rates compared with many other world regions, likely reflecting stronger healthcare systems, earlier diagnosis, and broader access to nephrological care and renal replacement therapy (88,90).

Overall, these continental differences indicate that the burden of CKD is not determined solely by prevalence, but also by the capacity of health systems to ensure prevention, early detection, and long-term management. Thus, some regions with moderate prevalence may still experience a high mortality burden when access to care remains limited, whereas other regions with high prevalence may achieve better outcomes through more effective healthcare delivery (87,88,90).

- **Morocco:**

Chronic kidney disease (CKD) constitutes an important and growing public health concern in Morocco, in the context of demographic and epidemiological transition characterized by population ageing, progressive urbanization, and the increasing prevalence of non-communicable diseases, particularly hypertension and diabetes mellitus (92,93). This burden is reflected not only in the rising number of affected individuals, but also in the substantial medical, social, and economic consequences associated with advanced kidney disease (92,93).

The burden of CKD in Morocco is particularly evident in patients with end-stage renal disease (ESRD). National estimates suggest an annual incidence of ESRD ranging between 50 and 100 cases per million population, corresponding to approximately 1,650 to 3,300 new cases per year (93). In addition, a recent study from the Rabat-Salé-Kénitra region reported an incidence of 27% and a mortality rate of 15.7% among patients undergoing hemodialysis, underlining the severity of the disease in its advanced stages (92). The economic impact is also considerable, as ESRD management consumes a disproportionate share of healthcare resources; it has been estimated that nearly 12% of total health expenditure is allocated to dialysis, despite ESRD patients representing only a small fraction of the population receiving care. Furthermore, Moroccan patients initiating hemodialysis often present with a substantial burden of comorbidities, including hypertension in 62% of cases, ischemic heart disease in 12.5%, and hepatopathy in 8.4% (93).

The prevalence of CKD in Morocco varies according to the study setting and the population under investigation. In the general population, the MAREMAR study reported an overall CKD prevalence of 6.6% in crude estimates and 2.9% after adjustment to the Moroccan population structure, suggesting that approximately 957,000 individuals may be living with CKD nationwide (93). In rural settings, a study conducted in agricultural communes of the Fez-Meknes region found a prevalence of 6.5%, indicating that CKD is also highly relevant outside urban centers (94). With

regard to disease staging, available rural data suggest that stage 3 CKD is the most frequent category, accounting for 46.4% of identified cases, including 38.2% in stage 3a and 7.14% in stage 3b. By comparison, stage 1 represented 32.1% of cases and stage 2 accounted for 21.4%, whereas stages 4 and 5 were reported much less frequently in population-based screening studies (94). This distribution suggests that a substantial proportion of Moroccan patients are identified at a moderately advanced stage of renal impairment.

CKD in Morocco also demonstrates important demographic disparities according to sex and age. In line with international data, prevalence tends to be higher among women in population-based estimates; however, hospital-based and dialysis cohorts often report a predominance of men among patients receiving renal replacement therapy (90,95). For example, a clinical series from the Military Hospital in Rabat found that men represented 64% of patients with ESRD, compared with 36% for women (95). This discrepancy may reflect differences in disease progression, healthcare access, referral patterns, or treatment uptake between the sexes. In addition, hypertension, one of the principal drivers of CKD, appears to be more prevalent among Moroccan women than men, with reported rates of 37.0% and 30.2%, respectively (93).

Age is another major determinant of CKD burden in Morocco. Prevalence increases markedly with advancing age, as shown in the MAREMAR study, where CKD affected only 0.5% of individuals aged 26–40 years, but rose to 6.6% among those aged 56–70 years (93). Similarly, rural screening data demonstrated a prevalence of 10.9% in individuals aged 60 years and older (94)[2]. In patients with advanced disease, the weight of older age is even more pronounced; in the Rabat-Salé-Kénitra region, 73.3% of hemodialysis patients were aged 65 years or older. These findings confirm that CKD in Morocco is strongly age-related and is likely to become an even greater healthcare challenge as population ageing continues (92,93).

## 2.2. Burden of dyslipidemia

- **Globally:**

The global epidemiology of dyslipidemia, defined by abnormal levels of total cholesterol, LDL-cholesterol, triglycerides, and/or HDL-cholesterol, is marked by a major epidemiological transition. Over the past four decades, many high-income Western countries have experienced substantial declines in plasma total cholesterol and non-HDL-cholesterol, whereas several low- and middle-income regions have shown rising lipid levels in parallel with rapid urbanization, dietary change, and broader lifestyle transitions (96,97).

In Africa, dyslipidemia is increasingly recognized as an important public health issue. A meta-analysis of 177 studies including 294,063 participants reported pooled prevalences of 25.5% for elevated total cholesterol, 28.6% for elevated LDL-cholesterol, 37.4% for low HDL-cholesterol, and 17.0% for hypertriglyceridemia, with low HDL-cholesterol being the most frequent abnormality. The same review showed that dyslipidemia tends to be more common in urban than rural settings and is more frequent among individuals with diabetes, hypertension, or HIV (98). In Morocco, recent STEPS-based data reported a hypercholesterolemia prevalence of 13.0%, with rates of 14.2% in men and 12.6% in women (99).

In Europe, the burden remains high despite major improvements. WHO estimates cited in the reviewed literature indicated that Europe had the highest prevalence of raised total cholesterol in 2008, at approximately 53.7% (100). Western Europe has since recorded reductions of about 1 mmol/L in both total cholesterol and non-HDL-cholesterol over the past four decades, accompanied by marked declines in ischemic heart disease mortality. However, a clear east-west divide persists, with Central and Eastern Europe continuing to show high dyslipidemia prevalence and cardiovascular mortality. In Poland, for example, 77.2% of adults were reported to have dyslipidemia, while 67% had hypercholesterolemia (96).

In high-income North America, plasma lipid levels have also declined substantially since 1980. In men, mean total cholesterol fell from 5.67 to 4.72 mmol/L and non-HDL-cholesterol from 4.43 to 3.46 mmol/L; in women, the corresponding declines were from 5.71 to 4.81 mmol/L and from 4.24 to 3.29 mmol/L . These trends have paralleled reductions in cardiovascular mortality and reflect, at least in part, the contribution of lipid-lowering therapy, particularly statins (96,97).

Asia shows marked regional heterogeneity. East and Southeast Asia have experienced substantial increases in total cholesterol and non-HDL-cholesterol since 1980, with the burden increasingly shifting toward developing countries in these regions (97). In China, surveys have reported prevalences of 12.2% for high total cholesterol, 17.9% for high LDL-cholesterol, 12.0% for low HDL-cholesterol, and 15.1% for hypertriglyceridemia, with higher dyslipidemia prevalence in eastern areas and important contributions from age, obesity, hypertension, diabetes, and smoking. In contrast, some high-income Asia-Pacific settings have seen stabilization or decline in cholesterol levels over time (97,100).

Differences by sex are observed across populations. Globally, the age-standardized death rate attributable to high LDL-cholesterol in 2019 was substantially higher in men than in women, at 67.33 versus 46.50 per 100,000 population (96). In Africa, however, the prevalence of dyslipidemia overall appears broadly similar between men and women (98). Local variation remains important; in Morocco, hypercholesterolemia was slightly more frequent in men than in women in the 2017 STEPS survey (99).

Age-related differences are also consistent. Serum lipids generally change with age, and in Asia-Pacific populations men and women show distinct age-specific patterns (100). In Korea, the prevalence of hypercholesterolemia was highest in men in their 50s and in women in their 60s, reaching 16.9% and 32.2%, respectively (100). These findings support the view that dyslipidemia is dynamic across the lifespan and shaped by both biological and environmental factors.

- **Morocco:**

The epidemiology of dyslipidemia in Morocco is characterized by heterogeneity across lipid fractions, with a particularly high burden of low HDL-cholesterol. According to data from the Moroccan national STEPS survey, the prevalence of hypercholesterolemia among adults was estimated at 13.0%, while another national analysis reported a prevalence of 10.5%, confirming that elevated total cholesterol affects about one in ten Moroccan adults (99,101).

National data indicate that low HDL-cholesterol is the most frequent lipid abnormality in Morocco, affecting 59.3% of women and 54.3% of men (101). Hypertriglyceridemia is also common, with prevalences of 15.4% in men and 9.3% in women (101). Hypercholesterolemia varies according to metabolic status and reaches 19.0% among individuals with hyperglycemia (99).

Sex-related differences in lipid abnormalities are evident in the Moroccan population. Hypercholesterolemia appears slightly more frequent in men than in women, with prevalences of 14.2% and 12.6%, respectively. By contrast, women show a higher frequency of low HDL-cholesterol, whereas men have a higher prevalence of hypertriglyceridemia. Multivariable analysis from the STEPS survey further suggested that female sex was associated with slightly lower odds of hypercholesterolemia after adjustment for confounding factors (99,101).

Moroccan STEPS-based data did not show major variation in hypercholesterolemia prevalence across age groups, with relatively stable proportions from younger to older adults: 12.8% in those aged 18–29 years, 13.5% in those aged 30–44 years, 13.1% in those aged 45–59 years, 13.2% in those aged 60–69 years, and 12.9% in those aged 70 years or older (99).

Geographic differences appear modest. Hypercholesterolemia was slightly more frequent in rural than urban areas in one Moroccan analysis, although this difference was not statistically significant, whereas raised triglycerides were more common in urban settings. In contrast, metabolic factors showed clearer associations: overweight/obesity, abdominal obesity, and hyperglycemia were identified as important independent predictors of hypercholesterolemia. Lifestyle factors such as alcohol consumption and smoking were also associated with lipid abnormalities in Moroccan adults (99,101).

# 4. Biological Links Between Dyslipidemia and Renal Disease

## 4.1. General pattern of dyslipidemia in chronic kidney disease

Chronic kidney disease (CKD) is associated with a distinctive and complex form of secondary dyslipidemia, commonly referred to as **uremic dyslipidemia** (102–105). Rather than manifesting as isolated hypercholesterolemia, this condition is characterized by a broader disturbance involving the concentration, distribution, and composition of circulating lipoproteins (102,103). These abnormalities may appear early in the course of renal impairment and generally become more pronounced with progression of kidney dysfunction (102,103).

The most consistent lipid abnormality observed in CKD is **hypertriglyceridemia** (102,103,106). In parallel, patients frequently exhibit increased plasma concentrations of **triglyceride-rich lipoproteins and their remnants**, particularly **very-low-density lipoproteins (VLDL)**, **intermediate-density lipoproteins (IDL)**, and **chylomicron remnants** (102,103,106). This remnant-rich profile is one of the hallmark features of renal dyslipidemia and contributes substantially to its atherogenic nature.

*Table 43 characteristics of lipids between normal lipid profile and chronic kidney disease lipid profile.*

| Lipid components | Normal lipid profile | CKD/ESRD Profile |
|---|---|---|
| Triglycerides (TG) | Normal | Elevated (Hypertriglyceridemia) |
| LDL-C | High | Low (Deficient & Dysfunctional) |
| HDL-C | Variable | Normal to low (Deceptive) |
| LDL Subclass | Large, buoyant | Small, dense (sdLDL) |
| Remnants (VLDL/IDL) | Efficiently cleared | Elevated (Accumulated VLDL/IDL) |

A second major feature is a reduction in **high-density lipoprotein cholesterol (HDL-C)** (102,104,107). In many patients, this decrease is accompanied by lower levels of the major HDL-associated apolipoproteins, particularly **apolipoprotein A-I** and **apolipoprotein A-II**. Beyond the numerical reduction in HDL cholesterol, CKD is also associated with important qualitative abnormalities of HDL particles, which become structurally and functionally altered. As a result, the HDL fraction in CKD is not only reduced, but also less protective than in individuals with preserved renal function (104,107).

In contrast, **total cholesterol and low-density lipoprotein cholesterol (LDL-C)** are often **within normal limits or only mildly reduced** in patients with CKD who do not have nephrotic-range proteinuria, particularly in predialysis CKD and in many hemodialysis populations (102,103,105). Nevertheless, apparently normal LDL values should not be interpreted as reflecting a benign lipid profile. Indeed, the LDL fraction in CKD is frequently shifted toward **small, dense LDL particles**, which are considered substantially more atherogenic than larger native LDL particles (105,108,109). Thus, in CKD, the qualitative nature of LDL often carries greater clinical relevance than its absolute plasma concentration (105,109).

Another characteristic abnormality is the elevation of **lipoprotein(a) [Lp(a)]**, which has been reported in a considerable proportion of patients with advanced CKD and end-stage renal disease. Increased Lp(a) further contributes to the overall atherogenic burden of the CKD lipid profile (102,103,110).

In addition to these quantitative disturbances, CKD is associated with marked **qualitative and compositional lipoprotein abnormalities**. Circulating lipoproteins may become enriched in triglycerides and undergo structural modifications such as **oxidation, carbamylation, and glycation**, affecting both apoB-containing lipoproteins and HDL. These changes enhance lipoprotein atherogenicity and further distinguish renal dyslipidemia from the conventional lipid abnormalities seen in the general population. Accordingly, the dyslipidemia of CKD is better understood as a disorder of **lipoprotein quality as well as quantity** (103,104).

The pattern of dyslipidemia may vary in certain clinical settings. In patients with **heavy proteinuria or nephrotic syndrome**, **hypercholesterolemia** and increased **LDL cholesterol** become more prominent, superimposing a nephrotic pattern upon the usual CKD-related abnormalities (103,111). Similarly, patients treated with **peritoneal dialysis** often display a more overtly atherogenic lipid profile, with more frequent hypercholesterolemia and more marked hypertriglyceridemia (103,112). By contrast, patients on **hemodialysis** more commonly exhibit the classic pattern of elevated triglycerides, remnant lipoproteins, low HDL cholesterol, and normal or low LDL cholesterol (102,103,112). After **renal transplantation**, dyslipidemia may worsen further, often with increases in total cholesterol, LDL cholesterol, and triglycerides (103).

Overall, the general pattern of dyslipidemia in CKD may therefore be summarized as a constellation of **hypertriglyceridemia, accumulation of triglyceride-rich remnant lipoproteins, low HDL cholesterol, predominance of small dense LDL particles, elevated Lp(a), and widespread qualitative lipoprotein alterations** (102–105,108–110). This profile is highly atherogenic and represents one of the characteristic metabolic disturbances of chronic kidney disease.

