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# Correlation of Apolipoprotein a-i with Renal Function in Diabetic Patients

**Maria Liliane Luciano Pereira[1]**
https://orcid.org/0000-0002-4289-9603

**Mac Dionys Rodrigues da Costa[1]**
https://orcid.org/0000-0002-3809-0377

**Glautemberg de Almeida Viana[1]**
https://orcid.org/0000-0002-5848-3020

**Emanuel Paula Magalhães[1]**
https://orcid.org/0000-0002-8041-7935

**Bruna Ribeiro Duque[2]**
https://orcid.org/0000-0002-2886-6450

**Mateus Edson da Silva[1]**
https://orcid.org/0000-0003-4059-0298

**Izabell Maria Martins Teixeira[2]**
https://orcid.org/0000-0001-9396-659X

**Renata de Sousa Alves[2]**
https://orcid.org/0000-0003-0630-1499

**Ramon Róseo Paula Pessoa Bezerra de Menezes[1,2]**
https://orcid.org/0000-0003-3109-9683

**Alice Maria Costa Martins[1,2]**
https://orcid.org/0000-0001-8160-2027

**Maria Goretti Rodrigues de Queiroz[1,2]**
https://orcid.org/0000-0002-0971-3571

**Tiago Lima Sampaio[1,2*]**
https://orcid.org/0000-0002-3962-6508

[1]Universidade Federal do Ceará, Faculdade de Farmácia, Odontologia e Enfermagem, Programa de Pós-Graduação em Ciências Farmacêuticas, Fortaleza, Ceará, Brasil; [2]Universidade Federal do Ceará, Faculdade de Farmácia, Odontologia e Enfermagem, Departamento de Análises Clínicas e Toxicológicas, Fortaleza, Ceará, Brasil.

*Correspondence: tiagosampaio@ufc.br; Tel.: +55-85-33668263 (T.L.S.).
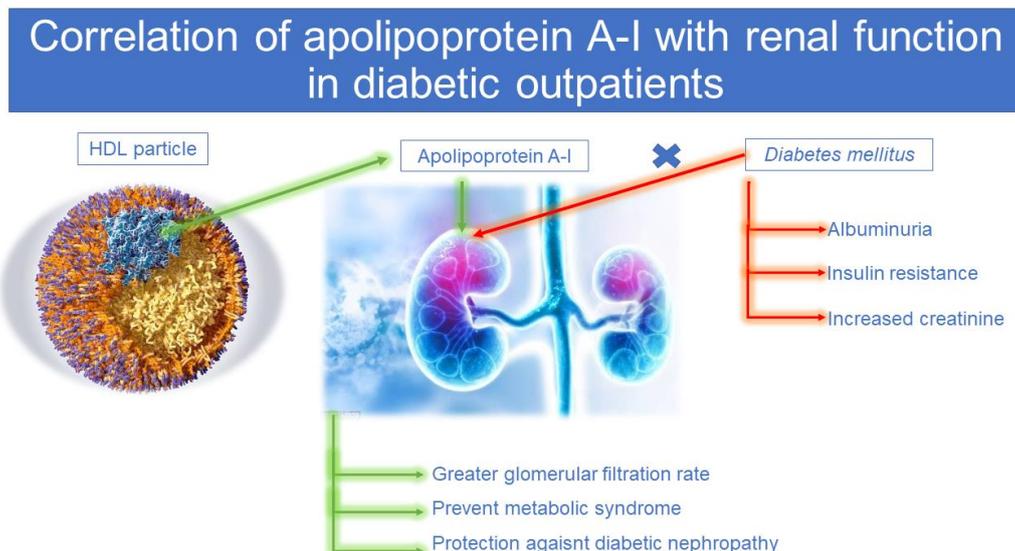
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**HIGHLIGHTS**

- Creatinine had negative correlation with HDLc and Apolipoprotein A-I;

- Insulin resistance was associated with lower Apolipoprotein A-I and albuminuria;

- Apolipoprotein A-I has better predictive potential of kidney disease than HDLc.

