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Lipocalin level and indicators of lipid metabolism in the initial stages of chronic kidney disease against the background of obesity

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Abstract

Introduction: In recent decades, the number of patients with chronic kidney disease (CKD) and obesity has increased. The pathological cascade that combines these pathologies is characterized by an imbalance of adipokines, a change in metabolic homeostasis indicators, in particular, a violation of lipid metabolism, and low-intensity inflammation. Neutrophil gelatinase-associated lipocalin (NGAL, lipocalin-2) is a small protein purified from neutrophil granules and can serve as a biomarker of kidney pathology against the background of obesity formation.

The purpose is to evaluate changes in lipocalin-2 level as a marker of early diagnosis of damage to the renal tubular apparatus and its relationship with individual indicators of lipid metabolism in patients with the initial stages of CKD against the background of obesity.

Materials and methods: 304 patients with chronic kidney disease (134 women and 170 men) and 30 practically healthy persons were examined. Patients were divided into 2 groups: the first group consisted of 148 patients with stage 1 of CKD and obesity and the second group consisted of 156 patients with stage 2 of CKD and obesity. All patients underwent general clinical examinations, determination of body mass index, indicators of glomerular filtration rate, microalbuminuria, and determination of lipocalin in urine and lipid panel indicators. Statistical processing of the obtained results was carried out using the Statistica 10.0 statistical analysis program.

Results: The increase of NGAL excretion with urine was greater in patients of the second group with an increased body mass index. An increase in NGAL level in urine was found to be a significant predictor of albuminuria, especially among patients of the second group. Calculated according to the CKD-EPIcysC/cr formula, GFR indicates a 1.5-fold decrease ($p<0.001$) of this indicator in patients of the second group compared to the first group, which confirms the impairment of kidney function, despite normal creatinine values.
A direct correlation of medium strength was established between NGAL and BMI in both groups - $r1=0.45$, $r2=0.58$, respectively ($p1.2<0.05$), between NGAL and microalbuminuria - $r1=0.45$, $r2=0.48$, respectively ($p1.2<0.05$). In patients of the second group, a direct correlation of average strength was found between the indicator of daily albuminuria and BMI ($r=0.56$, $p<0.05$), and an inverse correlation of average strength between NGAL and GFR (CKD-EPIcysC/cr) - $r2= - 0.53$. A weak positive correlation was established between microalbuminuria and triglyceride levels in patients of group 2 ($r2=0.3$, $p>0.05$). Analysing correlations between NGAL and specific indicators of lipid metabolism, there was no reliable relationship between the level of lipocalin and general cholesterol as well as between lipocalin and high- and low-density lipoproteins. Instead, a positive correlation was observed between NGAL and triglyceride levels in patients of group 2 ($r2= 0.51$, $p<0.05$).

Conclusion: Thus, the study of changes in the level of lipocalin-2 in the early stages of CKD, which developed against the background of obesity, can serve as a marker of damage to the tubular apparatus, as indicated by the average inverse correlation between the glomerular filtration rate and the direct correlation between lipocalin and microalbuminuria. Also, in the early stages of CKD against the background of obesity, there is a lipid metabolism imbalance – an increase of general cholesterol, triglycerides, low-density lipoprotein levels, and a decrease of high-density lipoprotein levels. Dyslipidemia, which develops in the early stages of CKD and is associated with obesity, probably increases the progression of renal tissue damage and is a risk factor for cardiovascular events.

Keywords: Chronic kidney disease, Obesity, Albuminuria, liPocalin, Lipid metabolism