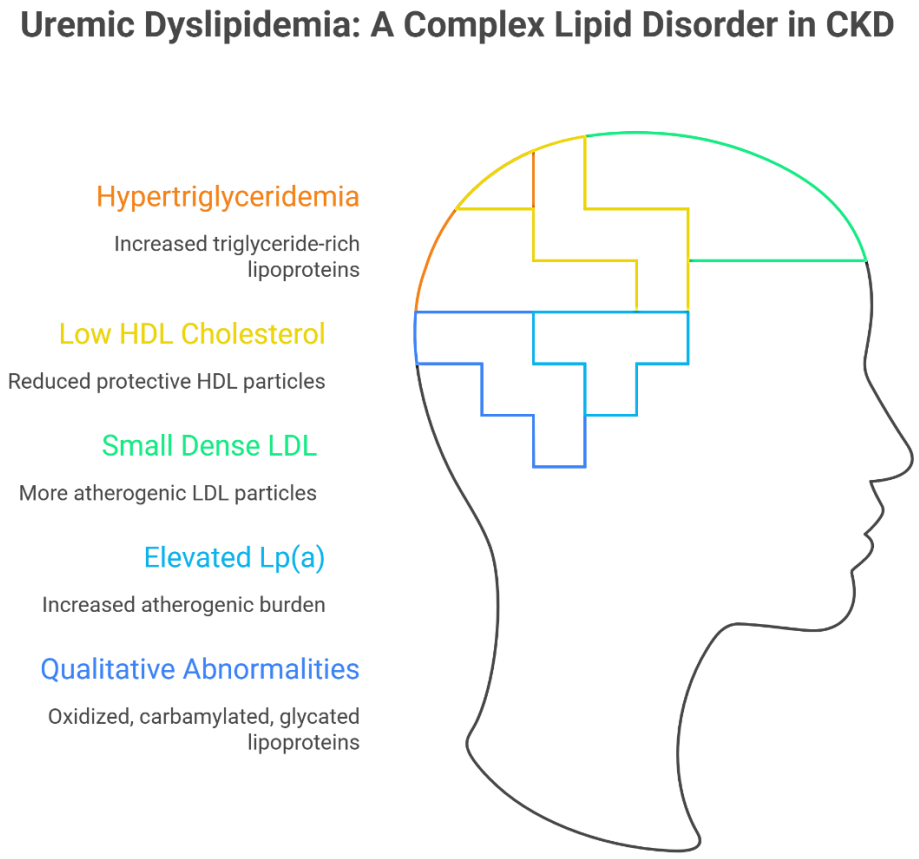



*Figure 48 Summary of chronic kidney disease lipid profile characteristics*

## 4.2. CKD-induced alterations in triglyceride-rich lipoprotein metabolism

Chronic kidney disease (CKD) induces profound alterations in the metabolism of **triglyceride-rich lipoproteins (TGRLs)**—which include very-low-density lipoproteins (VLDL), chylomicrons (CM), and their remnants—primarily by **impairing their clearance (catabolism)** rather than increasing their production. These metabolic disruptions lead to persistent **hypertriglyceridemia**, which is an early feature of renal failure (113,114).

### Impaired Enzymatic Lipolysis

The primary mechanism for elevated TGRL levels is a significant reduction in the activity and expression of key enzymes responsible for breaking down triglycerides.

- **Lipoprotein Lipase (LPL) Deficiency:** CKD causes a downregulation of LPL gene expression and a decrease in its protein abundance in skeletal muscle, adipose tissue, and the myocardium. LPL is the rate-limiting enzyme for the hydrolysis of triglycerides in chylomicrons and VLDL (115,116).

- **Hepatic Lipase (HL) Deficiency:** Hepatic lipase expression and activity are also significantly reduced in CKD. Because HL is responsible for removing triglycerides and phospholipids from remnants (IDL) and HDL, its deficiency contributes to the accumulation of intermediate-density lipoproteins (IDL) and triglyceride-enriched HDL particles (117).
- **GPIHBP1 Deficiency:** CKD reduces the expression of **GPIHBP1**, the molecule that anchors LPL to the capillary endothelium and serves as the ligand for binding chylomicrons. This deficiency prevents the LPL enzyme from effectively interacting with its lipoprotein substrates (118).

## Dysregulation of Apolipoproteins and Inhibitors

The efficiency of TGRL metabolism is further hindered by changes in the proteins that regulate enzyme activity.

- **Imbalance of ApoC-II and ApoC-III:** In uremic patients, there is a disproportionate increase in **Apolipoprotein C-III (ApoC-III)**, a potent inhibitor of LPL, and a relative decrease in **Apolipoprotein C-II (ApoC-II)**, a necessary activator of the enzyme. This leads to a decreased ApoC-II/ApoC-III ratio, effectively inactivating LPL (119–121).
- **Elevated ApoC-I:** CKD is also associated with increased levels of **Apolipoprotein C-I (ApoC-I)**, which acts as another powerful inhibitor of LPL-mediated clearance (122,123).
- **Uremic Toxins:** Poorly characterized "middle range" molecules or uremic toxins found in the plasma of CKD patients have been shown to directly inhibit LPL activity (124).

## Receptor-Mediated Clearance Defects

Even after partial lipolysis, the removal of TGRL remnants by the liver and peripheral tissues is impaired.

- **VLDL Receptor Downregulation:** The abundance of the **VLDL receptor** is severely reduced in skeletal muscle and adipose tissue, hindering the uptake of VLDL particles (125–127).
- **LDL Receptor-Related Protein (LRP) Deficiency:** Hepatic expression of **LRP**, the primary receptor for clearing chylomicron remnants and IDL, is significantly diminished in CKD (128).

## Impact of HDL Scarcity on TGRL Maturation

Normally, nascent VLDL and chylomicrons must "mature" in the circulation by acquiring **Apolipoprotein E (ApoE)** and **ApoC-II** from mature high-density lipoproteins (HDL-2).

- Because mature **HDL-2 particles are scarce** in CKD (due to LCAT deficiency), nascent TGRLs fail to acquire sufficient amounts of these essential proteins (129).
- Without ApoE, TGRLs cannot bind effectively to the endothelial surface; without ApoC-II, the LPL enzyme cannot be activated to perform lipolysis (129).

**Secondary Metabolic and Hormonal Factors**

- **Secondary Hyperparathyroidism:** Elevated levels of parathyroid hormone common in CKD have been shown to downregulate LPL mRNA expression and protein abundance (126,130).
- **Insulin Resistance:** This early feature of CKD promotes the **hepatic overproduction of VLDL**, which, when combined with impaired clearance, further exacerbates hypertriglyceridemia (112).

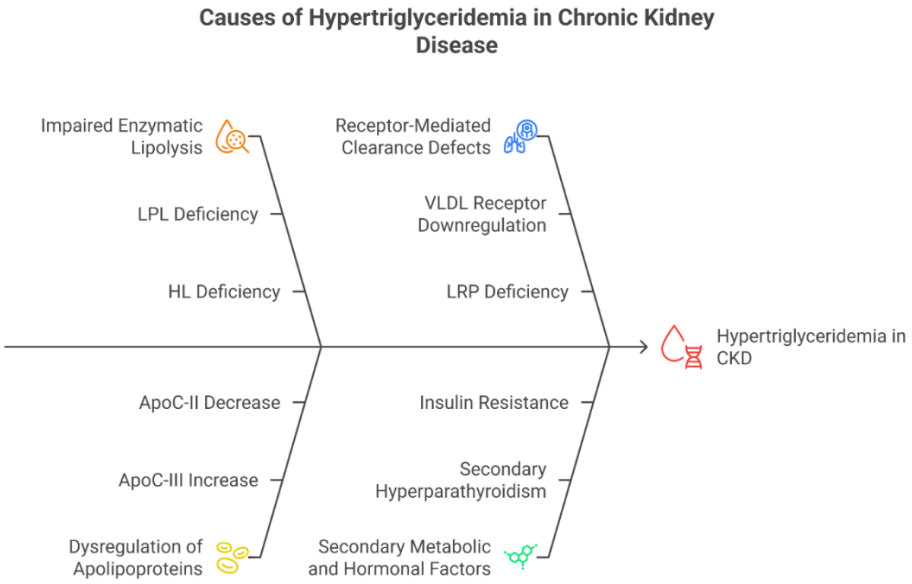



*Figure 49 Summary of all causes of hypertriglyceridemia in chronic kidney disease*

## 4.3. CKD-induced alteration in cholesterol and LDL Metabolism

Chronic kidney disease (CKD) profoundly alters cholesterol and low-density lipoprotein (LDL) metabolism. In most patients, the abnormality is not simply a matter of increased LDL quantity, but rather a shift toward a more atherogenic qualitative phenotype characterized by triglyceride-enriched, small dense, and structurally modified LDL particles.

In non-proteinuric CKD, total cholesterol and LDL-cholesterol concentrations are often normal or even reduced, and hepatic expression of LDL receptor, HMG-CoA reductase, and cholesterol 7α-hydroxylase appears largely preserved (131). By contrast, in nephrotic-range proteinuria, hypercholesterolemia and elevated LDL levels become prominent because heavy protein loss induces acquired LDL-receptor deficiency and stimulates hepatic cholesterol synthesis through upregulation of HMG-CoA reductase (111,131,132). A similar pattern may be observed in peritoneal dialysis, where peritoneal protein losses mimic nephrotic syndrome and glucose absorption from dialysate further promotes hepatic lipoprotein production (133).

Another major disturbance in CKD concerns the defective conversion of intermediate-density lipoprotein (IDL) into mature LDL. Under physiological conditions, IDL is progressively depleted of triglycerides and enriched in cholesterol through the coordinated actions of lipoprotein lipase,

cholesteryl ester transfer protein (CETP), and especially hepatic lipase. In CKD, this pathway is impaired by reduced hepatic lipase activity and expression, as well as by abnormalities in lipoprotein remodeling, leading to delayed catabolism of triglyceride-rich particles and accumulation of atherogenic IDL remnants (117,125,132). In addition, impaired HDL maturation limits the availability of mature HDL particles required for normal lipid exchange, which further compromises IDL-to-LDL conversion. As a result, LDL in advanced CKD is not typically cholesterol-rich mature LDL, but rather a population of incompletely processed, triglyceride-rich particles (105,134).

The hallmark of uremic dyslipidemia is therefore the predominance of small dense LDL (sdLDL) particles. Even when measured LDL-cholesterol remains within the normal range, LDL subfraction analysis in CKD and end-stage renal disease shows a shift toward smaller, denser particles that are relatively depleted in cholesterol esters and enriched in residual triglycerides (108,109). These sdLDL particles are particularly atherogenic because they penetrate the arterial wall more readily, show reduced affinity for the classical LDL receptor, persist longer in the circulation, and are more susceptible to oxidative modification. This explains why CKD patients may have high cardiovascular risk despite the absence of overt hypercholesterolemia (135,136).

Beyond these compositional abnormalities, the uremic milieu also promotes extensive post-translational modification of LDL, transforming it into a biologically toxic particle. Oxidative stress in CKD favors the formation and accumulation of oxidized LDL (oxLDL), which activates pro-atherogenic pathways through binding to scavenger receptors and contributes to foam-cell formation and vascular injury (137). Myeloperoxidase-driven reactions also generate carbamylated LDL (cLDL) from thiocyanate and urea-derived intermediates; cLDL has potent pro-atherogenic properties, promotes macrophage transformation into foam cells through CD36, induces endothelial toxicity, and enhances platelet aggregation (137). Glycation further alters LDL structure and impairs receptor-mediated clearance, thereby increasing LDL residence time and susceptibility to oxidation. Collectively, these modifications support the concept that altered LDL in CKD behaves as a genuine uremic toxin rather than a passive lipid abnormality.

Hepatic cholesterol handling is also disrupted in CKD. Increased activity of acyl-CoA:cholesterol acyltransferase (ACAT) has been demonstrated in the liver, kidney, and vascular tissues, promoting cholesterol esterification, intracellular retention, foam-cell formation, and lipotoxicity (134,138). Although non-proteinuric CKD does not seem to markedly stimulate HMG-CoA reductase, nephrotic states clearly do, further amplifying cholesterol accumulation (139). At the same time, levels of lipoprotein(a) [Lp(a)], an LDL-like and highly atherogenic particle, are frequently elevated in advanced CKD and ESRD. Available evidence suggests that this rise is due mainly to reduced renal catabolism rather than increased synthesis, since plasma residence time is prolonged and concentrations fall after kidney transplantation (110,134). Because routine laboratory methods do not distinguish LDL-derived cholesterol from Lp(a)-derived cholesterol, elevated Lp(a) may substantially contribute to measured LDL-cholesterol in CKD despite apparently normal conventional lipid profiles.

## 4.4. CKD-Induced Alteration of HDL and reverse cholesterol transport

Chronic kidney disease (CKD) profoundly disrupts high-density lipoprotein (HDL) metabolism and the reverse cholesterol transport (RCT) pathway, thereby converting HDL from a predominantly atheroprotective particle into a structurally abnormal and functionally impaired lipoprotein. Reverse cholesterol transport is the process by which excess cholesterol is removed from peripheral tissues, particularly macrophage foam cells in the arterial wall, and delivered to the liver for reuse or excretion. In CKD, this pathway is impaired at several sequential steps, including ApoA-I production, HDL maturation, cholesterol efflux, hepatic unloading, and the antioxidant and anti-inflammatory functions of HDL (140–144).

### Impaired component synthesis and increased catabolism

Apolipoprotein A-I (ApoA-I), the principal structural apolipoprotein of HDL and a key activator of lecithin-cholesterol acyltransferase (LCAT), is reduced in CKD. Experimental and clinical studies indicate that this reduction is driven by downregulation of hepatic ApoA-I synthesis, instability of ApoA-I mRNA, and increased ApoA-I catabolism in uremic states (140–143). Uremic plasma has also been shown to inhibit ApoA-I production in cultured hepatocytes, further supporting a direct suppressive effect of the uremic milieu on HDL biogenesis (141,142). The net result is a fall in circulating HDL particles and a reduction in their functional capacity (143,144).

### Defective HDL maturation

Under normal conditions, nascent discoidal HDL acquires free cholesterol from peripheral tissues, and LCAT esterifies this cholesterol on the HDL surface, allowing the newly formed cholesteryl esters to move into the particle core and convert small, cholesterol-poor HDL into larger, spherical, cholesterol ester-rich HDL. In CKD, hepatic LCAT expression, plasma LCAT concentration, and enzymatic activity are reduced, leading to defective esterification of free cholesterol and impaired maturation of HDL (143,145). Consequently, patients with advanced CKD accumulate lipid-poor pre-β HDL and HDL3, whereas the more mature HDL2 fraction becomes relatively deficient (143–145). This defect is central to the loss of effective reverse cholesterol transport in CKD.

### Compositional changes and remodeling

CKD also alters the lipid composition of HDL. In advanced CKD, HDL becomes relatively cholesteryl ester-poor and triglyceride-rich. This change reflects abnormal remodeling of HDL through transfer pathways involving cholesteryl ester transfer protein (CETP), which exchanges cholesteryl esters in HDL for triglycerides from apoB-containing lipoproteins (117,146). However, the role of CETP in CKD is not entirely uniform across studies: some reports found increased CETP levels, especially in heavy proteinuria, whereas others in hemodialysis populations found CETP activity to be unchanged (146,147). By contrast, hepatic lipase deficiency is a more consistent finding in CKD and contributes directly to retention of triglycerides within HDL, thereby generating smaller, unstable particles with shortened residence time (117).