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**Abstract:** Diabetes mellitus (DM) is a major cause of chronic kidney disease (CKD) and changes in lipoprotein. Literature data suggest that cholesterol associated with high-density lipoprotein (HDLc) plays a protective role against albuminuria and diabetic nephropathy. These factors are related with changes in serum apolipoproteins such Apo A-I. This work aims to evaluate the correlation of apolipoprotein A-I with renal function in diabetic outpatients. Samples were collected from 281 outpatients for analyses of glycated hemoglobin (HbA1c), serum creatinine (SCr), urea (BUN), cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDLc) and estimation of glomerular filtration rate (eGFR). Urinary samples were obtained to assess urine albumin creatinine ratio (UACR). Triglyceride-glucose index (TyG) was calculated to estimate insulin resistance. The mean age was 61,5 ± 16,4 years. Most patients were female, Afro-Mestizo and over 50 years of age. Pearson's revealed negative correlation of creatinine with HDLc and Apo A-I. There was a

correlation of eGFR with HbA1c, TG and HDLc. TyG presented a negative correlation with Apo A-I and HDLc. The highest quartiles of UACR presented the highest TyG and the lowest Apo A-I. In conclusion, Apo A-I indicated an association with insulin resistance and changes in renal function parameters, especially as a factor associated with the onset of albuminuria, with a better predictive potential than the HDLc.

**Keywords:** Insulin resistance; Glomerular filtration; Albuminuria; Lipoproteins.

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**GRAPHICAL ABSTRACT:**



Correlation of apolipoprotein A-I with renal function in diabetic outpatients

HDL particle — Apolipoprotein A-I — Diabetes mellitus
- Albuminuria
- Insulin resistance
- Increased creatinine

- Greater glomerular filtration rate
- Prevent metabolic syndrome
- Protection agaisnt diabetic nephropathy

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## INTRODUCTION

Diabetes mellitus (DM) is among the major causes of chronic and end-stage kidney disease in the world. Type 1 and type 2 diabetes mellitus can both cause long-term microvascular and macrovascular complications, altering hemodynamics, metabolic, and inflammatory pathways, which causes diabetic nephropathy (DN), and contributing to the increased morbidity and mortality. In clinical practice, the evaluation of renal function is pragmatically done based on serum creatinine (SCr) and urea (BUN), but these markers have severe limitations, such as low sensitivity, specificity, and analytical limitations. In this context, there is a sought to trace an association between the creatinine-based estimated glomerular filtration rate (eGFR) and the progression of albuminuria in patients with Diabetes [1].

Damage of glomerular basement membrane results in leaking of albumin and, subsequently, larger proteins into the urine. Thus, over the years, the assessment of microalbuminuria (defined as 24-hour albumin excretion between 30 and 300 mg/24h) was established as a laboratory marker for the development of diabetic nephropathy. However, despite its sensitivity and precocity, this test is performed using 24-hour urine, which may be inconvenient in certain situations [2]. In this sense, urinary albumin/creatinine ratio (UACR) spot analysis of first morning collection is preferred for proteinuria quantification [3].

Damage to the glomerular filtration barrier associated with DM is mostly related to injuries to the vascular endothelium. Dyslipidemias, qualitative and quantitative changes in serum lipids and lipoprotein metabolism, are among the main cardiovascular risk factors. Diabetic patients with chronic kidney disease also suffer changes in lipid metabolism, which corroborates the high rates of morbidity and mortality in cardiovascular diseases and dyslipidemia, in addition to being associated with a high risk of developing kidney disease progression [4]. It is still unclear whether lipid changes precede the development of albuminuria or occur as a result of kidney disease. Studies in microalbuminuric type 1 DM patients show an increase in serum levels of triglycerides, total cholesterol, and cholesterol associated with pro-atherogenic particles such as VLDL (very low-density lipoprotein) and LDL (low-density lipoprotein), in addition to a decrease in cholesterol of HDL (high-density lipoprotein). These factors are commonly correlated with changes in serum levels of apolipoproteins such as Apo A-I, showing a direct relationship between the occurrence of DN and changes in lipid metabolism and transport pathways [5].

