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RESEARCH ARTICLE – GENERAL BIOCHEMISTRY (MISCELLANEOUS)

Assessment of Serum Cystatin C and Apolipoprotein Levels in Chronic Kidney Disease Patients

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Abstract

Background: Chronic Kidney Disease (CKD) is the presence of kidney dysfunctions less than sixty (ml/min) of the estimated glomerular filtration rate (eGFR) per 1.73 square meters that has prolonged for at least three months; it is widespread and affects over 10% of individuals worldwide.

Objective of Study: The objective of this study was to assess how well the kidney function indicators cystatin C, apolipoprotein A, and apolipoprotein B functioned in people with CKD.

Materials and Methods: In this study cystatin C, apolipoprotein A, apolipoprotein B, creatinine, urea, and uric acid levels were determined. A total of 150 samples of blood, which were gathered from one hundred patients who had chronic kidney disease aged between 20 and 69 years and fifty healthy subjects as controls aged between 23 and 67 years, at the medical City-Baghdad hospital/Iraq during the period from December 2022 to April 2023. Cystatin C, apolipoprotein A, and apolipoprotein B were evaluated by using an enzymatic linked absorption assay (Sandwich Elisa), and the assessments of urea, creatinine, and uric acid were accomplished with apparatus Cobas c111.

Results: Patients with chronic kidney disease had highly significantly raised levels of cystatin C, apolipoprotein B levels, serum creatinine, urea, and uric acid in comparison with the control group (P-value = 0.000). In contrast, the apolipoprotein A levels in the patient groups were considerably lower than in the control group (P-value = 0.000).

Conclusion: In conclusion, cystatin C and apolipoprotein B levels were elevated with kidney dysfunction, while a reduction of apolipoprotein A levels may be used as an indicator of probable risk for individuals with chronic kidney disease (CKD).

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Keywords: CKD; GFR; Apo A; Apo B; Cystatin C.

1. Introduction

Chronic kidney disease is characterized by a decrease in the rate of glomerular filtration and an increase in the amount of albumin in urine excretion, or both of them, globally, the expected range is between 8 and 16 percent, as well as high morbidity and mortality rates, are related with chronic kidney failure which is a substantial burden on the public's health [1]. All cardiovascular mortality over the long term, the evolution of kidney failure, acute renal damage, injuries, elements, and anemia are examples of issues, diabetes continues to be the most prevalent kind of chronic kidney failure. Worldwide, in addition, its numerous causes have become more common in some areas [2]. The most vulnerable are those who live in poverty, to determine end-stage chronic renal failure, both glomerular filtration rate and albuminuria are measured [3]. Depending on their GFR, patients with CKD are categorized into one of five phases. GFR is the best general measure of kidney function and is thought to be a marker of the early stages of chronic kidney disease. Because kidney disease is asymptotic in its early stages and hence difficult to diagnose and identify, it is a silent killer. The patient will experience symptoms and seek medical attention when they reach the end stage of renal disease (ESRD), which is defined as a loss of more than 50% of kidney function [4].

Determining the actual glomerular filtration by utilizing external filtration markers would take extremely much time and impractical, Therefore, Plasma creatinine concentrations are used to calculate values [5]. Cystatin C (Cys C) a 13.3kDa molecular weight endogenous cysteine protein enzyme inhibitor belongs to a protein family with an important function in the intracellular breakdown of various peptides and proteins [6].

Renal function has been evaluated using cystatin C. But in contrast to serum creatinine, the last decades have seen extensive use of cystatin C as a technique for studying how function affects health outcomes. GFR (90 ml/min/1.73 m^2) is the rate at which the glomeruli filter blood, which is considered to be within the normal range for kidney function [7]. One of the parameters used to determine GFR is serum creatinine, along with age, weight, race, gender, and others. The GFR (mGFR) assessed by timed urine collection is claimed to be unaffected by alterations in muscle mass and therefore not rely on serum creatinine when additional factors such as comorbidities exist [8]. apolipoproteins are lipid-binding proteins that create lipoproteins. Compounds that are soluble in oil, such as (lipids, cholesterol, and vitamins that are soluble in fat). lipids are transported by the lymph, cerebral spinal fluid, and the bloodstream. The lipid parts of lipoproteins do not dissolve in water. Nonetheless, apolipoproteins as well as amphoteric molecules, like phospholipids, can surround the lipids to create lipoprotein dissolved in water that can be carried across bodily fluids. apolipoproteins link with lipid transport proteins and receptors of lipoprotein to promote lipoprotein uptake, clearance, structural stabilization, as well as lipid component solubility [9].