## Failures in the reverse cholesterol transport pathway

The first step of reverse cholesterol transport requires the interaction of lipid-poor ApoA-I/HDL with the ABCA1 transporter on peripheral cells, enabling phospholipid and free cholesterol efflux onto nascent HDL. In CKD, oxidative and myeloperoxidase-mediated modification of ApoA-I and HDL impairs this interaction, thereby reducing cholesterol efflux and limiting the initiation of reverse cholesterol transport (148). In parallel, CKD increases the activity of acyl-CoA:cholesterol acyltransferase (ACAT) in tissues, promoting intracellular esterification and storage of cholesterol, which reduces the pool of free cholesterol available for export to HDL (138). Thus, CKD weakens both the acceptor function of HDL and the availability of cholesterol for efflux (148,149).

At the hepatic level, the terminal step of reverse cholesterol transport is also impaired. Normally, cholesterol ester-rich HDL docks to scavenger receptor class B type 1 (SR-B1) for selective unloading of cholesterol in the liver. In CKD, this pathway may be compromised, particularly in proteinuric states, while cholesterol ester-poor HDL particles are increasingly internalized and degraded via the β-chain of ATP synthase, an endocytic ApoA-I receptor involved in hepatic HDL uptake. This favors HDL destruction rather than efficient recycling, further lowering ApoA-I and HDL levels (140,150).

## Functional impairment and HDL dysfunction

Beyond cholesterol transport, normal HDL exerts major antioxidant, anti-inflammatory, anti-adhesive, and anti-thrombotic effects. In CKD, these protective functions are blunted. The activity of HDL-associated enzymes such as paraoxonase-1 (PON1) and glutathione peroxidase is reduced, diminishing HDL's ability to prevent oxidative modification of LDL and to counter inflammation (151,152). As a result, HDL from CKD and especially ESRD patients shows impaired antioxidant activity and diminished vascular protection (151-153).

In advanced CKD, HDL may become not only ineffective but also pro-inflammatory. HDL isolated from hemodialysis patients has been shown to stimulate inflammatory cytokine production by immune cells, impair endothelial function, and enhance the expression of adhesion molecules such as VCAM-1 and ICAM-1 (153,154). This altered HDL phenotype has also been linked to abnormal protein cargo, including enrichment with serum amyloid A, and may contribute directly to accelerated atherosclerosis in the uremic milieu (153,154).

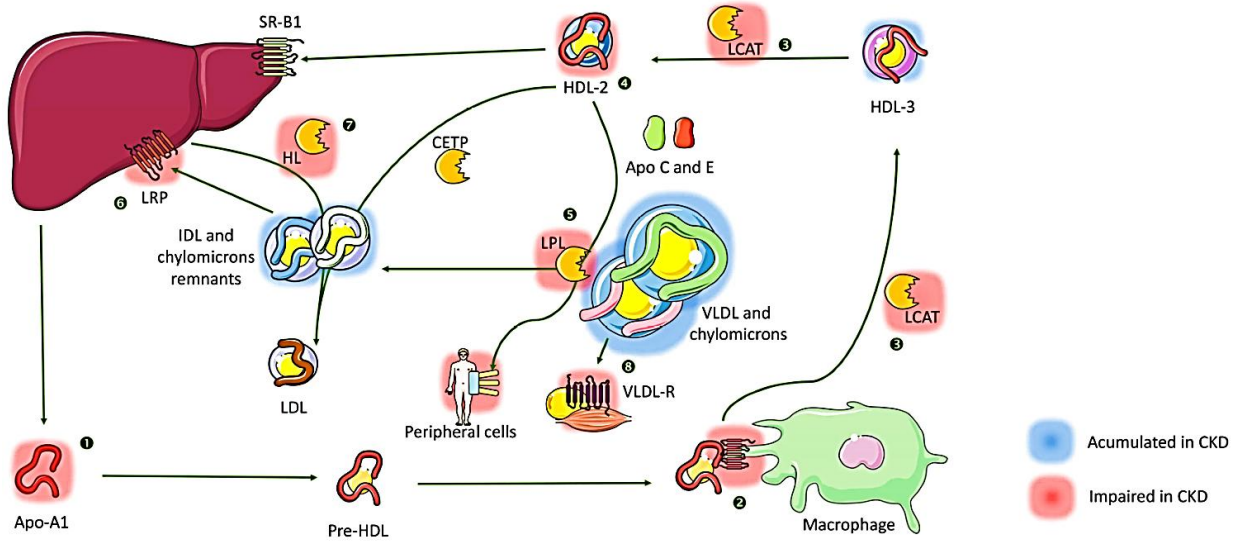



***Figure 50 Alterations in lipoprotein metabolism in chronic kidney disease (CKD)*** *(137).* CKD induces a deep modification in lipoprotein metabolism resulting in the accumulation of pro-atherogenic particles such as intermediary density lipoprotein (IDL) and triglyceride-rich lipoproteins (TGRL). Main modifications are listed below: In CKD, ApoA1 and A2 levels are decreased resulting in low level of circulating high density lipoprotein (HDL) (①). In CKD, modifications of ApoA1 decrease HDL binding to macrophages and participate in the observed impaired cholesterol efflux (②). Nascent HDL are transformed into discoid HDL-3 and then spherical HDL-2 enriched in cholesterol by the action of lecithin-cholesterol acyltransferase (LCAT). In CKD, LCAT level and activity are impaired (③), leading to the accumulation of HDL-3 and reduced level of HDL-2 (④). Thus, low HDL-2 concentration result in less transfer of triglycerides from TGRL to HDL-2 by cholesterol-ester transfer protein (CETP). Moreover, HDL-2 fail to enrich very-low density lipoprotein (VLDL) and chylomicrons with ApoC and E, essential for the binding and activation of lipoprotein lipase (LPL) respectively and such defect, associated with evidence of peripheral LPL lacking in CKD, leads to a reduced release of triglycerides into peripheral tissues and leads to an accumulation of TGRL (⑤). IDL and remnants accumulate in CKD because of a down-regulation of LDL receptor protein (LRP) (⑥), the lower level of CETP (④) and the down-regulation of hepatic lipase (HL) expression (⑦). A part of VLDL accumulates because of the down-regulation of the VLDL-receptor (VLDL-R) in myocytes and adipocytes (⑧). Adapted from Florens N, Calzada C, Lyasko E, Juillard L, Soulage CO. Modified lipids and lipoproteins in chronic kidney disease: a new class of uremic toxins. Toxins (Basel). 2016;8(12):376. doi:10.3390/toxins8120376.

# 5. How dyslipidemia may contribute to chronic kidney disease

Lipids contribute directly to the development and progression of chronic kidney disease (CKD) through a process known as *lipotoxicity*, defined as the abnormal accumulation of lipids within non-adipose tissues such as the kidney. This ectopic deposition occurs when circulating lipids, particularly free fatty acids and cholesterol, exceed the storage capacity of adipose tissue and spill over into renal cells. Once established, renal lipotoxicity does not merely reflect passive lipid storage; rather, it profoundly disturbs intracellular metabolism by impairing fatty acid handling, disrupting mitochondrial energy production, altering redox balance, and activating inflammatory, oxidative, and endoplasmic reticulum stress pathways. These metabolic disturbances modify both the intracellular and extracellular renal microenvironment, promoting cytokine release, cellular stress signaling, macrophage recruitment, and profibrotic remodeling. The harmful effects of lipotoxicity involve several renal cell populations, notably podocytes, tubular epithelial cells, mesangial cells, endothelial cells, and inflammatory foam cells, with each cell type exhibiting distinct patterns of injury that collectively contribute to proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, and progressive loss of renal function. The specific mechanisms through which lipotoxicity alters renal cell metabolism, reshapes the renal milieu, and damages each of these cellular compartments are detailed in the following sections.

## 5.1. Dysregulated pathways responsible for renal lipid accumulation

Lipid accumulation within the kidney, often referred to as ectopic lipid deposition or the "fatty kidney" phenotype, represents one of the earliest steps in lipid-induced renal injury. It arises from a disruption in the physiological balance between lipid uptake, synthesis, oxidation, and efflux. Once these regulatory pathways become dysregulated, lipids progressively build up within resident renal cells, particularly podocytes, mesangial cells, and tubular epithelial cells. This intracellular lipid excess initiates lipotoxicity, which contributes to cellular dysfunction, structural damage, and the progressive worsening of renal injury. The mechanisms through which this process occurs are outlined in the following section.

### *5.1.1.* Increased lipid influx:

One of the principal mechanisms underlying renal lipid accumulation is the excessive uptake of fatty acids and lipoproteins by renal cells. Free fatty acids (FFAs) are transported into cells mainly through CD36, fatty acid transport proteins (FATPs, particularly FATP2), and fatty acid-binding proteins (FABPs) (155,156). In pathological states such as diabetic kidney disease and obesity, CD36 expression is markedly increased, largely under the influence of hyperglycemia and chronic inflammation, thereby enhancing intracellular lipid deposition (155,157). Cholesterol and lipoproteins are taken up through the LDL receptor (LDLR) as well as scavenger receptors such as LOX-1 (OLR-1) and SR-A (155,157). In the uremic milieu, these pathways are often overactivated, and scavenger receptors in particular may escape normal feedback regulation, allowing excessive uptake of oxidized or otherwise modified lipoproteins (155,158). In addition, during proteinuric states, proximal tubular cells reabsorb large amounts of albumin-bound FFAs, a process often referred to as the "Trojan horse" effect (159–161). Although albumin itself is degraded intracellularly, the fatty acids remain within the cell, exceeding its metabolic capacity and accumulating in the form of lipid droplets (160,161).

### *5.1.2.* Enhanced De Novo Lipogenesis (Synthesis)

Increased endogenous lipid synthesis also plays an important role in renal lipid overload. This process is largely governed by the transcription factors SREBP-1 and ChREBP, which stimulate the synthesis of fatty acids and triglycerides (162,163). In obesity and diabetes, these regulators are activated by insulin resistance and elevated glucose levels, thereby promoting lipogenesis (162,164). Upregulation of SREBP-1 increases the expression of key lipogenic enzymes, notably acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), which drive the conversion of carbohydrate substrates into saturated fatty acids such as palmitate (162,165). Increased expression of stearoyl-CoA desaturase-1 (SCD1) further favors triglyceride formation and storage, thereby aggravating intracellular lipid accumulation (162,164,166).

### *5.1.3.* Defective Fatty Acid Oxidation

Impaired fatty acid utilization is another major determinant of renal lipotoxicity. Under physiological conditions, fatty acid oxidation is regulated predominantly by PPARα and its coactivator PGC-1α, which coordinate the expression of genes involved in mitochondrial lipid catabolism (167,168). In both acute kidney injury and chronic kidney disease, the PGC-1α-PPARα axis is markedly suppressed, leading to reduced fatty acid oxidation capacity (167,169). In parallel, abnormalities in CPT1 and CPT2, the enzymes responsible for mitochondrial fatty acid transport, further compromise β-oxidation (7,170–172). As a result, fatty acids are not adequately metabolized and instead accumulate as toxic lipid intermediates, including ceramides and diacylglycerols, which promote mitochondrial dysfunction, oxidative stress, and cell death (7,168,173).

### *5.1.4.* Impaired Lipid Efflux (Outflow)

Renal lipid accumulation is further exacerbated when the mechanisms responsible for lipid export are impaired. Cholesterol efflux from cells depends mainly on the transporters ABCA1 and ABCG1, which transfer free cholesterol and phospholipids to apolipoproteins and nascent HDL particles as part of the reverse cholesterol transport pathway (174,175). In diabetic and inflammatory conditions, the expression of ABCA1 and ABCG1 is significantly reduced (175,176). This defect limits the ability of renal cells to remove excess cholesterol, resulting in its intracellular retention, particularly within podocytes, where it contributes to cellular dysfunction and injury (176,177).

### *5.1.5.* Reduced Extracellular Lipolysis (Catabolism)

Finally, systemic disturbances in lipoprotein catabolism also contribute to renal lipid overload. In chronic kidney disease, lipoprotein lipase (LPL) activity is often diminished, impairing the hydrolysis of triglyceride-rich lipoproteins such as VLDL and chylomicrons (178,179). This defect is aggravated by increased levels of Angptl4, an inhibitor of LPL, as well as by alterations in apolipoprotein composition, including elevated ApoC-III, which further suppresses LPL function (4,180). The resulting hypertriglyceridemia prolongs the circulation of atherogenic lipoprotein remnants, thereby increasing their availability for uptake by renal tissues and amplifying lipid-mediated renal injury (178–180).

## 5.2. Lipid induced renal injury mechanisms

Lipotoxicity, resulting from excessive lipid accumulation, induces renal injury through several interrelated cellular mechanisms that disrupt renal homeostasis and drive structural remodeling. These mechanisms often interact in a vicious cycle, accelerating the progression of chronic kidney disease (CKD) (181,182).

### *5.2.1.* Oxidative Stress and Lipid Peroxidation

Excessive lipids stimulate the production of **reactive oxygen species (ROS)**, primarily through mitochondrial oxidative phosphorylation and pro-oxidant enzymes such as the NADPH oxidase system. This imbalance leads to **lipid peroxidation**, a process that generates reactive aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). These products are highly cytotoxic, attacking cellular proteins, DNA, and nucleic acids, which further exacerbates tissue damage. In some contexts, even antioxidants like uric acid can shift to a pro-oxidant role when in a lipophilic environment (158,183).

### *5.2.2.* Mitochondrial Dysfunction

Mitochondria are primary targets of lipid-induced injury. Lipid overload leads to:

- **Impaired Energetics:** Suppression of fatty acid oxidation (FAO) results in **ATP depletion**, loss of mitochondrial cristae structure, and swelling.
- **Cardiolipin Peroxidation:** Peroxidation of cardiolipin, a unique phospholipid in the inner mitochondrial membrane, disrupts the electron transport chain and bioenergetics.
- **DNA and Dynamics Damage:** ROS-induced **mitochondrial DNA (mtDNA) damage** and excessive dynamin-related protein 1 (DRP1)-mediated fission lead to mitochondrial fragmentation and the activation of pro-apoptotic pathways (32,167).

### *5.2.3.* Endoplasmic Reticulum (ER) Stress

Lipid overload, particularly from saturated fatty acids like palmitate, overwhelms the ER's protein-folding capacity. This triggers the **unfolded protein response (UPR)** through pathways such as IRE1α, PERK, and ATF6. While initially a protective mechanism to restore homeostasis, prolonged ER stress activates apoptotic pathways in podocytes, mesangial cells, and tubular cells. ER stress also participates in an **auto-amplification loop** by repressing enzymes like CPT2, which further increases lipid accumulation (183–186).

### *5.2.4.* Inflammation and Fibrosis

Lipotoxicity fosters a pro-inflammatory environment characterized by:

- **Cytokine Release:** Excess lipids trigger the production of pro-inflammatory cytokines such as **TNF-α, IL-6, and MCP-1**, which recruit immune cells to the renal interstitium.
- **Pathway Activation:** This includes the activation of the **NLRP3 inflammasome** and the **cGAS-STING pathway**, the latter often triggered by leaked mtDNA.