HDL particles are the protagonists of reverse cholesterol transport. Its functionality can prevent the occurrence of cardiovascular events, as well as promote antioxidant and anti-inflammatory potential, protect the endothelium, prevent thrombotic phenomena and protect organs such as the kidneys, heart and brain. Apolipoprotein A-I (apo A-I) is the main protein component of the HDL particle; it coordinates HDL formation and reverse cholesterol transport by activating lecithin: cholesterol acyltransferase (LCAT), which esterifies plasmatic cholesterol. Studies suggest that apo A-I determinations have greater discriminatory power, as they present smaller analytical variations than the cholesterol associated with the HDL particle (HDLc) in defining cardiovascular risk [6].

Literature data suggest that lower levels of HDLc and apolipoprotein A-I are related to changes in glomerular filtration rate both in individuals with and without kidney disease, supporting the possibility that renal hemodynamic factors may contribute to the metabolism of Apo A-I, thus affecting levels of HDLc [7]. In this context, the search for biomarkers associated with high-density lipoproteins in atherosclerotic kidney disease is a new challenge in laboratory medicine. It is known that persistently elevated plasma glucose levels in people with diabetes and poor glycemic control can lead to non-enzymatic and irreversible glycation of plasma proteins, including Apo A-I, without altering their detection but changing their biochemical functions, especially functions related to reverse cholesterol transport, which may interfere with blood supply to the glomeruli. Evidence suggests that glycated Apo A-I inhibits the LCAT reaction and impairs some of the cardioprotective properties of HDL. In addition, glycated Apo A-I has a longer plasma half-life, which may decrease mRNA expression for this protein [8]. Despite the evidence, studies associating serum levels of Apo A-I with renal function are still scarce, especially in the population of diabetic patients. Thus, the present work aims to evaluate the correlation of apolipoprotein A-I with renal function in diabetic patients treated at a reference outpatient clinic.

## MATERIAL AND METHODS

### Subjects

Blood samples were collected from 281 patients, presented to the outpatient clinic of Integrated Center for Diabetes and Hypertension (CIDH - Fortaleza, Ceará, Brazil), after giving written informed consent. Adult patients (>18 years old) diagnosed with diabetes were included; of these, pregnant women, patients on hemodialysis and kidney transplant recipients were excluded. The study was performed under the tenets of the Helsinki Declaration (as revised in 2013) and all relevant national regulations and institutional policies. The study protocol was approved by the authors' Institutional Review Board (CAAE 34218720.0.0000.5054).

### Sample collection

Venous blood sampling was performed via venipuncture with the BD Vacutainer® blood collection system (Becton Dickinson, NJ, USA), at the cubital fossa and collected in 2,2',2'',2'''-(Ethane-1,2-diyldinitrilo) tetraacetic acid (EDTA) and serum tubes (Vacuette®, Greiner Bio-One GmbH, Kremsmünster, Austria) after a 10- to 12-hour overnight fast. First morning urine samples were kindly provided by patients. Patients were instructed about genital hygiene and a sterile 100 mL plastic tube was provided in individual packaging for urine collection. The samples were immediately sent for analysis at the Clinical and Toxicological Analysis Laboratory (LACT-UFC) and then were aliquoted in microtubes and stored in a freezer at -80ºC.

### Biochemical analysis

The samples were used for biochemical analysis of total albuminuria, urinary creatinine, glycated hemoglobin (HbA1c), serum creatinine (SCr), urea (BUN), cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDLc) using Mindray BS-120 automated equipment (Mindray Bio-Medical Electronics Co., Shenzhen, China). The cholesterol content associated with LDL (LDLc) was determined using the Friedewald formula, where: LDLc = TC - HDLc – VLDLc, being VLDLc = TG/5 [9]. Additionally, serum apolipoprotein A-I was measured by turbidimetric immunoassay (Randox Laboratories Ltd, Crumlin, UK), using the Mindray BS-120 automated equipment.

The Estimated Glomerular Filtration Rate (eGFR) was performed according to an equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [10]. Urine albumin creatinine ratio (UACR) was calculated using albuminuria divided by urinary creatinine [11]. Triglyceride-glucose index (TyG) was calculated as a parameter for estimating insulin resistance as the ln (fasting triglyceride level [mg/dL] × fasting glucose level [mg/dL]/2) [12].

