Al-Rafidain J Med Sci. 2024;6(1):1-8.
DOI: https://doi.org/10.54133/ajms.v6i1.380

Research Article

Association between Albuminuria, Glycated Hemoglobin with Comorbidities in Type 2 Diabetes Patients: Experience in Sulaimani City, Iraq

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Received: 26 October 2023; Revised: 8 December 2023; Accepted: 1 January 2024

Abstract

Background: Diabetes nephropathy is one of the most important complications of type 2 diabetes mellitus (T2DM). Albuminuria is an early clinical indicator for investigating diabetes nephropathy. Age, poor glycemic control, long duration of diabetes, and hypertension increase the risk of albuminuria. ***Objectives***: To determine the relationship between albuminuria, HbA1c, and comorbidities in elderly patients with T2DM. ***Methods***: A cross-sectional study was carried out on 136 elderly patients with T2DM at the Diabetes and Endocrine Center in Sulaimani City. Data was obtained from each patient through face-to-face interviews and laboratory tests for HbA1c, serum lipid profiles, and albumin levels in the urine. ***Results***: Out of 136 patients, 82 elderly patients with T2DM were normoalbuminuric, 37 had microalbuminuria, and 17 had macroalbuminuria, respectively. The female gender was at greater risk of developing albuminuria (19.1% microalbuminuria and 6.6% macroalbuminuria) than the male gender (8% microalbuminuria and 5.8% macroalbuminuria). The risk factors for microalbuminuria and macroalbuminuria were poor glycemic control (HBA1c >7.5) (16.9% microalbuminuria and 6.6% macroalbuminuria), long-term diabetes (5–10 years) (13.9% microalbuminuria and 5.1% macroalbuminuria), and coexisting comorbidity conditions (21.3%) microalbuminuria and 10.2% macroalbuminuria, mainly hypertension (20.5% microalbuminuria and 8.8% macroalbuminuria). ***Conclusion***: Our findings showed that the incidence of albuminuria in elderly patients with T2DM was high in patients with poor diabetes control, a long duration of diabetes, and comorbidity conditions, particularly in patients with hypertension.

Keywords: Albuminuria, Comorbidities, HBA1c, Sulaimani City, Type 2 diabetes mellitus.

العلاقة بين بيلة الألبومين والهيموغلوبين السكري و الأمراض المصاحبة في مرضى السكري من النوع 2: الخبرة السريرية في السليمانية، العراق

الخلاصة

الخلفية: اعتلال الكلية السكري هو واحد من أهم مضاعفات داء السكري من النوع. البيلة الزلالية هي مؤشر سريري مبكر للتحقيق في اعتلال الكلية السكري. تقدم العمر، وضعف التحكم في نسبة السكر في الدم، والمدة الطويلة للمرض السكري، وارتفاع ضغط الدم يزيد من خطر بيلة الألبومين. **الأهداف**: تحديد العلاقة بين بيلة الألبومين، HbA1c ، والأمراض المصاحبة في المرضى المسنين الذين يعانون من T2DM. **الطريقة**: أجريت دراسة مقطعية على 136 مريضا مسنا يعانون من T2DM في مركز السكري والغدد الصماء في مدينة السليمانية. تم الحصول على البيانات من كل مريض من خلال المقابلات وجها لوجه والاختبارات المعملية لHbA1c ، وملامح الدهون في الدم، ومستويات الألبومين في البول. **النتائج**: من بين 136 مريضا، 82 مريضا مسنا يعانون من بيلة ألبومينية عادية، و 37 يعانون من بيلة ألبومينية دقيقة، و 17 يعانون من بيلة ألبومينية كبيرة، على التوالي. كان الجنس الأنثوي أكثر عرضة للإصابة بالبيلة الزلالية من جنس الذكور. كانت عوامل الخطر للبيلة الزلالية الدقيقة والبيلة الزلالية الكبيرة هي ضعف التحكم في نسبة السكر في الدم، ومرض السكري طويل الأمد (5-10 سنوات)، وظروف الاعتلال المشترك المتعايشة، وبشكل رئيسي ارتفاع ضغط الدم. **الأستنتاج**: أظهرت النتائج أن حدوث بيلة الألبومين في المرضى المسنين الذين يعانون من T2DM كان مرتفعا لدى الذين يعانون من ضعف السيطرة على مرض السكري، ومدة المرض الطويلة، وحالات الاعتلال المشترك، وخاصة في المرضى الذين يعانون من ارتفاع ضغط الدم.