- **Fibrotic Remodeling:** Sustained inflammation activates fibroblasts and promotes **epithelial-mesenchymal transition (EMT)**, leading to the excessive deposition of extracellular matrix (ECM), which results in irreversible fibrosis and glomerulosclerosis (186–188).

#### *5.2.5.* Autophagy Disruption

While lipid overload initially activates autophagy to clear excess lipids, prolonged exposure leads to **autophagy stagnation**. This occurs due to lysosomal dysfunction and the accumulation of phospholipids in dysfunctional lysosomes, which impairs autophagic flux and further disrupts cellular survival mechanisms (189).

### 5.3. Specific cell injuries in the kidney by renal cell type

Damage from lipotoxicity manifests through specific structural and functional injuries across the various specialized cell types of the kidney, ultimately leading to the progression of chronic kidney disease (CKD) (159,190–192).

#### *5.3.1.* Podocytes

Podocytes are highly energy-intensive epithelial cells that integrate the structural maintenance of the glomerular filtration barrier. Their injury is a hallmark of lipotoxicity-induced renal damage:

- **Morphological Changes:** Excess lipids cause **foot process effacement** and podocyte detachment, which disrupts the selective permeability of the filtration barrier (185,190,193).
- **Proteinuria:** The loss of podocyte integrity and the reduced expression of key structural proteins, such as **nephrin and podocin**, lead to heavy albuminuria and proteinuria (185,193,194).
- **Cell Death:** Saturated fatty acids like palmitate trigger dose-dependent **apoptosis and necrosis** in podocytes through mechanisms involving reactive oxygen species (ROS), mitochondrial membrane depolarization, and endoplasmic reticulum (ER) stress (185,190,193).

#### *5.3.2.* Tubular Epithelial Cells (TECs)

The tubular epithelium, particularly the proximal tubules, is highly vulnerable to lipotoxicity because it relies heavily on fatty acid oxidation (FAO) to meet its massive energy demands for reabsorption.

- **The "Trojan Horse Effect":** In proteinuric states, proximal tubular cells reabsorb excessive amounts of **albumin-bound fatty acids**; while the albumin is degraded, the fatty acids remain and accumulate as toxic lipid droplets (159,161,195).
- **Structural Damage:** Intracellular lipid accumulation leads to **tubular flattening, loss of the brush border, and tubular atrophy** (159,195).

- **Fibrosis and EMT:** Lipotoxicity in tubular cells promotes **epithelial–mesenchymal transition (EMT)** and the release of profibrotic factors, contributing to irreversible tubulointerstitial fibrosis (159,186).

### *5.3.3.* Mesangial Cells

Mesangial cells provide structural support for glomerular capillaries and can actively internalize lipoproteins.

- **Foam Cell Formation:** Excessive lipid internalization leads mesangial cells to transform into **foam cells**, which are loaded with neutral lipid droplets (191,196–198).
- **Glomerulosclerosis:** Lipid-laden mesangial cells produce excessive **extracellular matrix (ECM)** components, such as collagen and fibronectin, leading to thickening of the glomerular basement membrane and expansion of the mesangial matrix (165,196–198).
- **Functional Loss:** Mesangial foam cells exhibit **impaired contraction** and abnormal phagocytosis (196,197).

### *5.3.4.* Endothelial Cells and Macrophages

- **Endothelial Injury:** Although less prone to direct accumulation, glomerular and vascular endothelial cells can also transform into **foam cells** or experience lipid inclusion, contributing to endothelial dysfunction and vascular disease in CKD (192,199).
- **Macrophage Activation:** Lipid accumulation in renal cells promotes the recruitment of macrophages, which then internalize modified lipoproteins to become **foam cells** themselves. These cells release proinflammatory cytokines that disseminate systemic inflammation and aggravate renal lesions (192,199,200).

# 6. Lipid management in chronic kidney disease patients

## 6.1. A brief history of the paradigm shift in lipid management

Historically, dyslipidemia management was often based on achieving predefined LDL-cholesterol targets, such as <100 mg/dL or <70 mg/dL. This treat-to-target strategy required repeated lipid measurements and often led to treatment intensification when LDL-C goals were not reached. In chronic kidney disease, however, contemporary guidance—particularly KDIGO—favors a risk-based "fire-and-forget" approach. In this model, clinicians first identify whether the patient belongs to a CKD subgroup shown to benefit from lipid-lowering therapy, then prescribe an appropriate statin, or in some patients a statin/ezetimibe combination, at doses tested in CKD trials rather than escalating therapy to achieve a specific LDL-C target. For most patients, routine follow-up lipid testing is not necessary unless the result would alter management or support adherence (201,202).

The rationale for this paradigm shift is both biological and clinical. First, LDL-C is a less reliable marker of cardiovascular risk in CKD than in the general population. KDIGO highlights that as kidney function declines, the excess coronary risk associated with higher LDL-C becomes progressively weaker, making LDL-C a less useful discriminator for deciding who should receive therapy. In other words, patients with reduced eGFR are often at high absolute cardiovascular risk regardless of whether their LDL-C is markedly elevated, so relying on LDL-C alone may fail to identify many CKD patients who could benefit from treatment. Second, in dialysis patients, the relationship between cholesterol and outcomes becomes paradoxical. Both very high and very low cholesterol levels may be associated with adverse outcomes, and low cholesterol in this setting may reflect **protein-energy wasting, inflammation, and malnutrition** rather than true cardiovascular protection. This "reverse epidemiology" makes cholesterol an especially poor standalone marker of risk in advanced kidney failure. Third, statin benefit appears to depend more on the patient's **baseline cardiovascular risk** than on the starting LDL-C level itself. KDIGO notes that the relative risk reduction associated with statins is fairly constant across a broad range of baseline LDL-C values, implying that absolute benefit is driven mainly by the patient's underlying coronary risk rather than by cholesterol level alone (3,202–204).

This change in strategy is also strongly supported by trial data. In non-dialysis CKD, lipid-lowering therapy—particularly statins, with or without ezetimibe—has been shown to reduce major atherosclerotic cardiovascular events, which justifies treatment in many adults with CKD even when LDL-C is not used as a treatment target. By contrast, the benefit of initiating statins in prevalent dialysis patients has been far less convincing. KDIGO notes that when the major dialysis trials and SHARP are considered together, the clinical benefit of statins in patients already on dialysis is uncertain and, if present, clearly smaller than in earlier stages of CKD (3,201,202,205,206).

This likely reflects the changing cardiovascular phenotype of advanced kidney disease, where non-atherosclerotic processes such as heart failure, arrhythmia, vascular calcification, inflammation, and malnutrition play a greater role in outcomes and reduce the impact of LDL lowering alone. For this reason, KDIGO does not recommend starting statins in most prevalent

hemodialysis patients, although continuation may be reasonable in patients who were already receiving them before dialysis initiation. Overall, the contemporary CKD approach therefore prioritizes **global cardiovascular risk, evidence from outcome trials, and treatment safety** over repeated pursuit of numerical LDL-C targets (3,201,202).

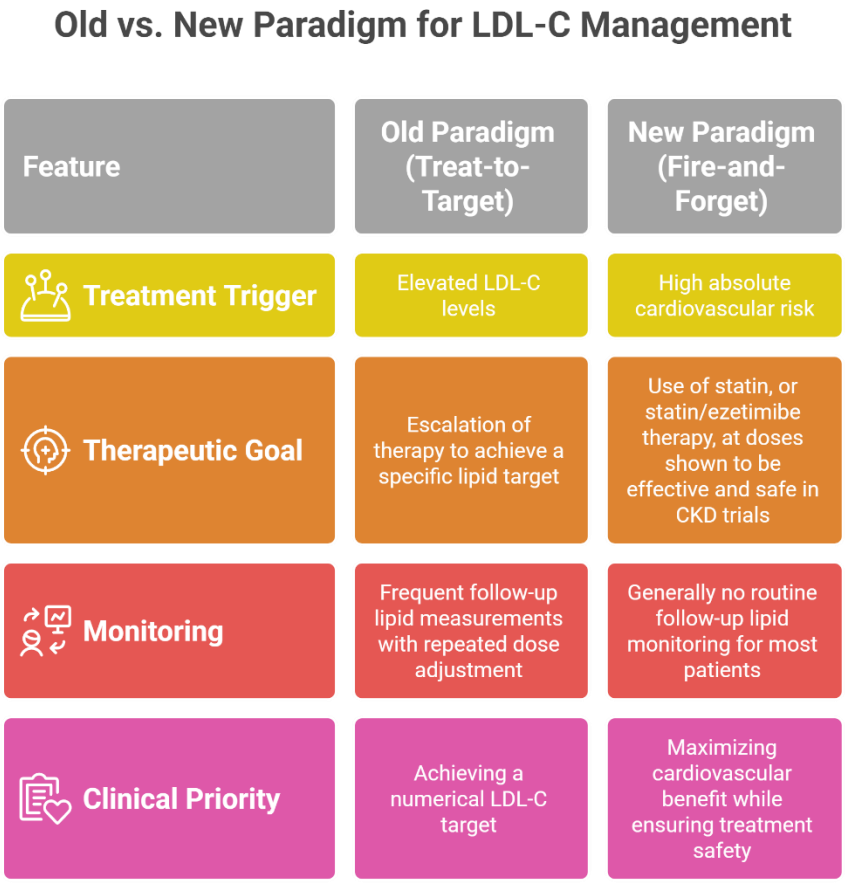



*Figure 51 Old vs new paradigm for lipid management.*

## 6.2. Lipid Management: from diagnosis to treatment

### 6.2.1. Lipid assessment:

A baseline lipid profile remains essential in all newly identified adults with CKD. Although treatment is no longer directed toward achieving a specific lipid target, the initial profile is still necessary to detect severe lipid abnormalities, particularly **fasting triglycerides >11.3 mmol/L (1000 mg/dL)** or **LDL-C >4.9 mmol/L (190 mg/dL)**. An LDL-C value above this threshold should prompt specialist referral to evaluate for possible inherited lipid disorders (201,202).

Before initiating long-term statin therapy, clinicians should also assess for **secondary causes of dyslipidemia**, especially those that are potentially reversible (201,203).

Important medical causes include:

- **Diabetes mellitus**, which commonly produces complex dyslipidemia and requires optimized glycemic control
- **Hypothyroidism**, a reversible cause of lipid elevation that should be corrected before committing the patient to lifelong statin therapy
- **Nephrotic syndrome**, in which massive proteinuria alters lipid metabolism and improvement may follow treatment of the underlying renal disease
- **Liver disease** and **excessive alcohol intake**, both of which can disrupt lipid synthesis and clearance
- Medication-related causes should also be considered. Drugs such as **cyclosporine**, **sirolimus**, **corticosteroids**, certain **diuretics**, **beta-blockers**, **oral contraceptives**, **androgens**, and **anticonvulsants** may contribute to dyslipidemia and should be reviewed carefully before therapy is started (201,203).

A complete lipid evaluation should include **total cholesterol, LDL-C, HDL-C, and triglycerides**. While fasting samples remain preferable for accurate triglyceride assessment, non-fasting measurements are acceptable when fasting is impractical, since total cholesterol and HDL-C are not substantially affected by fasting status (201,203).

### 6.2.2. Treatment for non-dialysis and non-transplant CKD patients

The management of dyslipidemia in adult patients with chronic kidney disease (CKD) who are not dialysis-dependent or not transplanted is based on a **risk-oriented strategy** rather than on predefined LDL-cholesterol targets. In this population, treatment decisions rely primarily on the patient's overall cardiovascular risk and on the demonstrated benefit of lipid-lowering therapy in reducing atherosclerotic events (3,201,202).

❖ **Indications for pharmacological treatment**

The decision to initiate statin therapy depends mainly on the patient's age and level of renal function.

- For **adults aged 50 years or older**, treatment is generally recommended. Patients with an **eGFR <60 mL/min/1.73 m²** (G3a–G5) should receive either a **statin alone or a statin/ezetimibe combination**, whereas those with an **eGFR ≥60 mL/min/1.73 m²** (G1–G2) should receive a **statin** (201,202).
- For **adults aged 18 to 49 years**, statin therapy is considered more selectively. It is suggested only when one or more major high-risk features are present, including **established coronary artery disease** such as previous myocardial infarction or coronary revascularization, **diabetes mellitus**, **prior ischemic stroke**, or an **estimated 10-year risk of coronary death or non-fatal myocardial infarction greater than 10%** (201,202).

❖ Main pharmacological agents

- **Statin-based regimens** remain the cornerstone of treatment, as they are the only lipid-lowering therapies that have consistently shown cardiovascular benefit in the CKD population (3,201,205).

- **Statins (HMG-CoA reductase inhibitors)** effectively reduce LDL-C levels and lower the risk of cardiovascular events. Evidence from the **SHARP trial** showed that the combination of **simvastatin 20 mg/day and ezetimibe 10 mg/day** significantly reduced major atherosclerotic events in patients with non-dialysis CKD (201,202,205).
- **Ezetimibe** is not recommended as monotherapy in this setting, but it can be combined with a statin to enhance LDL-C reduction while avoiding the potential toxicity associated with higher statin doses (201,202).
- **Fibrates** are used mainly in cases of **marked hypertriglyceridemia** such as triglyceride levels above **500 mg/dL**. However, they are not routinely recommended for cardiovascular risk reduction in CKD, since their benefit is less well established than that of statins and their use is associated with a greater risk of adverse effects (3,201,204,206).

❖ Recommended doses and safety considerations *(201–204)*

Because patients with CKD are more susceptible to drug-related toxicity due to reduced renal clearance and frequent polypharmacy, treatment should rely on doses that have been shown to be safe in CKD-specific studies.

For patient with CKD G1-G2 is equivalent to the general population treatment.

Recommended regimens for patients with **CKD G3a–G5** include:

- **Atorvastatin:** 20 mg (no adjustment for eGFR needed)
- **Fluvastatin:** 80 mg
- **Rosuvastatin:** 10 mg
- **Simvastatin/Ezetimibe:** 20 mg / 10 mg
- **Pravastatin:** 40 mg

Caution is required with combination therapy. The concomitant use of statin **and a fibrate** is **not recommended** in CKD because of the increased risk of **myopathy and rhabdomyolysis**. In addition, statins are contraindicated in **pregnant or breastfeeding women** and in patients with **active liver disease**.

❖ Non-pharmacological management *(201,206,207)*

- **Therapeutic lifestyle changes** should be recommended for all CKD patients with lipid abnormalities.
- Dietary interventions play an important role. Healthy dietary patterns such as the **Mediterranean diet**, **DASH diet**, and **plant-based diets** may improve lipid parameters and may also contribute to better overall outcomes in CKD. These approaches emphasize **whole grains, vegetables, fruits, legumes, and nuts**.
- In patients with hypertriglyceridemia, **omega-3 fatty acids** may also be beneficial. Increased intake of oily fish, typically **two to three servings per week**, or supplementation providing at least **1 g/day of EPA plus DHA**, may help reduce triglyceride levels and possibly improve cardiovascular outcomes.