## Statistical analysis

All statistical tests were performed using GraphPad Prism, version 6.0. For the determination of the type of distribution of the variables, the Kolmogorov-Smirnov test was used. Pearson's correlation test was used to analyze linear relationships between variables. Data were represented by mean ± standard error of mean (SEM), comparison between means was performed by One-way ANOVA, followed by Tukey's post-test. The significance level considered was p < 0.05.

## RESULTS

A total of 281 patients were enrolled in the study. The mean age was 61,5 ± 16,4 years old (Table 1). It is interesting to note that most patients were female, mostly Afro-Mestizo and aged over 50 years. Pearson's correlation was used to investigate linear relationships between laboratory parameters for assessing cardiovascular risk and markers of renal function (Table 2). Creatinine showed a negative correlation only with HDLc (p = 0.010), although it was a weak correlation (r = -0.163). Urea, on the other hand, did not present significant correlation. Considering that UACR is a more accurate parameter for the diagnosis and follow-up of diabetic nephropathy, the same analyzes were performed considering this marker, with no correlation. The same analysis was performed using the eGFR, obtained through the CKD-EPI formula as a basis. There was a significant correlation with glycated hemoglobin, triglycerides and HDLc.

**Table 1.** Patient characteristics.

| Total, n(%) | 281 (100) |
|---|---|
| Age (years), mean (SEM) | 61.5 (16,4) |
| **Gender n(%)** | |
| Female | 174 (61.9) |
| Male | 107 (38.1) |
| **Ethnicity** | |
| Black, n(%) | 39 (13.9) |
| Caucasian, n(%) | 90 (32) |
| Brown, n(%) | 152 (54.1) |
| **Diabetes type** | |
| Type I diabetes, n(%) | 65 (23.1) |
| Type II diabetes, n(%) | 216 (76.9) |
| **Health history** | |
| Diabetes family history, n(%) | 197 (70.1) |
| Time from diagnosis, median [IQR] | 14 [8 – 23] |
| Presence of comorbidities, n(%) | 220 (78.3) |
| **Lifestyle habits** | |
| Healthy eating, n(%) | 145 (51.6) |
| physical activity, n(%) | 111 (39.5) |
| Smoking, n(%) | 62 (22.1) |
| Drink alcohol, n(%) | 75 (26.7) |

**Table 2.** Pearson's correlation between parameters of cardiovascular risk and markers of renal function.

|  | SCr | BUN | UACR | eGFR |
|---|---|---|---|---|
| **HbA1c** | p = 0.881 | p = 0.381 | p = 0.795 | p = 0.005* |
| | r = 0.009 | r = 0.061 | r = -0.018 | r = 0.180 |
| **TG** | p = 0.600 | p = 0.780 | p = 0.521 | p = 0.037* |
| | r = 0.033 | r = 0.0196 | r = 0.046 | r = -0.134 |
| **TC** | p = 0.999 | p = 0.978 | p = 0.724 | p = 0.421 |
| | r < 0.001 | r <0.001 | r = 0.025 | r = 0.051 |
| **HDLc** | p = 0.010* | p = 0.087 | p = 0.201 | p < 0.001* |
| | r = -0.163 | r = -0.1210 | r = -0.091 | r = 0.232 |
| **LDLc** | p = 0.887 | p = 0.285 | p = 0.282 | p = 0.407 |
| | r = 0.010 | r = -0.083 | r = 0.086 | r =0.061 |
| **VLDLc** | p = 0.443 | p = 0.9679 | p = 0.733 | p = 0.379 |
| | r = 0.048 | r = 0.045 | r = 0.023 | r = -0.055 |