Apolipoproteins, are composed of lipoproteins in the plasma and are mostly produced in the small intestine and liver. There are four primary apolipoproteins found in humans: apolipoprotein A, apolipoprotein B, a polipoprotein C, and apolipoprotein E [10]. Apolipoprotein B is the principal structuring protein of particles, and it is essentially needed for the development of the complicated membrane enclosing/carrying molecules of lipids throughout. The main factor in the formation of the plaques that lead to atherosclerosis, or vascular disease, involves elevated levels of apolipoprotein B, particularly those that are linked with increased levels of Low-density lipoprotein particle levels apolipoprotein B-48 and apolipoprotein B-100 which are the two main protein isoforms present in plasma. The liver produces apoB48, whereas the small intestine produces the largest member of the a polipoprotein B family which is apo B-100, that contains 4563 amino acids [11].

Apolipoprotein A1 (apoA1) is an important protein that affects cardiovascular health and the metabolism of lipids. It constitutes an important part of the particles of lipoprotein with a high density (HDL), commonly referred to as "beneficial cholesterol" Apo A1 is essential for regulating cholesterol levels, avoiding the development of atherosclerosis, and enhancing cardiovascular health [12]. Apo A1 structurally makes up a single-chain polypeptide with 243 amino acids. It is divided into two primary domains: firstly, the N-terminal α- -helix domain and secondly, the C-terminal β- sheet domain, ESRD has been linked with reduced apo A-I levels with higher apo B levels, Events associated with coronary artery disease are predicted by apolipoprotein A-I. However, these indicators may be useful for monitoring the efficacy of treatments that affect heart disease mortality [13].

Among those with chronic renal failure, there may be more female patients than male patients for a variety of factors, including (a) Hormonal Differences: variations in sex hormones among females and males can affect the release of these biomarkers and kidney function, For instance, estrogen and other female sex hormones can affect kidney filtration and function [14], (b) Genetic Factors: Individual responses to levels of biomarkers may be influenced by genetic variables [15], (c) Environmental and Lifestyle Factors: These biomarker levels can be impacted by environmental and lifestyle factors, such as nutrition and pollution exposure [16]. This study aimed to identify patients who have chronic kidney disease (CKD) by estimating the levels of cystatin C, apolipoprotein A and apolipoprotein B in patients with CKD.

2. Materials and Methods

2.1. Design of study

The research was planned as a case-control study. The study was accomplished in the following locations within the Medical City Complex in Baghdad City, Iraq (Ghazy Al Hariri Hospital for Surgical Specialists, Kidney Diseases and Transplant Center, the Dialysis Center, Baghdad Teaching Hospital and Nursing Home Private) between the 4th of December 2022 and 9th of April 2023.

This study was done on 150 participants who were divided into 2 groups (100 patients with chronic kidney disease aged between 20 and 69 years and 50 healthy subjects aged between 23 and 67 years). Include every patient who received an expert diagnosis of chronic kidney disease (CKD). In order to investigate certain biochemical markers in both patients and healthy controls.

For people who have chronic kidney dysfunction, apolipoprotein A was measured using a total of 100 samples in the study, apolipoprotein B and levels of cystatin C. Then assess urea, creatinine, and uric acid levels and contrasted with healthy individuals. The laboratories of the medical City of Baghdad Teaching Hospital were used for this research.

2.2. Sample collection

A specially created questionnaire was designed and used for select patients which includes private information (age, sex, place of residency, education, job, etc.) and healthcare information (medical history and medications) information The data was gathered by the researcher speaking directly with the subjects themselves. The technician requested the patient's case files such as blood tests and any other investigations that would be useful to confirm the nephrologist's diagnosis of chronic kidney. Then a venous puncture was performed on each patient to collect five milliliters of blood by disposable five-milliliter syringes. The sample of blood was put in a gel tube and then centrifuged at 3000 rpm just for 10 minutes to separate it. and coagulated at room temperature for approximately (25 C^o) To collect the blood serum and then perform the assay renal function test urea, creatinine and uric acid level by using an automated clinical chemical analyzer (Cobas C111), The residual from serum was split into eppendorf tubes of equal size and then kept at (-20 C) until it used for assessment apolipoprotein A, apolipoprotein B and cystatin C by using the elisa kit (Cloud Clone-USA).