- At the same time, dietary counseling in CKD must account for disease-specific precautions. Patients should be advised to avoid hidden sources of **potassium** and **phosphorus**, and cooking techniques such as **double-boiling** may help reduce mineral content when needed.

❖ **Monitoring and the "fire-and-forget" approach** *(201,202)*

Current recommendations support a **"fire-and-forget"** strategy once treatment has been initiated.

This means that **routine follow-up measurement of LDL-C or other lipid parameters is generally not required** after the initial evaluation. The rationale is that LDL-C targets have not been shown to improve outcomes in CKD trials, and intensifying therapy to achieve specific targets may expose patients to higher statin doses whose safety has not been clearly established in this population.

Repeat lipid testing should therefore be reserved for selected situations in which the result is likely to influence management, such as when evaluating **treatment adherence** or reassessing **cardiovascular risk in younger patients**.

### 6.2.3. Treatment for special CKD population: dialysis and transplanted patients

Lipid management in adult patients who are either dialysis-dependent or living with a kidney transplant follows a distinct clinical rationale, shaped largely by evidence from major randomized controlled trials and reflected in the 2013 KDIGO recommendations. In these populations, treatment decisions are guided less by lipid values themselves than by the stage of kidney disease, the expected cardiovascular benefit of therapy, and the balance between efficacy and safety (3,201,202).

❖ **Lipid management in dialysis-dependent patients** *(3,201,202,204,206)*

In patients receiving chronic dialysis, the key principle is the distinction between **initiating** and **continuing** therapy. This approach is based on evidence showing that lipid-lowering treatment is considerably less effective at this stage of CKD than in earlier stages.

Current recommendations suggest **not initiating** statins or statin/ezetimibe combinations in most adults with dialysis-dependent CKD. By contrast, in patients who were already taking these agents before starting dialysis, treatment is generally **continued** rather than stopped. This approach is supported by observational data suggesting that continuation during the transition to dialysis may be associated with lower all-cause and cardiovascular mortality.

The major trials underlying this recommendation are well known. In the **4D study**, atorvastatin 20 mg markedly reduced LDL-cholesterol levels in diabetic hemodialysis patients, but did not significantly reduce the composite outcome of cardiac death, nonfatal myocardial infarction, and stroke. Similarly, the **AURORA trial** showed that rosuvastatin 10 mg effectively lowered LDL-C in hemodialysis patients without translating into a significant reduction in major cardiovascular events. In the **SHARP trial**, simvastatin plus ezetimibe reduced atherosclerotic events in the overall CKD population, but this benefit was not statistically significant when the dialysis subgroup was considered separately.

Several explanations have been proposed for this reduced benefit in dialysis patients. One is the phenomenon of **reverse epidemiology**, in which low cholesterol may reflect malnutrition or chronic inflammation rather than a lower cardiovascular risk. Another is that cardiovascular mortality in dialysis is often driven by mechanisms other than classic atherosclerotic disease, including **sudden cardiac death, arrhythmia, and heart failure**, which are less likely to be modified by statin therapy.

- **Lipid management in kidney transplant recipients** *(3,201–203)*

Adult kidney transplant recipients are considered a population at persistently high cardiovascular risk and are generally viewed as more likely to benefit from lipid-lowering treatment.

For this reason, current guidance suggests treatment with a **statin** in most adult kidney transplant recipients. The strongest evidence comes from the **ALERT trial**, which included more than 2,000 transplant recipients. Although the primary endpoint was not significantly reduced during the initial 5-year analysis, fluvastatin produced a **significant reduction in cardiac death and nonfatal myocardial infarction**. Longer follow-up in the extension phase further supported a reduction in major cardiac events over time.

Post-transplant dyslipidemia is also frequently aggravated by **immunosuppressive therapy**, especially **corticosteroids**, **calcineurin inhibitors** such as cyclosporine and tacrolimus, and **sirolimus**. These treatment-related factors reinforce the importance of active lipid assessment and management in this group.

- **Safety considerations and drug interactions** *(201–204)*

Safety remains a central concern in both dialysis and transplant populations because these patients are often exposed to multiple medications and may have altered drug handling.

Caution is required with **cyclosporine**, which inhibits the metabolism of several statins and can substantially increase circulating drug concentrations. In patients receiving cyclosporine, lower doses of agents such as **pravastatin** and **fluvastatin** are generally preferred, whereas **simvastatin**, **lovastatin**, and in many cases, **atorvastatin** should be avoided or used only with great caution because of the increased risk of toxicity.

The concomitant use of a **statin and a fibrate** is also discouraged in these patients because it significantly increases the risk of **myopathy and rhabdomyolysis**. More broadly, when statins are prescribed in stage 5 CKD, including dialysis and transplant settings, clinicians should rely on doses that have already been shown to be safe in renal studies, such as **atorvastatin 20 mg**, **rosuvastatin 10 mg**, or **simvastatin/ezetimibe 20/10 mg**.

- **Non-pharmacological management and monitoring** *(3,201,202,204,206)*

Non-pharmacological measures remain important in both dialysis and transplant patients, especially when **hypertriglyceridemia** is present. **Therapeutic lifestyle changes** should be encouraged, including dietary modification, weight control when appropriate, and attention to secondary causes of lipid abnormalities. Fibrates are generally avoided in patients with stage 5 CKD because of safety concerns and are considered only in exceptional cases of very severe hypertriglyceridemia, particularly when the risk of pancreatitis becomes a priority.

Monitoring also follows the KDIGO **"fire-and-forget"** principle. For most adult dialysis and transplant patients, **routine follow-up lipid measurements are not required** once the initial assessment and treatment decision have been made. Repeat testing is usually reserved for situations in which the result would alter management, such as a change in renal replacement modality, suspected non-adherence, or a major change in clinical status.

| Statin | eGFR G1-G2 | eGFR G3a-G5, including patients on dialysis or with a kidney transplant |
|---|---|---|
| Lovastatin | GP | nd |
| Fluvastatin | GP | 80[1] |
| Atorvastatin | GP | 20[2] |
| Rosuvastatin | GP | 10[3] |
| Simvastatin/Ezetmibe | GP | 20/10[4] |
| Pravastatin | GP | 40 |
| Simvastatin | GP | 40 |
| Pitavastatin | GP | 2 |

All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, as it may increase the risk of adverse renal events. Cyclosporin inhibits the metabolism of certain statins resulting in higher blood levels. Data based on [1]ALERT, [2]4D, [3]AURORA, [4]SHARP. Abbreviations: eGFR, estimated glomerular filtration rate; GP, general population; nd, not done or not studied.

*Figure 52 Recommended doses (mg/d) of statins in adults with CKD. Adapted from the KDIGO 2013 Lipid Management guidelines in CKD patients.*

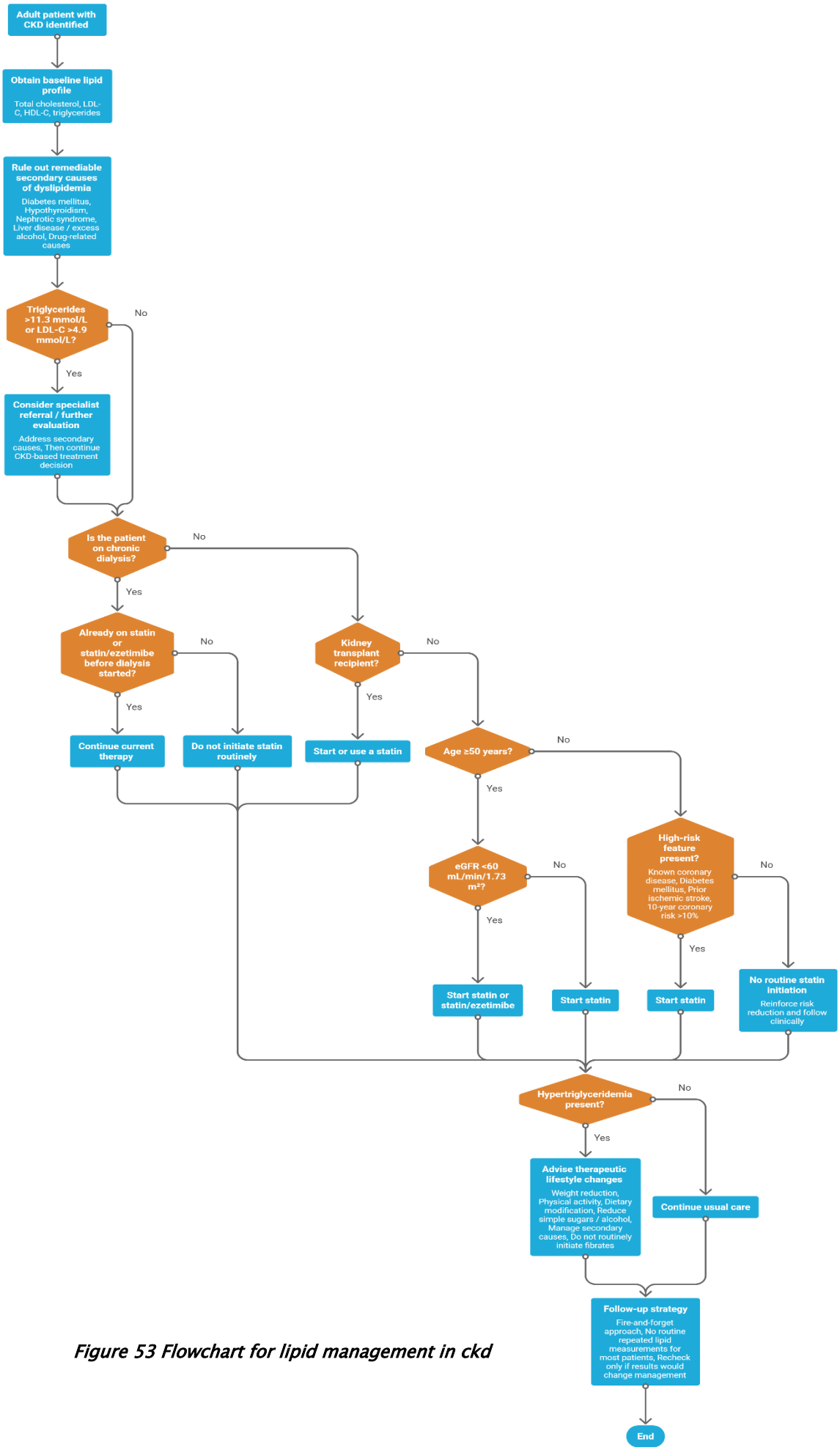



*Figure 53 Flowchart for lipid management in ckd*

# 2. Discussion of results

## 2.1. Principal findings overview

In this cross-sectional study conducted at CHU Mohammed VI, 276 adult patients with chronic kidney disease were analyzed over the 2022-2024 period. The study showed a substantial renal burden within the cohort, as nearly two-thirds of patients had impaired renal function with an eGFR below 60 mL/min/1.73 m², more than four-fifths had moderately to severely increased albuminuria (A2-A3), and over half were classified in the very high KDIGO renal risk category. These findings indicate that the study population was characterized not only by established CKD, but also by a predominance of patients with advanced renal risk profiles.

A second major finding was the high burden of dyslipidemia in this population. Overall dyslipidemia was present in 73.6% of patients, while low HDL-cholesterol was the most frequent lipid abnormality (50.7%), followed by hypertriglyceridemia (43.1%), hypercholesterolemia (40.9%), and elevated LDL-C/hyperlipoproteinemia (30.7%). In parallel, the cardiovascular profile of the cohort was unfavorable, with 58.7% of patients classified as having intermediate or high ASCVD risk. Together, these results support the view that lipid abnormalities and cardiovascular risk are highly prevalent among adult CKD patients in this hospital-based population.

From the analytical perspective, overall dyslipidemia was not clearly associated with the conventional markers of renal impairment, since serum urea, creatinine, eGFR, albuminuria categories, and KDIGO renal risk did not differ significantly between dyslipidemic and non-dyslipidemic patients. However, dyslipidemic patients exhibited a more altered biological profile, with lower hemoglobin, more frequent anemia, lower proteinemia, lower albuminemia, and a significantly less favorable ASCVD risk distribution. When individual lipid abnormalities were examined separately, a more nuanced pattern emerged: hypercholesterolemia was associated with greater albuminuric burden and worse renal risk stratification despite similar overall renal function, whereas hypertriglyceridemia showed the clearest adverse cardio-renal profile, being associated with higher urea, higher ACR, more severe albuminuria, worse KDIGO risk, and higher cardiovascular risk. By contrast, low HDL-C appeared to be linked mainly to hematological disturbance, particularly anemia, rather than to a clear worsening of renal severity.

The study further showed that worsening renal severity was accompanied by significant changes in lipid and cardiovascular profiles. Across eGFR stages, total cholesterol, HDL-C, LDL-C, and ASCVD risk varied significantly, and advancing CKD was associated with higher blood pressure, greater anemia burden, and a marked shift toward intermediate and high cardiovascular risk. Across albuminuria categories, total cholesterol and triglycerides increased significantly with worsening albuminuria, while severe albuminuria was also associated with lower proteinemia, lower albuminemia, more hypertension, and a distinctly less favorable ASCVD risk profile. These findings suggest that albuminuria and global renal risk may be more closely linked to lipid disturbance than eGFR decline alone.

Finally, in multivariable analysis, lipid abnormalities were not independently associated with impaired renal function after adjustment for age, sex, hypertension, and diabetes. Likewise, most lipid parameters were not independently associated with elevated albuminuria; although hypertriglyceridemia was significantly associated with albuminuria in crude analysis, this association lost statistical significance after adjustment. Overall, these results suggest that while dyslipidemia—

particularly hypertriglyceridemia and hypercholesterolemia—tracks with markers of renal and cardiovascular severity in unadjusted analyses, these relationships are at least partly explained by the broader clinical and metabolic context of CKD rather than representing fully independent associations.

## 2.2. Profile of the study population

In the present study, the population was characterized by a relatively young-to-middle-aged profile, with a mean age of 45.18 ± 16.98 years and a median age of 45 years, together with a clear female predominance (64.1%). The cohort also showed a substantial burden of comorbidity, particularly anemia (57.6%), hypertension (42.4%), and diabetes (33.0%), with an overall median Charlson Comorbidity Index of 3. In addition, the etiological spectrum was heterogeneous, dominated by undocumented or unspecified nephropathies (34.8%) and systemic glomerular diseases (31.9%), particularly diabetic and lupus-related nephropathy. Overall, these findings suggest that our sample reflects a tertiary-care CKD population with mixed etiologies and an already important metabolic and comorbid burden, rather than a narrowly selected renal subgroup.