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Article citation: Hama Salh HJ, Aziz TA, Ahmed AA, Mahwi TO. Association between Albuminuria, Glycated Hemoglobin with Comorbidities in Type 2 Diabetes Patients: Experience in Sulaimani City, Iraq. *Al-Rafidain J Med Sci*. 2024;6(1):1-8. doi: https://doi.org/10.54133/ajms.v6i1.380

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease featuring high levels of blood glucose that is currently known as a worldwide health emergency [1]. Several factors may contribute to rising Type 2 diabetes mellitus (T2DM), including urbanization, population aging, and related lifestyle changes, especially in people over 65. In 2015, it was estimated that there would be 415 million adults with diabetes worldwide; by 2040, that figure is expected to rise to 642 million [2]. The complications of diabetes are common among patients, and they are responsible for significant morbidity and mortality [3]. Complications of diabetes consist of acute, like diabetic ketoacidosis and hyperglycemic hyperosmolar state [4], and chronic complications, which include macrovascular, such as cerebrovascular, coronary, and peripheral artery disease, and microvascular, like diabetic neuropathy, retinopathy, and nephropathy conditions [3–7]. The most common complication of diabetes is nephropathy, which is considered the most common reason behind end-stage renal disease [8]. Studies show that up to 40% of T2DM patients eventually end up with nephropathy [9]. The main pathogenesis of diabetic nephropathy (DN) is hyperglycemia. Although the exact mechanism of DN is not well defined, many factors, such as advanced glycation end products (AGEs), angiotensin II, growth factors, endothelin, glomerular hyperfiltration or hyperperfusion, may exert pressure on the glomerular and capillary elements and cause structural and/or functional changes in the glomerulus [10]. Other factors such as high calorie intakes, genetic factors [11], inactive physical activity [3,12], age, smoking, hypertension, and dyslipidemia may also contribute to the pathogenesis of the disease [12]. Albuminuria is the most important early clinical risk factor for DN [9,13]. Early detection of DN is done depending on the measurement of microalbumin in urine (microalbuminuria) [14]. Microalbuminuria can be defined in two ways: either by measuring urinary albumin excretion rate (UAE), which is between 30 and 300 mg/24 hours [9,11,15,16], or as an albumin/creatinine ratio (ACR) of 30 and 300 mg albumin/g of creatinine [9,15-17], or by excretion of 20–200 mg/l of albumin in the spot urine samples [15–17]. The progression of DN can be avoided by early diagnosis of microalbuminuria and its control, which can be achieved by lowering plasma glucose and blood pressure in addition to administering medications such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers [10,18] and sodium-glucose cotransporter 2 (SGLT2) inhibitors [18]. A large body of evidence suggests associations between albuminuria and the risk of cardiovascular diseases (CVDs) [12,19]. Previous studies showed that the prevalence of albuminuria is high in elderly patients [16,20-22]. Accordingly, the current study was designed to determine the relationship between albuminuria, HbA1c, and comorbidities in elderly patients with T2DM.

METHODS

Study design and setting

A cross-sectional study was conducted at the Diabetes and Endocrine Center in Sulaimani City involving patients diagnosed with T2DM from July to September 2023. In total, 136 patients were involved in the research. The study protocol was approved by the Local Research Ethics Committee of the University of Sulaimani, College of Pharmacy (Certificate No: PH116-23 on October 26, 2023) in accordance with the Helsinki Declaration for Human Studies.

Sample selection

Patients were eligible for inclusion if they were at least 65 years old, had been diagnosed with type 2 diabetes mellitus, and were taking hypoglycemic medications. Patients who met the exclusion criteria had a history of steroid treatment, other types of diabetes mellitus, urinary tract infections, or cancer.