The population being studied was selected based on specific criteria for inclusion in the patient group, such as being adults, in compliance, accepting follow-up, and being diagnosed with chronic renal failure (CKD; GFR tests of less than 60 mL/min/1.73 m^2 or suffering from recurrent proteinuria. Otherwise, the following were excluded criteria: Smokers, Alcoholics, pregnant women, patients with diabetes mellitus, HIV, HCV, multiple myeloma, liver failure, renal carcinoma, kidney transplantation, patients who had chemotherapy and immunotherapy.

2.3. Statistical analysis

The information for each questionnaire was processed and inserted into an Excel sheet file and then analyzed by using the "Statistical Package for Social Science (SPSS) version 26.0". Measurements of the mean and standard deviation were used to present quantitative data. A t-test on

a separate independent sample was used to assess the significance of the variance between the two means; if the P-value was 0.05 or lower, statistical significance was taken into consideration.

The compassion of statistical significance (p-value) of each test was evaluated as follows:

- P-values higher than 0.05 (P>0.05) were considered non-significant (NS).
- P-values below 0.05 (P<0.05) were considered significant in statistical terms (S).
- P-values below 0.01 (P<0.01) were considered to be highly significant in statistical terms (HS).

3. Results

3.1 The distribution of serum apoA, apoB, and cystatin C concentrations in the study groups

The data presented in Table 1 sheds light on differences in several biomarkers, which may be important for understanding the pathophysiological mechanisms that explain the condition under study. The results presented in Table 1, observe that the mean Apolipoprotein A concentration in the CKD patients group (0.2462± 0.142 µg/dl) significantly decreased (P = 0.000) compared to the healthy controls group (1.104 ± 0.13µg/dl), this result agreed with [17].who mentioned how raised lipoprotein(a) levels in CKD patients are at an elevated risk for coronary artery disease.

In contrast, the mean apo B level in CKD patients (3.143± 0.373µg/dl) was highly significantly higher (P = 0.000) than in healthy controls (0.9996± 0.135µg/dl). Moreover the mean of cystatin C were highly significant variations in the mean (5.75± 0.73Vs. 2.158± 0.45mg/dl) between the control group and the patient group.

Table 1. Comparisons between the levels of apolipoprotein A, apolipoprotein B and cystatin C for the study groups

Variables	Control group Mean ± Std.	Case group Mean ± Std.	P-Values
apolipoprotein A (mg/dl)	1.104 ± 0.13	0.2462± 0.142	< 0.0001
apolipoprotein B (mg/dl)	0.9996± 0.135	3.143± 0.373	< 0.0001
cystatin C (ng/dl)	2.158± 0.45	5.75± 0.73	< 0.0001

3.2 Distribution of S.creatinine, urea and uric acid concentrations in the study groups

The results presented in Table 2, observe urea, creatinine, and uric acid levels in serum were significantly different between the patient and control groups with a p- value of less than 0.01. The mean of urea (139.0± 41.1Vs. 4.53± 0.57), correspondingly, there were highly significant variations in the mean of serum creatinine (8.984± 3.1Vs. 0.96± 0.1303) and the of mean serum uric acid (12.42± 2.2Vs. 4.53± 0.57) between the control group and the patient group.

Table 2. Comparisons between the levels of urea, creatinine and uric acid between cases and controls

Variables	Control group Mean ± Std.	Case group Mean ± Std.	P-Value
urea (mg/dl)	33.10± 7.23	139.0± 41.1	< 0.0001
S. creatinine (mg/dl)	0.96± 0.1303	8.984± 3.1	< 0.0001
S. uric acid (mg/dl)	4.53± 0.57	12.42± 2.2	< 0.0001

Data illustrated in Fig. 1 demonstrated that the apo A levels are significantly lower in patients across all age groups compared to the control group (p < 0.0001), indicating potential alterations in lipid metabolism associated with the studied conditions as with the study by Henry et al. [27] , in contrast patients exhibit significantly higher levels of apo B than the control group (p < 0.0001) in all age groups, suggesting a possible increased risk of cardiovascular complications.