When compared with previously published CKD cohorts, the age profile of our population appears broadly comparable, but the sex distribution differs more clearly. The mean age in our study was close to that reported by **Adejumo et al.** in southern Nigeria (46.98 ± 16.81 years), but lower than that described by **Sujatha et al.** in India (52.3 ± 16.4 years), **Wang et al.** in China (mean age 55 years), and **Behera** in India (56.66 ± 12.22 years). By contrast, most of these comparison studies reported a male-predominant CKD population, including **Akpan et al.** (63% male), **Adejumo et al.** (62.9% male), **Behera** (64.5% male), **Sujatha et al.** (69.7% male), and **Omole et al** (70% male) (208–213). Thus, although our patients fall within the age range commonly reported in hospital-based CKD studies, the marked female predominance in our cohort appears to be a more distinctive feature.

Several factors may explain this demographic pattern. First, the etiological composition of our cohort was not dominated exclusively by hypertensive nephrosclerosis or advanced age-related CKD, but included a meaningful proportion of systemic and primary glomerular diseases, including lupus-associated nephropathy and focal segmental glomerulosclerosis. Second, recruitment from several hospital departments, including nephrology, internal medicine, endocrinology, cardiology, and rheumatology, may have enriched the study population for metabolic and autoimmune phenotypes, thereby influencing both sex distribution and age structure. In this respect, the contrast with studies such as Akpan et al. and Adejumo et al., where chronic glomerulonephritis, hypertensive nephropathy, and diabetic nephropathy predominated in more male-heavy populations, supports the idea that differences in case-mix and referral pathways may substantially shape the final study profile. Clinically, this is important because the background characteristics of the cohort condition how lipid abnormalities should be interpreted: a younger and more female population with mixed nephropathy mechanisms may not express exactly the same dyslipidemic profile as older, predominantly male cohorts with more uniform vascular or diabetic CKD (208,212).

The comorbidity profile of our patients also deserves emphasis. Hypertension and diabetes were common in our cohort, but their frequencies remained lower than in some comparison studies, particularly for hypertension, which was reported in 75% of patients by Akpan et al., 58.6% by Sujatha et al., and 56.9% in the cohort studied by Wang et al.; diabetes was also more frequent in Wang et al. (46.1%) than in our study, whereas it was less frequent in Akpan et al. (11%). These discrepancies likely reflect differences in age, CKD severity, underlying etiologies, and especially study eligibility

criteria. For example, Behera specifically studied non-diabetic CKD, while Sujatha et al. excluded patients with diabetes mellitus, nephrotic-range proteinuria, lipid-lowering therapy, and certain diuretics. Therefore, direct comparison of raw prevalence figures should remain cautious. Nevertheless, the coexistence in our cohort of anemia, hypertension, diabetes, and moderate-to-high comorbidity burden indicates that dyslipidemia in our population must be interpreted within a broader cardio-renal and inflammatory context rather than as an isolated metabolic abnormality (3,11,209–212).

These comparisons should, however, be interpreted with caution. The selected studies differed substantially in design, sample size, inclusion and exclusion criteria, and CKD stage structure. **Behera** focused on non-diabetic CKD, **Sujatha et al.** excluded diabetes, nephrotic-range proteinuria, lipid-lowering therapy, and some diuretic use, **Omole et al.** included only stages 3–5, while **Wang et al.** and **Nakano et al.** were much larger Asian cohorts with different underlying epidemiologic structures and broader multicenter sampling. Accordingly, the differences observed between our study and the literature likely reflect both true population variation and important methodological differences in case-mix and recruitment (209–211,213,214).

*Table 44 Comparison of the general profile of the population between studies*

| Characteristic | This thesis | Akpan et al. 2014 (212) | Adejumo et al. 2016 (208) | Behera 2020 (211) | Omole et al. 2024(213) | Sujatha et al. 2026 (209) |
|---|---|---|---|---|---|---|
| Country / setting | Morocco, tertiary multispecialty hospital | Nigeria, tertiary hospital | Nigeria, tertiary hospital | India, tertiary hospital | Nigeria, tertiary health facility | India, tertiary care center |
| Design / population | cross-sectional CKD cohort | Cross-sectional, pre-dialysis CKD | Case-control, pre-dialysis CKD | Observational, non-diabetic CKD | Cross-sectional, CKD stage 3–5 | Cross-sectional CKD cohort |
| CKD sample size | 276 | 100 | 105 | 262 | 150 | 99 |
| Mean age (years) | 45.18 ± 16.98 | 38.4 ± 12.6 | 46.98 ± 16.81 | 56.66 ± 12.22 | Majority aged 40–59 years | 52.3 ± 16.4 |
| Sex distribution | **64.1% female**, 35.9% male | 37% female, 63% male | 37.1% female, 62.9% male | 35.5% female, 64.5% male | 30% female, 70% male | 30.3% female, 69.7% male |
| Hypertension | 42.4% | 75% | --- | 32.8% | NR | 58.6% |
| Diabetes | 33.0% | 11% | --- | Excluded by design | NR | Excluded by design |

## 2.3. Burden and severity of renal disease

In our cohort, the renal burden was substantial and clinically advanced. Median eGFR was 39.95 mL/min/1.73 m², and nearly two-thirds of patients (62.68%) were classified in stages G3a–G5, while only 37.32% remained in G1–G2. The stage distribution also showed a notable concentration at the severe end, with G5 alone accounting for 26.81% of the sample and G4 for 15.21%. Kidney damage markers were likewise markedly abnormal: median ACR was 217.4 mg/g, 82.4% of patients were in albuminuria categories A2–A3, 43.1% were already in A3, and more than half of the cohort (56.2%) fell into the very high KDIGO risk category. Taken together, these findings indicate that our study population was not composed mainly of mild CKD, but rather of patients carrying a high burden of advanced renal dysfunction and marked albuminuric injury .

This pattern is broadly consistent with several hospital-based CKD studies, although the degree of severity in our cohort appears particularly marked. In the recent Indian cross-sectional study by Sujatha et al., stages III–V together represented the majority of patients (26.3%, 24.2%, and 22.2%, respectively), and albuminuria was present in 68.7% of cases, also suggesting a cohort enriched with moderate-to-advanced disease. Similarly, Adejumo et al. reported that 68.6% of their pre-dialysis Nigerian CKD patients were in stages 3 and 4. An even more severe distribution was observed by Behera, where 79.01% of patients belonged to stages 4 and 5. In addition, the large Japanese Fukuoka Kidney Disease Registry showed that urinary protein/creatinine ratio increased steadily across CKD stages, from 0.12 g/gCr in G1 to 1.80 g/gCr in G5, confirming that worsening renal function is commonly accompanied by heavier proteinuric burden. Compared with these studies, our cohort seems especially notable for the combination of reduced eGFR, very high ACR burden, and a predominance of very high KDIGO risk (208,209,211,214).

Several factors may explain this pronounced renal severity. First, our work was conducted in a tertiary university hospital and included patients recruited from nephrology and other specialist departments, which likely increased the probability of capturing patients with more complex or established disease. Second, the use of both eGFR and albuminuria, along with KDIGO risk stratification, provides a more comprehensive assessment of renal severity than stage classification alone and may reveal a heavier burden than studies relying mainly on serum creatinine or GFR categories. Third, the very high proportion of A2–A3 albuminuria in our sample suggests that glomerular injury was not only frequent but often advanced; this is clinically plausible, since albuminuria typically intensifies as structural kidney damage progresses, as also reflected in the progressive rise in proteinuria across CKD stages in the Fukuoka registry. Finally, the coexistence in our cohort of anemia, hypoalbuminemia, and substantial comorbidity burden further supports the presence of a biologically advanced CKD population rather than an early-screened community sample (1,13–15,214).

Clinically, these findings mean that our study population represents a group at high cardio-renal risk, in whom renal impairment is not limited to filtration decline but also includes substantial kidney damage burden. This distinction is important because albuminuria and reduced eGFR convey complementary prognostic information, and the predominance of A2–A3 albuminuria together with the high proportion of very high KDIGO risk suggests an elevated risk of progression, cardiovascular

complications, and adverse outcomes. Therefore, the renal profile of our cohort provides a meaningful context for interpreting the dyslipidemia findings, because lipid abnormalities observed in this population are being examined against a background of clinically significant CKD rather than mild renal dysfunction (1, 13–15).

*Table 45 Comparison of renal burden and severity across the most comparable studies (Part 1)*

| Parameter | Your thesis | Sujatha 2026 (209) | Adejumo 2016 (208) | Behera 2020 (211) |
|---|---|---|---|---|
| Sample | 276 CKD patients | 99 CKD patients | 105 pre-dialysis CKD patients | 262 CKD patients |
| Renal stage distribution | G1 28.3%, G2 9.1%, G3a 9.1%, G3b 11.6%, G4 15.2%, G5 26.8% | Stage I 13.1%, II 14.1%, III 26.3%, IV 24.2%, V 22.2% | Stage 1 6.7%, Stage 2 21.0%, Stage 3 43.8%, Stage 4 24.8%, Stage 5 3.8% | Severe CKD predominated: 79.0% were stage 4–5 |
| Main severity summary | 62.7% were G3a–G5 | Majority were stage III–V | Most were stages 3–4 | Very severe case-mix |
| Albuminuria / proteinuria | Median ACR 217.4 mg/g; A1 17.8%, A2 39.1%, A3 43.1% | Albuminuria present in 68.7% | Proteinuria assessed, but no A1/A2/A3 distribution reported in the key results | CKD definition included proteinuria, but no KDIGO ACR distribution reported |
| Integrated renal risk | Very high KDIGO risk: 56.2% | Not reported as KDIGO heat map | Not reported | Not reported |

*Table 46 Comparison of renal burden and severity across the most comparable studies (Part 2)*

| Parameter | Your thesis | Omole/Airaodion 2024 (213) | Akpan 2014 (212) | Nakano 2021 (214) |
|---|---|---|---|---|
| Sample | 276 CKD patients | 150 CKD patients + 50 controls | 100 CKD patients + 100 controls | 4365 non-dialysis CKD patients |
| Renal stage coverage | Full G1–G5 spectrum | Stages 3–5 only | Pre-dialysis stages 1–5 | Full G1–G5 spectrum |
| Stage pattern | G5 was the single largest category (26.8%) | 50 patients each in stage 3, 4, and 5 | Included stages 1–5; used for pre-dialysis severity comparison | G4 had the largest group (1057), followed by G3b (909) and G3a (822) |
| Kidney function severity | Median eGFR 39.95 mL/min/1.73 m² | eGFR fell from 34.97 (stage 3) to 28.96 (stage 4) to 15.67 (stage 5) | Advanced pre-dialysis CKD population | Broad non-dialysis CKD spectrum with progressive worsening by stage |
| Albuminuria / proteinuria | Median ACR 217.4 mg/g; 82.2% were A2–A3 | Albuminuria present in CKD patients but no KDIGO ACR breakdown given in key table | Proteinuria assessed; lipid fractions correlated with proteinuria | Urinary protein/creatinine ratio rose from 0.12 g/gCr in G1 to 1.80 g/gCr in G5 |
| Integrated renal risk | Very high KDIGO risk in 56.2% | Not reported as KDIGO heat map | Not reported | No KDIGO heat map, but strong stage/proteinuria gradient |

## 2.4. Burden and pattern of dyslipidemia

In our cohort, dyslipidemia represented a major metabolic burden. Overall, 203 of 276 patients (73.6%) were classified as dyslipidemic, while 14.1% had undocumented lipid status, suggesting that the observed prevalence may even underestimate the true burden. The lipid profile pattern was heterogeneous, but low HDL-C was the most frequent abnormality (50.7%), followed by hypertriglyceridemia (43.1%), hypercholesterolemia (40.9%), and elevated LDL-C/hyperlipoproteinemia (30.7%). On descriptive analysis, median lipid values were 1.94 g/L for total cholesterol, 0.41 g/L for HDL-C, 1.15 g/L for LDL-C, and 1.51 g/L for triglycerides, with broad dispersion across all fractions. Among dyslipidemic patients, 46.8% were receiving lipid-lowering therapy, and statins were the most frequently documented treatment, although therapeutic information remained unknown in a substantial proportion.

The high prevalence observed in our study is consistent with the literature showing that dyslipidemia is common in non-dialysis CKD, although the exact magnitude varies across studies. Our prevalence of 73.6% was higher than the 60% reported by Adejumo et al. in pre-dialysis CKD patients in southern Nigeria and also higher than the 68.7% reported by Behera in non-diabetic CKD patients in India. Conversely, it was lower than the very high prevalence reported in a recent Indian tertiary-care study, where dyslipidemia affected more than 90% of CKD patients and reached 100% in stage V disease (208,209,211).

Regarding the pattern itself, our findings are broadly aligned with the classical CKD dyslipidemia phenotype, in which triglyceride elevation and low HDL-C tend to predominate. In our cohort, low HDL-C was the commonest abnormality and hypertriglyceridemia was the next most frequent, which is concordant with the Japanese registry analysis by Nakano et al., where advancing CKD stage was independently associated with hypertriglyceridemia and hypo-HDL-cholesterolemia, whereas LDL-C did not show a similar linear stage-related pattern. Likewise, Wang et al. found that triglyceride level was independently and inversely associated with measured GFR, supporting the close link between declining renal function and triglyceride-rich dyslipidemia. Behera also reported a significant decline in HDL with CKD progression, while the Heart India study found low HDL in 96/160 patients and a progressive rise in triglycerides across CKD stages (210,211,214,215).

At the same time, some of the comparison studies showed a somewhat more cholesterol-dominant profile than ours. Akpan et al. reported elevated total cholesterol in 44% of cases and elevated LDL-C in 48%, while Omole et al. similarly described elevated total cholesterol, LDL-C, VLDL-C, and triglycerides together with reduced HDL-C in CKD patients. These differences suggest that, although the general direction of lipid disturbance is shared, the dominant fraction may vary across cohorts (212,213).

This overall pattern is biologically plausible and fits the concept of **uremic dyslipidemia**. In CKD, hypertriglyceridemia is thought to arise mainly from impaired clearance of triglyceride-rich lipoproteins rather than simple overproduction, largely because of reduced lipoprotein lipase and hepatic lipase activity, together with inhibitory effects of apolipoprotein C-III. At the same time, HDL is not only reduced quantitatively but also becomes functionally abnormal, with impaired antioxidant, anti-inflammatory, and reverse cholesterol transport properties. These mechanisms

favor a profile dominated by high triglycerides and low HDL, even when LDL-C is not markedly elevated (3,102-105,107,113-127,135,137,140-154) .

In addition, LDL-related risk in CKD may be underestimated by routine concentration-based measurements alone. CKD is associated with a more atherogenic LDL phenotype, including small dense LDL particles and triglyceride-rich remnant accumulation, meaning that apparently "normal" LDL-C levels do not necessarily indicate a benign lipid state. This may help explain why our cohort showed a high overall burden of dyslipidemia despite a lower prevalence of overt LDL-C elevation than low HDL-C or hypertriglyceridemia (107-109,137).