Introduction

Chronic Kidney Disease (CKD) is a global healthcare problem. The frequency and prevalence of CKD are increasing, especially in the early stages, often asymptomatic, and thus its actual prevalence may be even higher, with an annual mortality rate exceeding 20% among patients undergoing renal replacement therapy. The burden of comorbid conditions and the cost of caring for CKD patients are high, so the primary focus should be on strengthening screening and early detection of CKD, when measures aimed at preventing CKD progression can be effective. There are several reasons for the development of CKD, the most common of which in Western countries are arterial hypertension and diabetes mellitus. However, according to D.D. Ivanov (2018), there is a broader spectrum of etiological factors, including infectious, autoimmune, genetic, obstructive, and ischemic kidney damage. Risk factors for CKD also include gender, age, smoking, overweight, obesity, arterial hypertension, and a family anamnesis [1, 2].
Regardless of the cause, patients with CKD are at an increased risk of Cardiovascular Diseases (CVD). Therefore, the National Kidney Foundation has classified patients with this disease as being in the ‘highest risk’ category for the letter [3].
As mentioned above, one of the significant risk factors for CKD is overweight or obesity. According to Csaba P. Kovesdy, S. Furth, C. Zocalli (2017), due to the increasing prevalence of obesity in the population, there has been a more frequent occurrence of both cardiovascular diseases and CKD. Additionally, a high body mass index (BMI) is considered one of the most significant risk factors for the development of CKD [4].
Currently, it is known that the main markers of kidney function, such as creatinine and Glomerular Filtration Rate (GFR), are not sensitive enough for the diagnosis of CKD, especially in its early stages. Therefore, new biomarkers that indicate kidney function impairment are being studied, and through their use, CKD can be diagnosed and its progression predicted earlier than changes in serum creatinine levels and GFR occur. [5].
Neutrophil Gelatinase-Associated Lipocalin (NGAL) is one of the modern and studied biological indicators used as a biomarker for both acute and chronic kidney damage. The presence of NGAL in urine indicates damage to

the renal tubules and interstitium. According to S.A. Jaberi et al. (2021), NGAL serves as a transport protein responsible for various physiological processes such as inflammation, immune response, and metabolic homeostasis. Lipocalin is also expressed in various tissues of the body, including the kidneys, liver, lungs, trachea, small intestine, bone marrow, macrophages, and adipose tissue [6, 7].

The results of certain studies have shown that in the group of patients with CKD against the background of increased body mass, the levels of NGAL in the blood and urine were higher than in the group without CKD. The low molecular weight of NGAL allows it to be easily filtered through the glomeruli and later reabsorbed in the proximal tubules. If damage to the renal tubules occurs, the reabsorption changes, and as a result, NGAL excretion begins earlier. It is likely that damage to the tubular epithelium leads to an increase in NGAL concentration in both blood serum and urine [8-10].

Chronic Kidney Disease (CKD) is also associated with dyslipidemia. Hyperlipidemia is a common companion of kidney diseases, and in some cases, it reflects the severity of renal impairment. The 'nephrotoxic' effect of lipids has been studied since 1982 when J. Moorhead proposed a theory about the damaging effects of lipid metabolism products on the endothelium of glomerular capillaries. Since then, it has been known that mesangial cells, which have receptors for Low-Density Lipoproteins (LDL), bind and oxidize them, initiating a cascade of pro-inflammatory cytokine production, stimulating mesangial proliferation, and leading to the development of glomerulosclerosis. Lipoproteins deposited in the basement membrane of cells bind to negatively charged glycosaminoglycans neutralizing their negative charge and increasing membrane permeability to proteins. At the same time, lipoproteins filtered in the glomeruli settle in the renal tubules, inducing tubulointerstitial processes and contributing to the progressive decline in their function [11, 12].

Low-grade systemic inflammation with progressive weight gain affects other organs, including the kidneys. Local lipid accumulation in various organs acts as a trigger for end-organ damage. There is currently evidence that dysfunction of adipose tissue in patients with increased body weight can lead to comorbidities, including Chronic Kidney Disease (CKD). However, the mechanisms of such an impact are not yet fully understood. Glomerulopathy associated with obesity requires the study of tubulointerstitial damage mechanisms and early diagnostic markers of CKD against the background of obesity [13-15].

The purpose is to evaluate changes in lipocalin-2 level as a marker for early diagnosis of renal tubular damage and its correlation with specific lipid metabolism markers in patients with early stages of Chronic Kidney Disease (CKD) against the background of obesity.

Materials and methods:

304 patients with chronic kidney disease (134 women and 170 men) hospitalized in the Department of arterial hypertension of Communal non-commercial enterprise 'Ivano-Frankivsk Regional Clinical Cardiologic Centre of Ivano-Frankivsk City Council' and in the Department of Urology and Cardiology Department of Communal Non-Commercial Enterprise 'Central City Clinical Hospital of Ivano-Frankivsk City Council' in Ivano-Frankivsk City (Ukraine) was examined. The average age of the examinees was 55.36±2.02 years for women and 47.45 years ± 2.66 years for men.