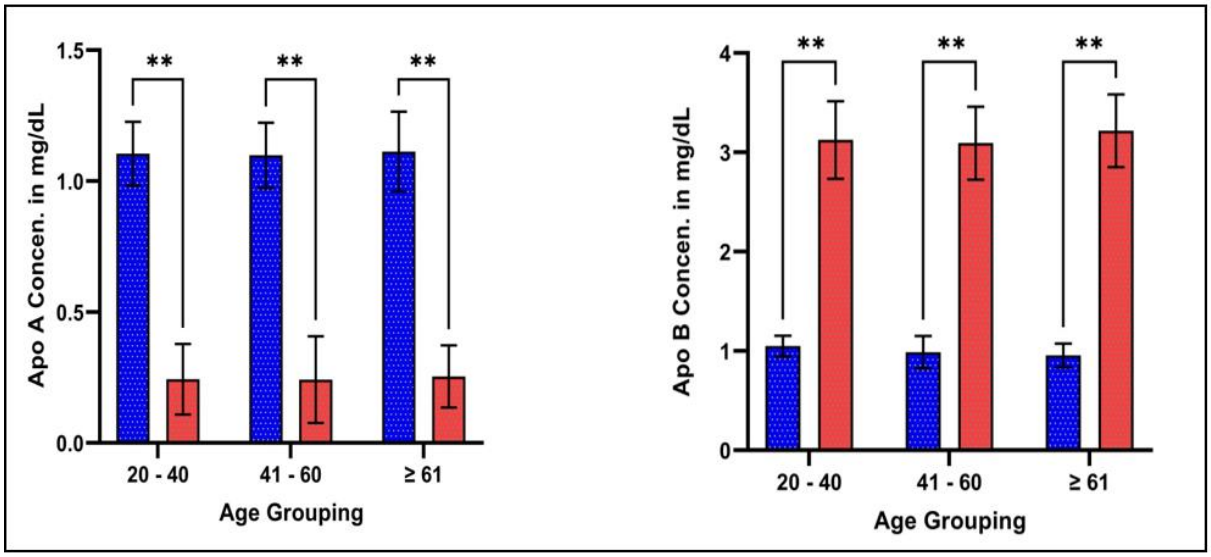

Fig. 1. The levels of Apo A and Apo B across all age groups

Data illustrated in Figs. 2 and 3 demonstrates significant discrepancies between various age groups (20 to 40, 41 to 60, and ≥ 61) within both the patient group and the control group across several chronic kidney disease (CKD) related parameters. These parameters include apo A, apo B, cys C, creatinine, urea, and uric acid.