Clinically, these findings indicate that dyslipidemia in our CKD population was not a marginal comorbidity but a central component of the cardio-renal risk profile. The predominance of low HDL-C and hypertriglyceridemia suggests that the lipid disturbance in this cohort corresponds more closely to the typical CKD-associated atherogenic pattern than to isolated primary hypercholesterolemia. This is important because such a pattern may contribute to cardiovascular risk even when LDL-C is not strikingly elevated. In our study, dyslipidemic patients were also more frequently classified in higher ASCVD risk strata, reinforcing the clinical relevance of these abnormalities within an integrated cardio-renal framework (3,103-105,107,135,137).

From a practical perspective, these results support systematic lipid assessment in CKD patients, with particular attention not only to total cholesterol and LDL-C but also to triglycerides and HDL-C. They also suggest that interpretation of lipid results in CKD should remain contextual, taking into account renal stage, albuminuria/protein loss, and treatment exposure rather than relying only on one lipid fraction in isolation (3,85,86,103-105,135).

*Table 47 Comparison of dyslipidemia studies in CKD: Part A*

| Variable | Your thesis | Sujatha 2026 (209) | Omole 2024 (213) |
|---|---|---|---|
| Country / setting | Morocco, CHU Mohammed VI | India, tertiary center | Nigeria, tertiary health facility |
| Design / sample | Retrospective cross-sectional; n=276 | Cross-sectional; n=99 | Cross-sectional case-control; 150 CKD + 50 controls |
| CKD population | Adult CKD, G1-G5, A1-A3 | Newly diagnosed CKD, stage I-V | CKD stages 3-5 |
| Overall dyslipidemia prevalence | **73.6%** | **>90%**, stage V **100%** | No single overall % stated in abstract snippet |
| Main lipid pattern | **Low HDL 50.7%**, hyperTG 43.1%, hypercholesterolemia 40.9%, high LDL 30.7% | HyperTG, high LDL, low HDL, high VLDL | Elevated TC, LDL, TG, VLDL with reduced HDL |

*Table 48 Comparison of dyslipidemia studies in CKD: Part B*

| Variable | Adejumo 2016 (208) | Akpan 2014 (212) | Behera 2020 (211) |
|---|---|---|---|
| Country / setting | Nigeria, tertiary hospital | Nigeria, pre-dialysis CKD center | India, hospital-based |
| Design / sample | Case-control; 105 CKD + 105 controls | Cross-sectional case-control; 100 CKD + 100 controls | Observational; 262 CKD + 20 controls |
| CKD population | Pre-dialysis CKD stages 1-5 | Pre-dialysis CKD stages 1-5 | Non-diabetic CKD; moderate vs severe CKD |
| Overall dyslipidemia prevalence | **60.0%** | **84.0%** had at least one abnormal fraction | **68.7%** |
| Main lipid pattern | High AIP, high TG, low HDL; LDL also higher | High TC, high LDL, high TG; HDL not clearly different overall | Dyslipidemia common; HDL abnormality most emphasized with progression |

*Table 49 Comparison of dyslipidemia studies in CKD: Part C*

| Variable | Bhattacharjee 2024 (215) | Nakano 2021 (214) | Wang 2016 (210) |
|---|---|---|---|
| Country / setting | India, tertiary care center | Japan, multicenter CKD registry | China, single-center CKD cohort |
| Design / sample | Cross-sectional; n=160 | Cross-sectional registry analysis; n=4,365 | Cross-sectional; n=2,036 |
| CKD population | CKD grades II-V | Non-dialysis CKD G1-G5 | CKD stages 1, 2, 3, 4/5 |
| Overall dyslipidemia prevalence | No single overall % reported in snippet | Focused on lipid subtype prevalence by stage | Focused on subtype associations, not one overall % |
| Main lipid pattern | Low HDL common; TG high; TC and LDL rise in advanced stages | **HyperTG + hypoHDL** are the specific CKD-linked patterns; LDL not linearly related to stage | TG showed the clearest independent inverse association with kidney function |

## 2.5. Relationship between lipid abnormalities and renal function

In our cohort, the relationship between lipid abnormalities and renal function was heterogeneous rather than uniform. Overall dyslipidemia status was not associated with significant differences in the conventional markers of renal impairment, since serum urea, creatinine, median eGFR, eGFR categories, dichotomized renal function, albuminuria categories, and KDIGO renal risk were broadly comparable between dyslipidemic and non-dyslipidemic patients, although albuminuria tended to be higher in the dyslipidemic group. In addition, multivariable logistic regression did not identify overall dyslipidemia, hypercholesterolemia, high LDL-C, hypertriglyceridemia, or low HDL-C as independent predictors of impaired renal function defined by G3a-G5 versus G1-G2. These findings suggest that, in our population, lipid abnormalities were not uniformly linked to reduced filtration function once the major clinical confounders were taken into account.

When total cholesterol was examined separately, patients with hypercholesterolemia showed a significantly more severe renal profile in terms of albuminuria and renal risk stratification, with higher median ACR, more frequent A3 albuminuria, and more severe KDIGO risk distribution. However, median urea, creatinine, eGFR, and the proportion of patients with eGFR <60 mL/min/1.73 $m^2$ did not differ significantly, and the adjusted model confirmed the absence of an independent association between hypercholesterolemia and impaired renal function. This pattern is only partly consistent with some of the comparison studies. Sujatha et al., Omole et al., and Behera reported a progressive rise in total cholesterol with advancing CKD severity and declining renal function, supporting a stage-dependent worsening of dyslipidemia. By contrast, Adejumo et al. did not find a significant difference in mean total cholesterol between CKD patients and controls, and Akpan et al. were likewise unable to clearly correlate lipid fractions with GFR stage. Taken together, the literature suggests that total cholesterol may not behave as a stable or universal marker of filtration decline across CKD cohorts. A plausible explanation is that total cholesterol in CKD is influenced not only by kidney function, but also by proteinuric status, nutritional state, inflammation, and treatment exposure. Indeed, In the literature, It notes that, in predialysis CKD without nephrotic-range proteinuria, total cholesterol may remain normal or only mildly abnormal, whereas proteinuric states tend to produce a more overt hypercholesterolemic pattern. Clinically, this means that total cholesterol in our study appears to reflect a more albuminuric and cardio-renal phenotype than pure loss of filtration. This interpretation should nonetheless remain cautious because the study is cross-sectional and because total cholesterol is sensitive to treatment effects and to the malnutrition-inflammation spectrum frequently present in advanced CKD (208,209,211–213).

High LDL-C showed an even more discordant pattern. In our study, patients with high LDL-C had a significantly higher median eGFR and a different distribution of eGFR stages, but no significant differences in dichotomized renal function, albuminuria categories, KDIGO renal risk, or ASCVD risk distribution after full comparison. Furthermore, LDL-C was not associated with impaired renal function in logistic regression. This result diverges from studies such as Sujatha, Omole, and Behera, which reported increasing LDL-C with more advanced CKD. However, it is consistent with the more methodologically robust findings of Nakano et al., who showed that CKD stage was not linearly associated with abnormal LDL-C after multivariable adjustment, and with Wang et al., who found no independent association between LDL-C and measured GFR. The most likely explanation is that LDL-C concentration alone incompletely captures the LDL abnormality of CKD. As emphasized in our literature overview, CKD is often characterized less by markedly elevated LDL-C concentration than by qualitative changes in LDL particles, especially a shift toward smaller, denser, more atherogenic particles. In addition, lipid-lowering therapy can attenuate differences in LDL-C across CKD stages, and advanced disease may also be accompanied by inflammatory or nutritional factors that lower circulating cholesterol concentrations. The clinical implication is important: a normal or even relatively lower LDL-C value in CKD should not be interpreted as evidence of a benign lipid milieu. The limitation here is that your dataset, like most clinical datasets, measures standard LDL-C concentration rather than LDL particle size, oxidation status, or apolipoprotein composition (209–211,213,214).

Among the individual lipid abnormalities, hypertriglyceridemia showed the most convincing link with renal severity in our data, although this link was stronger for albuminuric and global renal risk markers than for filtration decline itself. Patients with elevated triglycerides had significantly higher urea levels, markedly higher ACR, more severe albuminuria categories, and worse KDIGO renal risk distribution, but median eGFR, creatinine, eGFR categories, and dichotomized renal function were not significantly different. In the adjusted logistic model, hypertriglyceridemia was not an independent predictor of impaired renal function. This partially agrees with the comparison literature. Nakano et al. found that advanced CKD stages were independently associated with hypertriglyceridemia after adjustment, while Wang et al. demonstrated that triglycerides were negatively associated with measured GFR and that more advanced CKD stages carried higher odds of hypertriglyceridemia. Adejumo et al. also reported that elevated triglycerides increased with worsening renal function, and Behera described a significant inverse relationship between triglycerides and eGFR. Sujatha and Omole similarly observed progressive triglyceride elevation with CKD progression. Thus, our findings are directionally consistent with the literature in identifying triglycerides as one of the most relevant lipid fractions in CKD, but they suggest that in our cohort triglycerides were linked more strongly to albuminuric renal injury and integrated KDIGO severity than to eGFR decline alone. Mechanistically, this is biologically plausible, since CKD reduces lipoprotein lipase and hepatic lipase activity, increases apoC-III-mediated inhibition of triglyceride-rich lipoprotein clearance, and promotes accumulation of remnant lipoproteins. Clinically, hypertriglyceridemia in our thesis appears to be the lipid abnormality most suggestive of a heavier cardio-renal burden. Nevertheless, caution is required because its association with impaired filtration was not independent in the adjusted model and may be partly mediated by coexisting albuminuria, protein loss, diabetes, or treatment status (208–211,213,214).

Low HDL-C showed only a borderline relationship with renal function in our study. Patients with low HDL-C had lower median eGFR and a less favorable distribution of eGFR stages, with a larger proportion in G5, but these differences did not reach conventional statistical significance. Likewise, low HDL-C was not independently associated with impaired renal function in logistic regression. In contrast, low HDL-C in our cohort was much more clearly associated with lower hemoglobin levels and a higher prevalence of anemia, suggesting that it may reflect broader systemic illness rather than isolated renal filtration decline. Comparison with the literature again shows a mixed picture. Nakano et al. found that advanced CKD was independently associated with hypo-HDL-cholesterolemia, and Adejumo as well as Behera reported that reduced HDL became more frequent as renal function worsened. On the other hand, Wang et al. observed that although low HDL prevalence increased across CKD stages in crude analyses, the association was attenuated after multivariable adjustment. This makes your result plausible rather than anomalous. Biologically, HDL abnormalities in CKD are complex because they involve not only lower HDL-C concentrations, but also functional impairment of HDL particles, including defective reverse cholesterol transport, reduced antioxidant activity, and diminished anti-inflammatory capacity. Therefore, serum HDL-C concentration may underestimate the true extent of HDL dysfunction. The clinical meaning of your result is that low HDL-C should probably not be interpreted in isolation as a robust marker of reduced eGFR in your cohort, but rather as part of the broader dysmetabolic and inflammatory

profile of CKD. This conclusion remains tentative because your study did not assess HDL functionality, apolipoprotein A-I, or enzymes such as LCAT (208,210,211,214).

Overall, the present results suggest that the relationship between lipid abnormalities and renal function in our cohort is not a simple linear one. The most reproducible signal was observed for triglycerides, whereas total cholesterol and LDL-C showed less consistent associations with filtration decline, and low HDL-C showed only borderline renal associations. This global pattern is broadly compatible with the concept of "uremic dyslipidemia," in which hypertriglyceridemia and HDL abnormalities are generally more characteristic of CKD than isolated elevations in total cholesterol or LDL-C. In practical terms, this means that lipid abnormalities in CKD should not be interpreted solely through the lens of conventional hypercholesterolemia, but rather as part of a wider cardio-renal-metabolic disturbance. At the same time, because this study was cross-sectional, it cannot determine temporality or causality, and the observed relationships may have been modified by treatment exposure, residual confounding, and the heterogeneity of CKD etiologies within the cohort (3,102-105,135,137).

## 2.6. Relationship between lipid abnormalities and albuminuria / KDIGO risk

In our study, the association between lipid abnormalities and renal severity was more evident for **albuminuria and KDIGO prognostic risk** than for reduced eGFR alone. Overall dyslipidemia status was not significantly associated with albuminuria stages or KDIGO risk category, although dyslipidemic patients tended to have higher albuminuria values, with only a borderline trend for ACR. By contrast, when lipid fractions were analyzed separately, the strongest signal came from **triglycerides**, followed by **total cholesterol**, whereas **LDL-C** and **HDL-C** showed weaker or non-significant relationships. This pattern suggests that, in our cohort, lipid abnormalities were linked less to the mere presence of CKD and more to the **severity of glomerular injury and integrated cardio-renal risk burden**.

The most consistent association was observed for **hypertriglyceridemia**. Patients with elevated triglycerides had significantly higher median ACR values, a greater proportion of **A3 albuminuria**, and a less favorable KDIGO risk distribution than those with normal triglyceride levels. In unadjusted logistic analysis, patients with A2-A3 albuminuria had approximately threefold higher odds of hypertriglyceridemia, and high KDIGO renal risk was also significantly associated with hypertriglyceridemia. After adjustment, the association with albuminuria was attenuated to a borderline level, whereas **high KDIGO risk remained independently associated with hypertriglyceridemia**, with an adjusted odds ratio of about 4.07. These findings are broadly consistent with the literature. In the comparative Indian cross-sectional study by Sujatha et al., albuminuria emerged as an independent determinant of dyslipidemia, and the authors emphasized that protein loss and worsening CKD severity were closely linked to adverse lipid patterns. Mechanistically, this can be explained by reduced lipoprotein lipase and hepatic lipase activity, impaired clearance of triglyceride-rich lipoproteins, and increased hepatic lipoprotein synthesis in response to urinary protein loss. Clinically, these results suggest that hypertriglyceridemia may be a marker of a more severe **proteinuric and prognostically unfavorable renal phenotype**, rather than simply of impaired filtration. However, caution is required because the association with elevated

albuminuria itself did not remain formally significant after multivariable adjustment, which indicates possible confounding by hypertension, sex, diabetes, or other correlated renal factors (209).

A second notable finding concerned **high total cholesterol**. In our cohort, patients with elevated total cholesterol had significantly higher median ACR values, a higher proportion of **A3 albuminuria**, and significantly worse KDIGO risk stratification, despite similar median urea, creatinine, eGFR, and dichotomized renal function. In addition, across the three albuminuria categories, total cholesterol increased significantly from A1 to A3. This indicates that hypercholesterolemia in our population tracked more closely with **albuminuric burden and global renal risk** than with reduced filtration alone. This interpretation is compatible with the comparison literature and with pathophysiological reasoning. Proteinuric kidney disease is known to stimulate hepatic synthesis of apolipoprotein B-containing lipoproteins and cholesterol-rich particles, which can produce a more overt hypercholesterolemic pattern than non-proteinuric CKD. The clinical meaning is that elevated total cholesterol may help identify CKD patients with a heavier **glomerular leakage phenotype** and less favorable prognostic stratification. Nevertheless, this should be interpreted carefully, because hypercholesterolemia was not independently associated with the binary outcome of elevated albuminuria in the adjusted logistic model. This discrepancy likely reflects information loss from dichotomizing albuminuria into ACR >30 mg/g versus <30 mg/g, whereas the three-category A1–A3 analysis and the continuous ACR comparison captured gradations of severity more effectively (103–105,111,138,139,149).