*p<0.05. r = Pearson-s correlation coefficient. HbA1c = glycated hemoglobin. TG = triglycerides. TC = total cholesterol. HDLc = cholesterol of high-density lipoprotein. LDLc = cholesterol of low-density lipoprotein. VLDLc = cholesterol of very low-density lipoprotein. SCr = serum creatinine. BUN = Urea. UACR = urinary albumin creatinine ratio. eGFR = glomerular filtration rate obtained through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Therefore, considering the role of HDLc in protecting against cardiovascular risk and its significant correlation with SCr and eGFR, it was decided to evaluate the correlation between markers of renal function and serum levels of Apo A-I (Figure 1), presenting a significant result for correlation with serum creatinine (p = 0.0364).
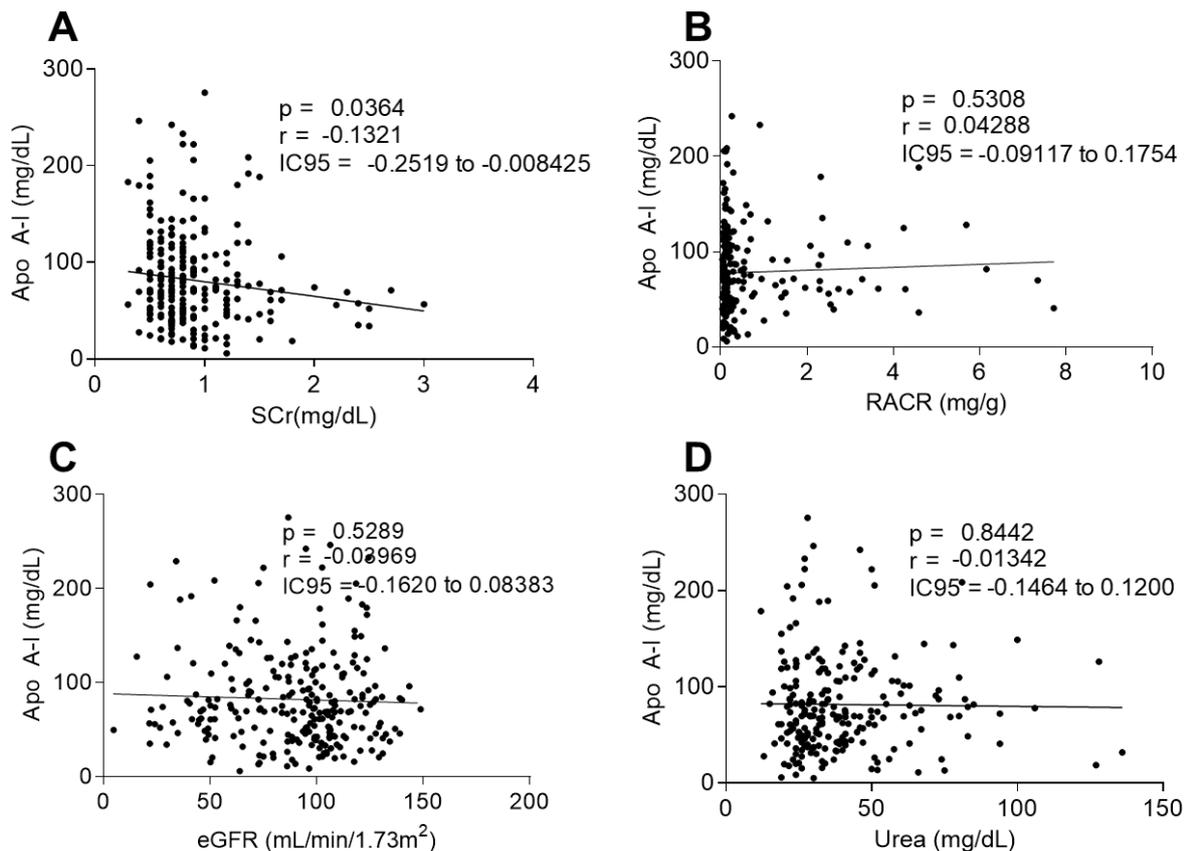


**Figure 1.** Pearson's correlation between serum levels of apolipoprotein A-I (Apo A-I) and markers of renal function: (A) serum creatinine (SCr); (B) Urea (BUN); (C) urinary albumin creatinine ratio (UACR); and estimated glomerular filtration rate (eGFR). *p<0.05. r = Pearson-s correlation coefficient. IC95 = confidence interval. eGFR = glomerular filtration rate obtained through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

The TyG index was calculated in order to verify the correlation of this index that estimates insulin resistance with serum Apo A-I (Table 3). The analysis showed a negative correlation, that is, the lower the serum levels of Apo A-I, the greater the estimate of insulin resistance measured by the TyG index.

The same analysis was performed to verify the correlation of TyG with HDLc and parameters of renal function. There was a negative correlation with HDLc (p < 0.0001). No significant results were observed for correlation analysis with SCr, UACR and eGFR (Table 3).