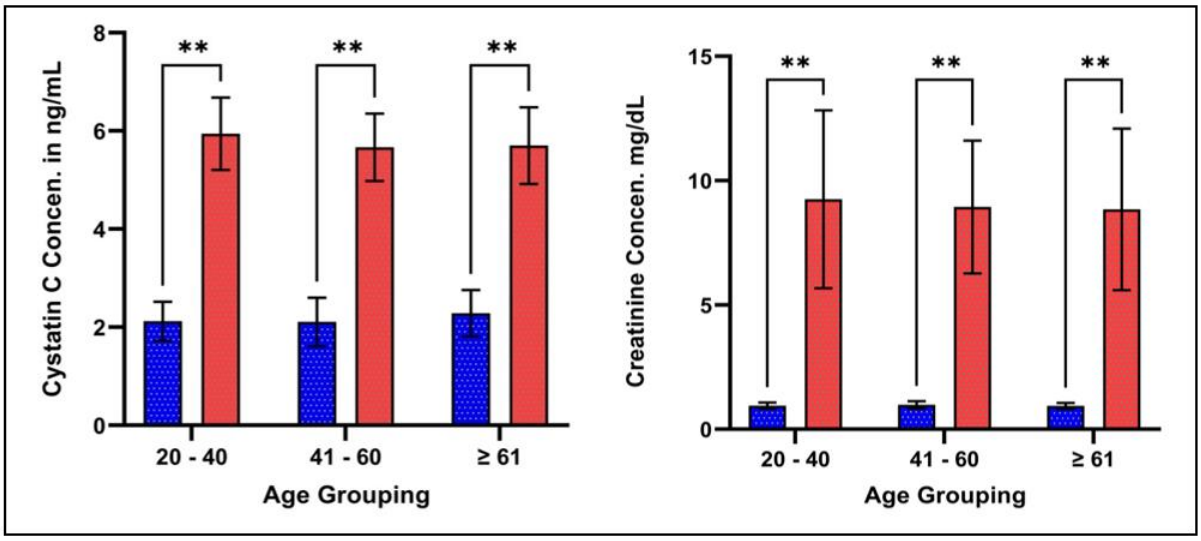

Fig. 2. The levels of cystatin C, creatinine, across all age groups

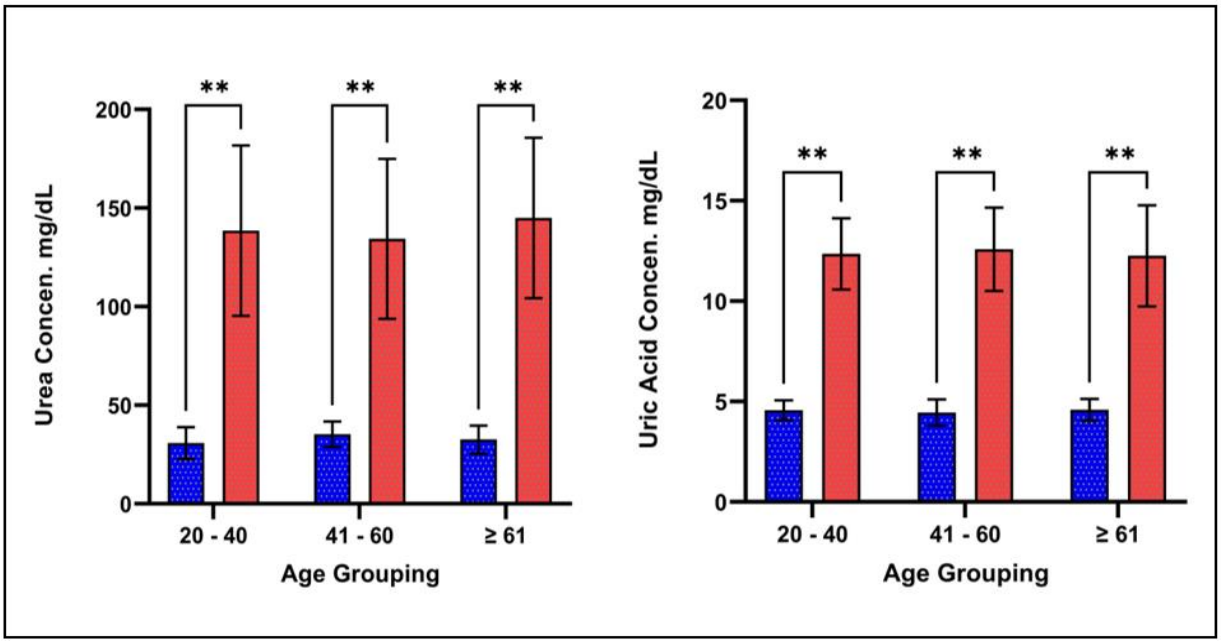

Fig. 3. The levels of urea and uric acid across all age groups

4. Discussion

Both Apo A and Apo B demonstrated highly significant differences between the two groups. Cardiovascular disorders have been linked to the dysregulation of these apolipoproteins. Showing that the patients had a higher risk of cardiovascular problems, the function of apolipoprotein A and apolipoprotein B as novel cardiovascular indicators in end-stage renal failure and chronic kidney disease.

Our research found a positive relationship between serum cystatin C, apo A1 and apo B levels with chronic kidney disease. It highlights how crucial it is to take all of these factors into consideration when estimating cardiovascular risk in individuals with renal disease. These results are compatible with another study done by Zhao, who suggested an assumption related to apolipoprotein A1 and apolipoprotein B levels in CKD patients and revealed that the mean had a substantial difference of the level of apolpoprotein B between the chronic renal disease patients and the control groups, as well as the incidence of CKD stages 2–5 were significantly correlated with increases in serum Apo B levels in chronic kidney patients [18]. While there are notable correlations between higher of serum apolipoprotein A1 and decreased chronic kidney disease prevalence as well as increased eGFR were identified in the study by Geok et al [19]. Additionally to apoA1 function in the metabolism of cholesterol, apoA1 includes anti-inflammatory properties. It reduces the expression of adhesion molecules, lowers the level of pro-inflammatory cytokines, and activates signaling pathways regarded as anti-inflammatory. These anti-inflammatory characteristics facilitate understanding

how apoA1 has cardioprotective benefits [20]. The concentrations of creatinine, and urea were significantly elevated in the patient group. This suggests possible renal impairment or dysfunction among the patients, highlighting the importance of monitoring kidney health in the studied population; additionally, levels of uric acid were highly significantly elevated in the patient group. Hyperuricemia has been linked to various metabolic disorders, indicating an increased risk of conditions like gout and chronic kidney diseases. several CKD-related indicators, such as apolipoprotein B, cystatin C, creatinine, urea, and uric acid were significantly higher in the patient group than in the control group as in the study by Yang et al [21].