By contrast, **high LDL-C** showed only limited evidence of association with albuminuria and KDIGO risk. Although patients with high LDL-C tended to have higher ACR values and a larger proportion of A3 albuminuria, these differences did not reach statistical significance, and LDL-C was not significantly associated with elevated albuminuria in logistic regression. Likewise, KDIGO risk categories were not significantly different according to LDL-C status. These findings suggest that LDL-C concentration alone may not adequately capture the lipid abnormality most relevant to renal severity in CKD. This is biologically plausible, because CKD is often characterized less by markedly elevated LDL-C concentration than by **qualitative LDL abnormalities**, including smaller, denser, and more atherogenic particles, which are not reflected by routine LDL-C measurement. Clinically, this means that a non-significant LDL-C concentration should not be interpreted as evidence of low lipid-related renal risk. A limitation, however, is that particle size, apolipoprotein B, oxidized LDL, and other qualitative indices were not available in our dataset (107–109, 137).

Similarly, **low HDL-C** was not significantly associated with albuminuria severity or KDIGO renal risk in our study. Across albuminuria categories, HDL-C remained relatively stable, and logistic regression showed no significant relationship between low HDL-C and elevated albuminuria or high KDIGO risk. This may initially appear discordant with the conventional concept of uremic dyslipidemia, in which low HDL is common, but it is not necessarily contradictory. CKD-related HDL abnormality is often more **functional than quantitative**: HDL particles may lose part of their antioxidant, anti-inflammatory, and cholesterol efflux capacities even when HDL-C concentration itself shows only modest differences. Therefore, the absence of a strong statistical gradient for HDL-C across albuminuria or KDIGO categories in our cohort does not exclude clinically relevant HDL dysfunction. The practical implication is that HDL-C concentration alone may be an insensitive

marker of renal severity in cross-sectional clinical datasets. This conclusion should remain cautious because HDL functionality, ApoA-I, lecithin-cholesterol acyltransferase activity, and related markers were not measured (107,140-154).

When the results are viewed together, they support a coherent interpretation: in our cohort, **albuminuria and KDIGO risk were most closely linked to triglyceride-rich dyslipidemia and, to a lesser extent, to hypercholesterolemia**, whereas LDL-C and HDL-C concentrations alone were less informative. This pattern is scientifically plausible because albuminuria reflects glomerular injury and endothelial dysfunction, both of which are associated with altered hepatic lipoprotein production, impaired lipoprotein clearance, and ongoing renal lipid accumulation. The comparison study by Sujatha et al. similarly identified albuminuria as a major determinant of dyslipidemia in CKD. Thus, the relationship between lipids and renal severity in your thesis appears to be driven primarily by the **proteinuric and prognostic dimensions of kidney disease**, rather than by filtration decline alone. Still, because your study is retrospective and cross-sectional, temporality cannot be established: lipid abnormalities may contribute to renal injury, but severe proteinuric CKD may also secondarily worsen the lipid profile (4-7;155-200,202).

## 2.7. Cardiovascular risk implications

The cardiovascular implications of our findings should be interpreted primarily in terms of **predicted ASCVD burden**, rather than documented cardiovascular events, since cardiovascular risk in this study was estimated using the **AHA PREVENT-ASCVD equation**, with incorporation of the kidney-enhanced option using ACR when available. In the overall cohort, the cardiovascular risk profile was already substantial: among 276 patients, **34.8% were classified as intermediate risk** and **23.9% as high risk**, meaning that **58.7% of the study population fell within the intermediate- or high-risk ASCVD categories**. This occurred in parallel with a marked dyslipidemia burden, since **73.6% of patients were classified as dyslipidemic**, and the most frequent lipid abnormalities were **low HDL-C (50.7%)**, **hypertriglyceridemia (43.1%)**, and **hypercholesterolemia (40.9%)**. Together, these findings indicate that the cohort carried not only a renal burden, but also a considerable **global cardio-renal risk burden**.

At the analytical level, overall dyslipidemia was significantly associated with a less favorable cardiovascular risk distribution. Compared with non-dyslipidemic patients, dyslipidemic patients were less often classified as low ASCVD risk (**29.6% vs 50.0%**) and far more often classified as high ASCVD risk (**28.1% vs 5.9%**), with a statistically significant overall difference (**$p = 0.023$**).

When lipid fractions were examined separately, the strongest cardiovascular signal emerged for **hypertriglyceridemia**. Patients with elevated triglycerides had a significantly less favorable ASCVD risk distribution (**$p = 0.010$**), with the proportion classified as high cardiovascular risk increasing from **16.9% in the normal-TG group to 33.6% in the hypertriglyceridemic group**.

A similar, though somewhat different, pattern was observed for **high total cholesterol**. Patients with elevated total cholesterol were more frequently classified as high ASCVD risk (**33.6% vs 16.9%, $p = 0.010$**).

By contrast, **LDL-C concentration alone** appeared less informative for cardiovascular implication in our dataset. Although high LDL-C was associated with some biological differences and showed borderline trends for ACR and ASCVD risk, the overall ASCVD risk distribution was **not significantly different** according to LDL-C status. This is an important point for interpretation. In CKD, LDL-C concentration may underestimate true atherogenic burden because routine LDL-C does not capture **qualitative lipoprotein abnormalities**, such as small dense LDL, oxidized LDL, or remnant-rich particles. Therefore, the absence of a strong statistical association for LDL-C concentration alone does not necessarily imply absence of cardiovascular relevance; rather, it may indicate that **quantitative LDL-C is an incomplete surrogate of vascular risk in CKD (107-109,137)**.

The cross-tabulated ASCVD categories differed significantly according to HDL-C grouping (**$p = 0.003$**), with a larger proportion of high-risk patients in the lower-HDL side of the comparison 107,140-154).

## 2.8. Strengths and limitations

Our study has several strengths. First, it included a relatively substantial hospital-based sample of **276 adult CKD patients**, selected from **1,000 screened records** over a **3-year period**, which provided a broad overview of dyslipidemia in CKD in our tertiary-care setting.

Second, the study used a clear methodological framework. The use of a patient-specific **index date** based on the lipid panel, together with a **±30-day window** for related measurements, improved consistency in data collection and reduced timing-related variability in this retrospective dataset.

Third, renal severity was assessed in a comprehensive way using not only **eGFR stages**, but also **albuminuria categories** and **KDIGO risk classification**. This is important because CKD severity is not fully captured by eGFR alone. In addition, the study included multivariable logistic regression, which allowed a more robust assessment of associations beyond simple bivariate comparisons.

However, some limitations must be acknowledged. First, the study had a **retrospective cross-sectional design**, which means that it can identify associations but cannot establish causality or temporal direction. Therefore, it is not possible to determine whether dyslipidemia contributed to renal severity, whether CKD altered lipid metabolism, or whether both were influenced by common underlying factors.

Second, the study was conducted in a **single tertiary hospital**, which may limit the generalizability of the findings. Patients seen in a referral center often have more severe or complex disease than the broader CKD population.

Third, as with many record-based studies, **missing data** may have affected the analysis. A large number of screened records were excluded for missing key information, and some variables remained incomplete even in the final sample, which may have reduced statistical power and introduced selection bias.

Finally, the study assessed only **conventional lipid parameters** and did not evaluate qualitative lipoprotein abnormalities such as apolipoproteins, small dense LDL, or HDL dysfunction,

which may also be important in CKD-related dyslipidemia. This may partly explain why some conventional lipid fractions showed weaker associations than expected.

## 2.9. Clinical implications and future research

### Clinical implications

Our findings suggest that dyslipidemia is common in CKD patients and should be assessed as part of routine cardio-renal evaluation. In clinical practice, lipid abnormalities should not be interpreted in isolation, but rather together with **eGFR, albuminuria, and overall cardiovascular risk**, because these dimensions together better reflect patient risk burden.

The results also support the importance of early identification of patients with combined renal and metabolic risk, particularly those with more severe albuminuria or advanced CKD, in whom cardiovascular prevention strategies may be especially relevant.

### Future research

Future studies should preferably use a **prospective longitudinal design** to clarify the temporal relationship between dyslipidemia and CKD progression. Multicenter studies with larger and more representative populations would also improve generalizability.

It would also be useful for future research to include:

- more complete treatment data,
- repeated lipid and renal measurements over time,
- and, if possible, more advanced lipid markers such as apolipoproteins or qualitative lipoprotein abnormalities.

Such approaches would help better define which lipid abnormalities are most strongly associated with renal progression and cardiovascular risk in CKD patients.

# V. Conclusion

In conclusion, our study shows that dyslipidemia is highly prevalent among adults with CKD at CHU Mohammed VI and occurs in the setting of a substantial renal and cardiovascular risk burden. In this cohort, dyslipidemia affected **73.6%** of patients, with **low HDL-C** and **hypertriglyceridemia** representing the most frequent abnormalities, while renal severity was marked by a high proportion of patients with **eGFR <60 mL/min/1.73 m²**, **A2-A3 albuminuria**, and **very high KDIGO risk**. These findings support the concept that CKD is commonly accompanied by an atherogenic lipid pattern, particularly involving triglyceride-rich lipoproteins and HDL disturbance, as also reported in other CKD cohorts.

In our data, lipid abnormalities appeared to be more closely related to **albuminuric burden, KDIGO risk, and overall cardiovascular risk** than to reduced eGFR alone. However, after multivariable adjustment, the associations between lipid abnormalities and impaired renal function or elevated albuminuria were no longer statistically independent, suggesting that these relationships are influenced by the complex interplay of comorbidities, renal severity, and metabolic factors. Therefore, our results should be interpreted as evidence of an important **cardio-renal association** rather than proof of causality. Overall, these findings underline the value of an integrated evaluation of CKD patients that includes not only renal function, but also albuminuria, lipid profile, and cardiovascular risk assessment, while prospective studies are needed to better clarify the temporal and prognostic significance of these abnormalities.

# Abstract:

**Background:** Dyslipidemia is a common metabolic abnormality in chronic kidney disease (CKD) and contributes substantially to cardiovascular burden. However, the relationship between lipid abnormalities and renal severity remains incompletely defined, particularly in hospital-based populations from low- and middle-income settings. This study aimed to determine the prevalence and pattern of dyslipidemia in adults with CKD, examine the relationship between blood lipid levels and renal function, and assess these findings within an integrated cardiovascular and renal risk framework.

**Methods:** We conducted a retrospective cross-sectional study at CHU Mohammed VI, Marrakech, Morocco, covering the period from January 2022 to December 2024. A total of 1,000 records were screened, and 276 adult CKD patients met eligibility criteria and were included in the final analysis. Renal severity was assessed using CKD-EPI estimated glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR), and KDIGO risk categories. Lipid abnormalities were evaluated from routine lipid profile measurements. Associations were explored using descriptive, comparative, and multivariable logistic regression analyses adjusted for age, sex, hypertension, and diabetes.

**Results:** Dyslipidemia was present in 203 of 276 patients (73.6%). Low HDL-C was the most frequent abnormality (50.7%), followed by hypertriglyceridemia (43.1%). Renal burden was substantial: 62.68% of participants had eGFR <60 mL/min/1.73 m², 82.4% had A2-A3 albuminuria, and 56.2% were classified in the very high KDIGO risk category. Intermediate or high ASCVD risk was observed in 58.7% of the cohort. In crude analyses, hypertriglyceridemia was associated with elevated albuminuria; after adjustment, it remained independently associated with high KDIGO renal risk (adjusted OR 4.066; 95% CI 1.098-15.061; p=0.036). By contrast, lipid abnormalities were not independently associated with impaired renal function, and associations with elevated albuminuria were attenuated after multivariable adjustment.

**Conclusion:** Dyslipidemia was highly prevalent among adults with CKD at CHU Mohammed VI and occurred alongside a marked renal and cardiovascular risk burden. In this cohort, lipid abnormalities appeared to be more closely related to albuminuric burden, KDIGO risk, and global cardiovascular risk than to reduced eGFR alone. These findings support the value of an integrated cardio-renal assessment in CKD patients and suggest that hypertriglyceridemia may identify a more unfavorable renal risk profile, although causality cannot be inferred from this cross-sectional design.

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# قسم الطبيب

أقسم بالله العظيم

أن أراقب الله في مهنتي،

وأن أصون حياة الإنسان في كافة أطوارها، في كل الظروف والأحوال, باذلًا وسعي في إنقاذها من الهلاك والمرض والألم والقلق.

وأن أحفظ للناس كرامتهم، وأستر عورتهم، وأكتم سرّهم،

وأن أكون على الدوام من وسائل رحمة الله، باذلًا رعايتي الطبية للقريب

والبعيد، الصالح والطالح، والصديق والعدو.

وأن أثابر على طلب العلم، وأسخّره لنفع الإنسان لا لأذاه،

وأن أوقّر من علّمني، وأعلّم من يصغرني، وأكون أخًا لكل زميل في المهنة الطبية

متعاونين على البر والتقوى.

وأن تكون حياتي بمصداق إيماني في سري وعلانيتي، نقيةً مما يشينها تجاه

الله ورسوله والمؤمنين.

**والله على ما أقول شهيد**

كليـــــــة الـطب
و الصيدلة - مراكش
FACULTE DE MEDECINE
ET DE PHARMACIE - MARRAKECH

الأطروحة رقم 135 سنة 2026

# شحوم الدم لدى البالغين المصابين بالقصور الكلوي المزمن بالمستشفى الجامعي محمد السادس: الانتشار، الارتباطات السريرية والتقييم المتكامل للمخاطر القلبية والكلوية (2022-2024)

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**أطروحة:**

## قُدِّمت ونوقشت علنًا بتاريخ
## 24/04/2026
## من طرف


**السيد بسام البشيري توفيق**

المزداد في 19/08/2000 بمراكش


## لنيل شهادة الدكتوراه في الطب

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**الكلمات المفتاحية:**

مرض الكلى المزمن؛ اضطراب شحوم الدم؛ فرط ثلاثي الغليسيريدات؛ انخفاض الكوليسترول الحميد(HDL-C) ؛ البيلة الألبومينية؛ معدل الترشيح الكبيبي المُقدَّر؛ الخطر القلبي الوعائي؛ خطر مرض الكلى وفق تصنيف KDIGO


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## لجنة المناقشة

| | | | |
|---|---|---|---|
| السيدة | ا. العواد | أستاذة أمراض الكلى | الرئيسة |
| السيدة | و. فاضيلي | أستاذة أمراض الكلى | المقررة |
| السيدة | س. لكريمي | أستاذة أمراض القلب | عضو |
| السيدة | س. الزاوي | أستاذة علم الأدوية | عضو |
| السيد | ع .مفتاح | أستاذ أمراض الغدد الصماء | عضو |