The body mass index was calculated according to the Quetelet formula: BMI=body weight, kg/ (height), m^2 (kg/m^2). Stage 1 of CKD was diagnosed in 148 patients (68 women and 80 men, whose average age was 46.43 years ± 3.77 years), and stage 2 was diagnosed in 156 patients (74 women and 82 men, whose average age was 53.07 years ± 2.61 years). Patients were divided into 2 groups: the first group consisted of 148 patients with stage 1 of CKD and obesity and the second group consisted of 156 patients with stage 2 of CKD and obesity. The control group consisted of 30 practically healthy people (13 women and 17 men), who's average age was 41.1 years ± 1.6 years.

Among the causes of CKD, upper urinary tract infections accounted for 11.8%, urolithiasis for 19.89%, previously diagnosed glomerulonephritis with symptomatic renoparenchymal arterial hypertension for 15.76%, developmental anomalies of the genitourinary system for 6.9%, essential arterial hypertension for 29.1%, and ischemic heart disease with stages 1-2A of heart failure for 18.89%. The average duration of CKD was 7.1 years ± 4.2 years. Exclusion criteria included diabetes mellitus, hypothalamic and endocrine obesity, acute myocardial infarction, stage 4 of congestive heart failure according to NYHA, liver failure, and stage 3-4-5 of CKD. All patients underwent a general clinical examination. Albumin in the 24-hour urine was determined using the

turbometric method with the Microalbumin diagnostic kit (Germany) and was evaluated in mg/day. Glomerular filtration rate was calculated using the CKD-EPI formula based on creatinine and cystatin C levels, and their combination (CKD-EPIcysC/cr) (ml/min/1.73 m^2) using the National Kidney Foundation calculator (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). Cystatin C levels in blood serum (in healthy patients - 0.79 mg/l–2.15 mg/l) were measured using the immunoassay method with the Human Cystatin C ELISA kit (Czech Republic) on a STAT FAX analyser (No. 7898). Levels of Neutrophil Gelatinase-Associated Lipocalin (NGAL) (ng/ml) in urine were determined using the sandwich immunoassay method (in healthy patients – 0.16 ng/ml–10 ng/ml) with the HUMAN NGAL ELISA Kit (USA). All immunoassay tests were performed on a STAT FAX analyser (No. 7898).

The determination of total cholesterol in blood serum was performed using the colorimetric method with the Liquick Cor-CHOL 30 kit (Poland). LDL cholesterol was determined using the CHOLESTEROL-LDL-CpL kit (Ukraine) and the colorimetric method. LDL particle number (LDL-P) was measured using the CORMAY LDL DIRECT 60 kit (Poland), and triglycerides were assessed by the colourimetric method with the Liquick Cor-TG 60 kit (Poland).

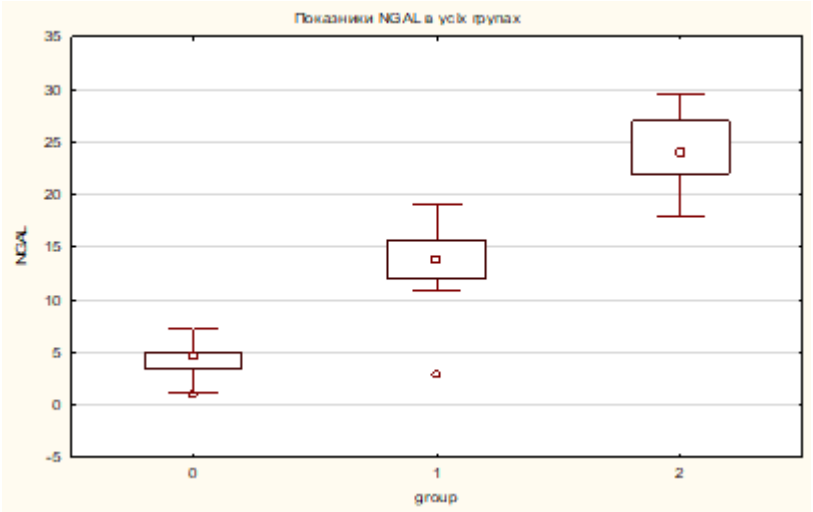
The research protocol was approved by the ethics committee of Ivano-Frankivsk National Medical University, protocol No. 97/17 of 19 October 2017. All patients provided informed consent to participate in the study. The research was conducted following the principles of the Helsinki Declaration of the World Medical Association, "Ethical Principles for Medical Research Involving Human Subjects" of 1 October 2008, No. 900_005.