Data collection and outcome measurements

The following information was gathered from each patient via interview: gender, duration of diabetes mellitus, comorbidity status, and utilization of ACEI/ARBs. The subjects' blood pressure was assessed utilizing a Mercury sphygmomanometer prior to the collection of urine and blood samples. Samples were collected from every patient while they were fasting. HbA1c, serum lipid profiles (triglyceride (TG), cholesterol, LDL, and HDL), and albumin in urine were laboratory parameters. As determined by the turbidimetric inhibition immune assay, HbA1c was quantified using Cobas c111. Furthermore, lipid profiles were quantified utilizing the colorimetric method and Cobas c111. Urine albumin was determined by means of the turbidimetry method using a spot urine sample. A Cobas c111 analyzer was employed to quantify albumin in urine through the utilization of ALBT2 kits produced by Roche/Germany. Microalbuminuria and macroalbuminuria are identified in patients with T2DM when the albumin concentration in the urine is between 20 and 200 mg/L [17,23,24] and greater than 200 mg/L [24], respectively.

Statistical analysis

The GraphPad Prism 8 software was used for the statistical analysis. The measured parameters' values were given as mean±standard deviation (SD). For group comparisons, one-way analysis of variance (ANOVA)

was used, followed by Tukey's test to compare each group to the positive control group. When the p-value was less than 0.05, the results were considered statistically significant. The associations were examined using descriptive analysis, which included frequencies and percentages.

RESULTS

A total of one hundred thirty-six (136) patients with T2DM participated in the study. Table 1 shows that among the 136 patients recruited in this study, 47 (34.5%) were male and 89 (65.4%) were female. 82 (60.2%) patients were normoalbuminuric, 37 (27.2%) had microalbuminuria, and 17 (12.5%) had macroalbuminuria, respectively. The percentage of patients who had uncontrolled HbA1c (6.5–7.5%) and > 7.5% were 35 (25.7%) and 84 (61.7%), respectively. However, only 17 (12.5%) had controlled HbA1c (< 6.5%). Most patients (74.2%) had comorbid diseases. In addition, 94 (69.1%) patients had hypertension, while patients with coronary artery disease and stroke were 27 (19.8%) and 19 (13.9%), respectively. 71 (52.2%) and 50 (36.76%) patients had diabetes duration > 10 years and 5–10 years, respectively, while only 15 (11%) patients had diabetes duration < 5 years. 79 (58%) of patients were taking ACEI or ARB.

Table 1: Baseline values of the study sample

Gender		Male	Female	*p*-value
		47(34.5)	89(65.4)	< 0.0001
Urine Albumin (mg/L)	Normoalbuminuric <20	Microalbuminuria 20-200	Macroalbuminuria >200	
	82 (60.2)	37 (27.2)	17 (12.5)	< 0.0001
HbA1c (%)	<6.5	6.5- 7.5	> 7.5	
	17(12.5)	35(25.7)	84(61.7)	< 0.0001
Comorbidities		Yes	No	
		101(74.2)	35(25.7)	< 0.0001
Comorbidities n(%)	Coronary artery disease	Hypertension	Stroke	
	27(19.8)	94(69.1)	19(13.9)	< 0.0001
Duration of diabetes (year)	< 5	5- 10	> 10	
	15(11)	50 (36.76)	71(52.2)	< 0.0001
Use of ACEIs/ARBs *n*(%)		Yes	No	
		79(58)	57(41.9)	0.0003

Figure 1 demonstrates that the percentage of female patients who had microalbuminuria and macroalbuminuria was 19.1% and 6.6%, respectively. However, 8% of male patients were diagnosed with microalbuminuria and only 5.8% with macroalbuminuria.

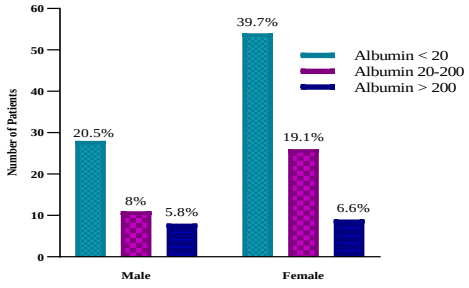

Figure 1: Incidence of Urine Albuminuria (mg/L) in association with gender.