**Table 3.** Pearson's correlation between TyG index and laboratorial markers.

|  | Apo A-I | HDLc | SCr | UACR | eGFR |
|---|---|---|---|---|---|
| **TyG** | p = < 0.001* | p = <0.001* | p = 0.643 | p = 0.577 | p = 0.753 |
|  | r = -0.2548 | r = -0.2296 | r = -0.0298 | r = 0.3944 | r = 0.0203 |

*p<0.05. r = Pearson-s correlation coefficient. TyG = triglyceride-glucose index. Apo A-I = apolipoprotein A-I. HDLc = cholesterol of high-density lipoprotein. SCr = serum creatinine. UACR = urinary albumin creatinine ratio. eGFR = glomerular filtration rate obtained through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Considering that the UACR has very dispersed data, which could influence the result of the correlation analysis, the patients were divided into quartiles according to this parameter. Patients were arranged in ascending order of UACR results. The 71 patients with the lowest UACR, with a mean of 0.064 ± 0,013 mg/g, comprised the first quartile. The next 70 patients made up the second quartile, with UACR mean 0.116 ± 0.017 mg/g, the third quartile was made up of the next 70 patients with sequentially higher UACR, mean 0.238 ± 0.079 mg/g; and the fourth quartile comprised the 70 patients with the absolute highest UACR, mean 9.72 ± 2.553 mg/g. A comparison was made of the means of Apo A-I, TyG and cHDL

according to the quartile's division (ANOVA with post Tukey's test). As illustrated in Figure 2, the analysis showed that the highest quartiles (ie, patients with the highest UACR values) were those with the highest TyG values and lowest Apo A-I values. It is interesting to note that serum Apo A-I levels in the two first quartiles (means 100.4 and 101.8 mg/dL, respectively) were approximately 30% higher compared to the last two quartiles (72.2 and 74.1 mg/dL), indicating an association between HDL particle and the protection of kidney function. However, when the same analysis was performed with HDLc, it did not show predictive potential, with no difference between groups.
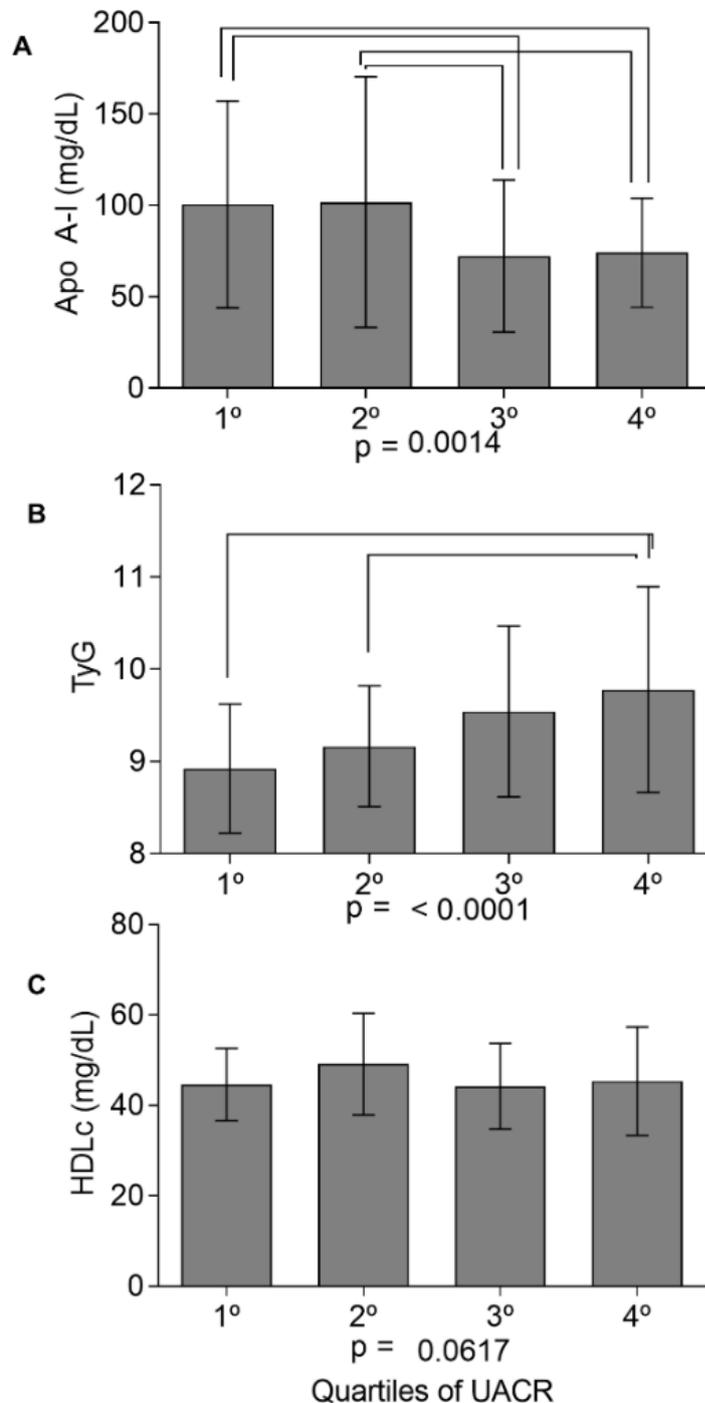