The statistical processing of the obtained results was carried out using the statistical analysis software Statistica 10.0. For quantitative variables, mean values (M) and standard deviations (SD) were calculated when the data followed a normal distribution and the median with lower and upper quartiles (Me [LQ; UQ]) when the distribution deviated from normal. For qualitative variables, the absolute frequency of manifestations (number of examined cases), the frequency of feature occurrence in percentage (%), or a 95% Confidence Interval (CI) were calculated. The distribution type of the data was analysed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Statistical analysis was performed using non-parametric methods (Kruskal-Wallis test) since most variables had a distribution different from normal. Spearman's rank correlation coefficient was used to assess correlation relationships. The results were considered statistically significant at $p<0.05$.

Results

In recent years, various early specific markers of kidney damage have been actively studied. In particular, Gharishvandi F., Kazerouni F., Ghanei E., et al. (2015), analysed the role of lipocalin-2 in the diagnosis of renal diseases, suggesting its role as a new biomarker of chronic kidney disease [16].

According to the results of our research, the excretion of lipocalin-2 in the urine of patients in The first and the second groups exceeded the values in healthy individuals by 3.6 and 6.3 times, respectively ($p1,2<0.001$) **(FIGURE 1).**The increase in NGAL excretion in the urine was more pronounced in patients in the second group with an elevated body mass index. When comparing u-NGAL values in patients from both groups, it was found that in patients with stage 2 of CKD with obesity, it was 1.8 times higher ($p<0.05$) than in stage 1 of CKD with obesity **TABLE 1.**



*NGAL levels in all groups

FIGURE 1. Lipocalin-2 levels in all studied patient groups

The level of daily microalbuminuria in patients in the first and the second groups also exceeded the values in healthy individuals by 7.4 and 8.9 times, respectively (p1,2<0.001) **(FIGURE 2).** When comparing the levels of daily microalbuminuria in patients from both groups, it was found that in patients with stage 2 of CKD with obesity, microalbuminuria was 1.2 times higher (p>0.05) than in stage 1 of CKD with obesity.

TABLE 1. Characteristics of laboratory parameters in patients with CKD of stages 1 and 2 and obesity.

Indices	**Healthy (Group 0), n=30**	**Group 1, n=148**	**Group 2, n=156**
Age, years	41.10 ± 1.6	46.43 ± 3.77	53.07 ± 2.61
BMI, kg/m^2	21.9 [21.00; 22.60]	34.2 [33.00; 35.50]	36.2 [36.10; 38.60]
Albuminuria, mg / day	19.00 [18.00; 22.00]	121 [100; 134]*	170 [156; 189]*
NGAL, ng/ml	4.6 [3.40; 4.99]	13.80 [12.00; 15.70]*	24.00 [22.00; 27.00] *°
Creatinine, µmol / l	78.00 [76.00; 87.20]	89.90 [88.00; 100.00]*	112.00 [96.00; 116.00]*°
GFR, ml / min / 1.73 m^2 CRD-EPIcysC / cr	110 [101; 118]	98 [91.00; 100.00]*	79.00 [62.00; 88.00] *°
Total cholesterol, µmol / l	4.30 [4.10; 4.80]	6.3 [5.35; 7.10]*	6.3 [5.70; 7.88]*
Triglycerides, µmol / l	1.57 [1.38; 1.67]	1.87 [1.79; 1.96]	1.90 [1.78; 2.50]
LDL, µmol / l	2.2 [1.99; 2.80]	3.40 [2.89; 3.80]	3.88 [3.56; 3.99]*
HDL, µmol / l	1.76 [1.60; 1.90]	1.09[0.92; 1.23]	0.81 [0.80; 0.94]*

* - statistically significant difference in indicators compared to the healthy group
° - statistically significant difference in indicators in comparison with group 1

The increasing level of NGAL in urine significantly predicted albuminuria, especially among patients in the second group. Calculated using the CKD-EPIcysC/cr formula, the eGFR indicates a 1.5-fold decrease (p<0.001) in this parameter in patients of the second group compared to the first group, confirming kidney function impairment despite normal creatinine levels.