The gold standard for measuring kidney function has been serum creatinine, often known as glomerular filtration rate (GFR).regardless of the age, gender, weight, illness condition, or endogenous production, the optimal GFR marker should be produced at a constant rate [22]. The use of cys C concentrations as an intrinsic indicator of kidney function in people at risk of or suffering from chronic renal failure, showing that Cys C performs comparably to or better than the clinical assessment of S.cr level in differentiating between healthy kidney function and kidney dysfunction [23]. Creatinine levels have been demonstrated to be less reliable than cystatin C in several patient populations. It recognizes previous, significant mild impairments in renal function; cystatin C is a highly well-established marker of morbidity, mortality, and the progression of end-stage renal disease [24]. We noticed that increased overall mortality and coronary artery disease are strongly associated with higher apolipoprotein B and lower apolipoprotein A1 in chronic kidney disease patients and can be used this result as a significant risk indicator in a different fields, including dialysis [25]. Investigated a diverse of chronic kidney disease (CKD) related particularly, the study assesses multiple criteria including apolipoprotein A, apolipoprotein B, cystatin C, creatinine, urea and uric acid levels in individuals with chronic kidney disease (CKD) comparing with the healthy subjects group. Based on the results, there are significant disparities in these biomarker concentrations between these two groups, pointing to their possible use in CKD diagnosis and monitoring [26].

Moreover, cystatins C levels in the patients group have significantly higher levels than the control group ($p < 0.0001$) in all age groups, indicating potential kidney dysfunction or impairment, creatinine levels in the patients group show significantly higher levels than the control group ($p < 0.0001$) in all age group, suggesting possible kidney dysfunction, Urea levels in Patients group have significantly higher levels than the control group ($p < 0.0001$) in all age groups, further indicating potential kidney dysfunction. Finally, uric acid levels in the patients group exhibit significantly higher levels than the control group ($p < 0.0001$) in all age groups, indicating potential metabolic disorders. These results indicate that the condition under study is linked to significant variations in various of biomarkers throughout different age groups. There may be clinical implications to the variances observed and highlight the significance of considering age-related variables when evaluating the results. However, further research and greater cohort studies are needed to confirm and expand upon these findings.

5. Conclusion

Patients with chronic kidney disease (CKD) frequently have complications, this study offers insightful information on several chronic kidney disease (CKD) related topics and their correlation with biomarkers, It was shown that there was a strong correlation between protein concentration and absorbance at 450 nm, pointing to the possibility of developing accurate quantitative techniques for determining protein concentration, this correlation has applications that promise to facilitate reliable protein assessment in biochemical and clinical research. The ability to accurately identify individuals who have abnormal biomarker levels was made possible by the exceptional specificity, sensitivity, and accuracy of the diagnostic tests for several CKD biomarkers. We observed that the level of cystatin C increased with renal dysfunction as well as useful as a diagnostic biomarker with considerable potential, moreover among all lipid indicators in patients, serum apolipoprotein B level had a significant association with chronic kidney disease. The development of chronic kidney disease may occur before the serum apolipoprotein B level rises. Screening and decreasing serum apolipoprotein B levels could be a different strategy for chronic kidney disease treatment and prevention. This is compatible with research indicating that CKD is significantly associated with decreased Apo A1 and increased Apo B and B/A1 ratio is significantly higher in CKD patients. According to our study reduction of apo A and elevation of apo B may raise cardiovascular risk and may serve as a predictor for potential risk in chronic kidney disease patients.

Ethical Approval

Ethical approval for this study was granted by the Ethical Committee of the Iraqi Ministry of Health (no.1831).

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Nomenclature & Symbols

CKD	Chronic Kidney Disease	GFR	Glomerular Filtration Rate
CysC	Cystatin C	ESRD	End Stage Renal Disease
HDL	High Density Lipoprotein	SPSS	Statistical Package for Social Science
VLDL	Very Low Density	Apo A	Apolipoprotein A
LDL	Low Density Lipoprotein	Apo B	Apolipoprotein B
CAD	Coronary Artery Disease	S.Cr	Serum Creatinine
CVD	Cardio Vascular Disease	LP(a)	Lipoprotein a

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