**Figure 2.** Comparison of (A) serum levels of apolipoprotein A-I (Apo A-I), (B) triglyceride-glucose index (TyG) and (C) cholesterol of high-density lipoprotein (HDLc) according to quartiles of urinary albumin creatinine ratio (UACR). (ANOVA with post Tukey's test). Brackets indicate intergroup difference. Patients were arranged in ascending order of UACR result. First quartile comprised patients with the lowest UACR with a mean of $0.064 \pm 0.013$ mg/g (n =71); second, third and fourth quartiles were composed of patients with progressively higher UACR (n = 70 each), with mean UACR equal to $0.116 \pm 0.017$, $0.238 \pm 0.079$ and $9.72 \pm 2.553$ mg/g, respectively.

## DISCUSSION

The present work showed that low HDLc values indicated compromised glomerular function, indicating a potential predictor of this laboratory parameter on the risk of alteration in renal homeostasis. Furthermore, the study demonstrated that insulin resistance has a direct relation with the filtration process. In order to make a more accurate analysis, lower serum levels of Apo A-I also indicated an association with insulin resistance and changes in renal function parameters, especially as a factor associated with the onset of albuminuria.

These results reinforce data from the literature that suggests that low levels of Apo A-I are associated with the progression of diabetic kidney disease and renal replacement therapy. Moreover, these effects are potentiated when there is a concomitant increase in apolipoprotein B, associated with LDL particles [13]. The relationship between lipoprotein metabolism, glucose homeostasis and renal function is complex and not fully understood. One study showed that lower serum concentrations of Apo A-I predict late-onset post-transplant diabetes mellitus in renal transplant recipients, prevalent in adults at a rate of 1.71 cases per 100 patient-years; the quartiles that had the highest Apo A-I had lower odds ratios [14].

The mechanisms related to these events seem to be complex and involve hemodynamic, endocrine, biochemical and inflammatory factors. For example, one study investigated associations between serum Apo A-I, HDLc, and urinary cytokine levels in elderly men and women; a strong negative correlation was observed with markers such as interleukin of the IL-1α type, commonly associated with the occurrence of fever or sepsis. There was also a correlation with IL-4, an interleukin produced by CD4-type T lymphocytes and by mast cells responsible for stimulating the differentiation and production of TH2 lymphocytes and activating the alternative pathway of macrophages. Another example of a correlated cytokine is nuclear factor receptor activator κ B, also known as the TRANCE receptor or TNFRSF11A, a member of the tumor necrosis factor receptor molecular subfamily, which regulates the transcription and translation of a number of pro-inflammatory factors. These findings indicate that the HDL particle has anti-inflammatory properties mediated, in part, by Apo A-I, which diminishes the subendothelial production of TNF-a, IL-1β, and IL-6. Many authors attribute these effects to the activation of paraoxonase, an antioxidant enzyme present in the HDL structure that has Apo A-I as a coenzyme [15]. Furthermore, it has already been described that ApoA-1 deficiency aggravates programmed cell death during ischemic events. These events regulate NF-κB expression, which alters cytokine translation [16].