A direct correlation of moderate strength was established between NGAL and BMI in both groups - r1=0.45, r2=0.58, respectively (p1, 2<0.05), and between NGAL and microalbuminuria - r1=0.45, r2=0.48, respectively (p1,2<0.05).

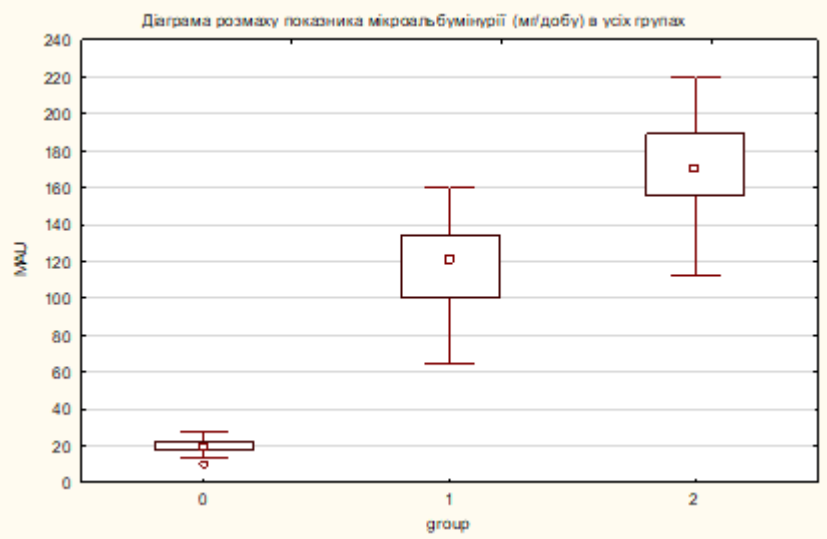


*Diagram of microalbuminuria indicators (mg/day) in all groups

FIGURE 2. Indicators of daily microalbuminuria in all groups of examined patients

In patients of the second group, a direct correlation was found between the average daily albuminuria and BMI ($r=0.56$, $p<0.05$), indicating a deterioration in kidney function in the context of obesity. Additionally, in patients of the second group, a reverse correlation was observed in the strength of the relationship between NGAL and eGFR (CKD-EPIcysC/cr) - $r2= -0.53$ ($p2<0.05$), indicating impaired tubular function even at the early stages of CKD.

Our findings align with the research of Dahiya K., Prashant P., Dhankhar R. (2023), which demonstrated that the onset of microalbuminuria and a slight decrease in eGFR occur later than the appearance of NGAL in the urine, reflecting earlier signs of kidney damage when urinary microalbumin may not yet be detectable. Various clinical studies have shown that the emergence of lipid metabolism disorders in patients with kidney disease and obesity worsens the prognosis of the disease due to the acceleration of the development of not only atherosclerosis and cardiovascular complications but also nephrosclerosis [17-18].

Analysing the lipid metabolism indicators, an increase in the levels of total cholesterol, triglycerides, LDL, and a decrease in HDL levels were observed in patients from both groups. A weak positive correlation between MAU and triglycerides in patients of the second group was established ($r2=0.3$, $p>0.05$). When analysing the correlation between NGAL and lipid metabolism parameters, no significant correlation was found between lipocalin and total cholesterol, between lipocalin and high and low-density lipoproteins. However, a positive correlation was found between NGAL and triglycerides in patients of the second group ($r2=0.51$, $p<0.05$). Our results are consistent with the findings of K. Rosenstein and Lisa R. Tannock (2022), who also showed that in CKD, proteinuria correlates with the levels of total cholesterol and triglycerides, although levels of LDL (and thus total cholesterol) are typically not elevated [19].

Discussion

CKD is a global healthcare problem, and its frequency and prevalence have been increasing in recent years. CKD, especially in its early stages, is often asymptomatic, which may lead to an actual prevalence of this condition higher than estimated. The relation between obesity and chronic kidney disease is quite complex, and this complexity can be explained by shared pathophysiological mechanisms (such as chronic inflammation, increased oxidative stress, and hyperinsulinemia), common clusters of risk factors, as well as comorbid conditions (insulin resistance, hypertension, and dyslipidemia). The burden of concomitant diseases, including obesity, and the consequences of CKD are intricate, prompting recent research in the direction of screening and early detection with an evaluation of both lipid and carbohydrate metabolism indicators and markers of renal tubular dysfunction [20-22].

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, is a small protein and identified adipokine purified from neutrophil granules that is considered a good marker of acute and chronic kidney disease. It belongs to the lipocalin family and is encoded by the lipocalin-2 (LCN2) gene on chromosome 9. NGAL is a transport protein responsible for various physiological processes, including inflammation, immune response formation, and metabolic homeostasis [23, 24].

Elevated levels of lipocalin-2 in serum and urine are associated with renal damage in patients with CKD, and the ratio of lipocalin-2 to urinary creatinine is positively correlated with mortality in such patients. According to Jasotani K., Dahiya K., Ahlawat R., et al. (2022), urinary NGAL is likely to have a positive relation with microalbuminuria and may be a non-invasive tool for early diagnosis and monitoring of renal dysfunction progression. The measurement of NGAL in urine is currently a more sensitive method than the detection of microalbumin [25, 26].

According to research by Wai Yan Sun, Bo Bai Cuiting Luo, Paul M. Vanhoutte, et al., (2018), the presence of NGAL in urine may also be a more specific marker of active renal tubular epithelial damage and tubulointerstitial inflammation, while plasma NGAL is more indicative for the state of the renal (and possibly extrarenal) vascular system, including the rate of glomerular filtration. We found a positive average correlation between NGAL in urine and BMI in patients of both groups and at the same time a negative average correlation between NGAL and GFR (CKD-EPIcysC/cr) in both groups, which indicates a violation of tubular function even at initial stages of CKD. According to Lakkis JI. and Weir MR., (2018), subjects with higher baseline lipocalin-2 levels show an increased risk of CKD progression compared to those with lower baseline values, even after adjusting for changes in glomerular filtration rate (GFR). Due to the close relation of chronic kidney disease (CKD) and obesity, studies by Rico-Fontalvo J., Daza-Arnedo R., Rodríguez-Yanez T. et al. (2022) explore the hypothesis that activation of the Renin-Angiotensin-Aldosterone System (RAAS) stimulates the production of lipocalin-2 by adipose tissue, which, in turn, leads to kidney damage and gradual fibrosis of renal tubules. The persistent upregulation of lipocalin-2 expression also contributes to the development of metabolic disorders associated with obesity [27-30].

According to data from Friedman AN., Kaplan LM., le Roux CW. and Schauer PR. (2021), circulating levels of lipocalin-2 are positively correlated with obesity and hypertriglyceridemia in humans but negatively correlated with high-density lipoprotein cholesterol levels. According to Hager, M.R., Narla, A.D. and Tannock, L.R. (2017), CKD leads to reduced regulation of lipoprotein lipase and low-density lipoprotein receptor, and the increased triglycerides in CKD result from slowed catabolism of triglyceride-rich lipoproteins without differences in production rates. In your study, there were almost no established correlations with total cholesterol and HDL levels, which is consistent with the findings of studies by Cruz D.N., Gaiao S., Maisel A., Ronco C., Devarajan P. (2012), and Gorshunska M.Y. (2015). This could be explained by the dominance of autocrine and paracrine effects of this protein over systemic functions of adipose tissue and may require further investigations at the cellular level [31-34].

Conclusion

Thus, studying changes in the level of lipocalin-2 in the early stages of CKD, which has developed in the context of obesity, can serve as a marker of tubular apparatus damage. This is indicated by the average inverse correlation between glomerular filtration rate (GFR) and the direct correlation between lipocalin and microalbuminuria. Additionally, in the early stages of CKD on the background of obesity, there is a disruption in lipid metabolism, characterized by increased levels of total cholesterol, triglycerides, low-density lipoprotein and decreased high-density lipoprotein levels.

Our study also found that in patients with early-stage CKD and obesity, urinary NGAL levels positively correlate with elevated triglyceride levels. Dyslipidemia that develops in the early stages of CKD and is associated with obesity likely increases the rate of progression of kidney tissue damage and is a risk factor for cardiovascular events.

Declarations

- **Conflict of interest**

The authors declare no conflict of interest.

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