The inflammatory process resulting from DM causes hemodynamic changes related to glomerular sclerosis and fibrosis, leading to DN that manifests itself as slowly progressive albuminuria with worsening of renal failure and hypertension. These concepts are realized when observing the results of studies that associate desirable serum levels of Apo A-I with protection of the glomerular filtration barrier. In general, UACR results below 30 mg albumin/g of creatinine are considered normal; values between 30 and 300 mg/g define microalbuminuria [17]. Surprisingly, of the 281 diabetic patients followed in the present study, only 10 met the microalbuminuria criterion, with the maximum observed value equal to 170 mg/g. These findings demonstrate the limitations of the method, justifying the need for more specific biomarkers and in-depth studies on the pathophysiology of diabetic nephropathy.

A previous study showed that mice that suffered podocyte injury had improvement in oxidative stress and retraction of the apoptosis process when treated with mimetic Apo AI, HDL and Apo AI, culminating in the reduction of albuminuria and atherosclerosis [18]. Ratifying this idea, a classic clinical trial showed that decreased levels of interstitial apolipoprotein A-I in patients with DM are directly associated with the occurrence of albuminuria. The study found that transcapillary filtration of Apo A-I was lower in patients with diabetic nephropathy. The authors associate these findings with the generalized vasculopathy observed in DM, which may increase transcapillary filtration of lipids and lipoproteins, resulting in a more atherogenic interstitial lipid profile [19].

Arteriopathy is a defining pathophysiological phenomenon of DN. In this context, several studies have sought laboratory markers that define cardiovascular risk. One study evaluated clinical and biochemical predictors of death or cardiovascular disease in 147 patients with type 1 diabetes mellitus (DM) followed for 14 years. The results found that mortality would be associated with higher serum creatinine, as well as urinary albumin/creatinine ratio concomitantly with lower serum apolipoprotein A1, with serum HDLc levels being a predictor of coronary artery disease [20]. Indeed, serum creatinine is largely associated with the occurrence and severity of coronary artery disease, one of the leading causes of death from DM. Interestingly, creatinine is a marker with low analytical sensitivity, requiring substantial glomerular involvement to cause       a significant increase. Its serum levels are commonly positively associated with TC and negatively with HDLc and ApoA1, and this association seems to be influenced by insulin resistance. Urea, on the other hand, despite being a sensitive marker, lacks specificity, which makes it have a low predictive power in isolation [21,22].

Furthermore, higher levels of SCr have been linked with insulin resistance. One cross-sectional study with 1432 patients investigated the relationship between TyG index and diabetic kidney disease in patients with type 2 DM. Results revealed that higher TyG had a higher risk of microalbuminuria and lower SCr-based eGFR. Additionally, patients in the high tertile of the TyG index had a higher risk of developing DN. ROC curve analysis was used to assess the sensitivity and specificity of the TyG Index in predicting ND, revealing 69% accuracy [23]. Furthermore, insulin resistance is traditionally related to the serum's apolipoprotein profile. A cross-sectional analysis of 7629 Chinese adults revealed that higher TG levels in association with low HDLc explained the greater percentage change in the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index. This index is limited by the need to measure insulin levels; however, regression analyses demonstrated a high association of HOMA-IR with TyG, which presents analytical practicality. Moreover, previous studies revealed that this index presents an analytical performance similar to the determination of serum apolipoproteins such as Apo A-I and B, and better than glycated hemoglobin, for predicting insulin resistance [24].

Overall, the results of the present study reinforce the importance of studying DM as a multifactorial disease with multiple complications and with complex biochemical mechanisms involved. Several studies point out that apolipoprotein A1 has a protective potential against cardiovascular risk, in this sense, the present work is innovative in the context of relating the role of this apolipoprotein with the nephroprotective potential, mainly on albuminuria, especially associated with lower insulin resistance. This appears to be involved with antioxidant, anti-inflammatory, endocrine and signaling mechanisms. Thus, the results of the present study reveal a field of laboratory medicine that needs to be investigated in multiple populations, in order to elucidate the metabolic pathways involved with diabetic nephropathy and with its early diagnosis and prevention.

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