The percentage of patients with microalbuminuria (16.9%) and macroalbuminuria (6.6%) were found to have poorly controlled diabetes (HbA1c > 7.5%). Furthermore, 6.6% and 5.8% of patients with microalbuminuria and macroalbuminuria were found to have poorly controlled diabetes (HbA1c 6.5-7.5%). Only 3.6% of patients had albuminuria in well-controlled diabetes (Figure 2).

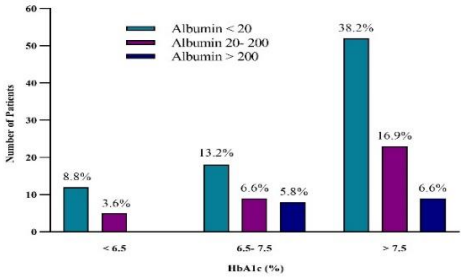

Figure 2: Incidence of microalbuminuria in association with HbA1c.

Figure 3 demonstrates that the majority of patients with microalbuminuria had a longer duration of diabetes: 5–10 years (13.9%) and > 10 years (11.7%). Additionally, the majority of patients with macroalbuminuria had a longer duration of diabetes: 5–10 years (5.1%) and > 10 years (5.8%).

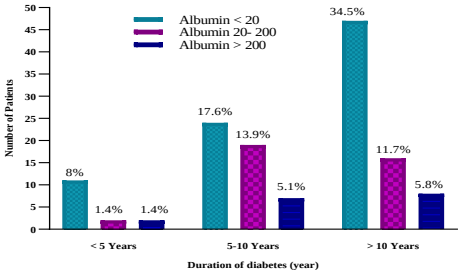

Figure 3: Prevalence of albuminuria according to duration of diabetes.

Figure 4 displayed that 21.3% of patients with microalbuminuria had comorbidity conditions, and 10.2% of patients diagnosed with macroalbuminuria had comorbidity conditions. In contrast, in patients without comorbidity conditions, only 5.8% and 2.2% represented microalbuminuria and macroalbuminuria, respectively.

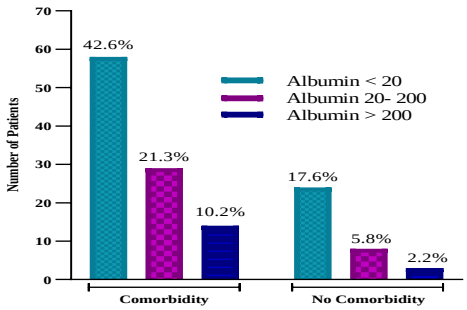

Figure 4: Incidence of albuminuria in association with existing comorbidity conditions.

Figure 5 indicated that most of the patients with hypertension had microalbuminuria (20.5%) and macroalbuminuria (8.8%). However, Figure 6 revealed no statistically significant difference in blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DSB)) in patients with microalbuminuria and macroalbuminuria compared to patients with normoalbuminuria.

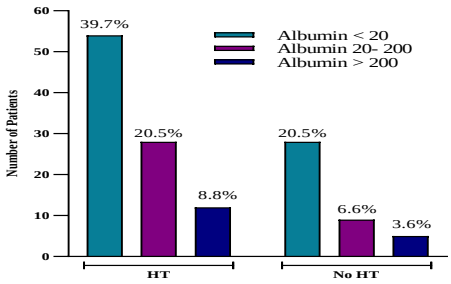

Figure 5: Incidence of albuminuria in association with co-existing hypertension.

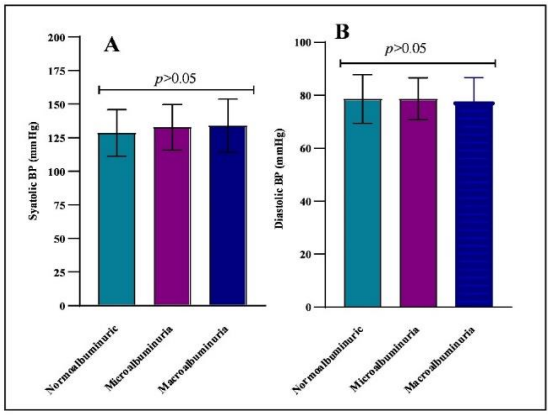

Figure 6: Differences in systolic and diastolic pressure among T2DM patients based on urinary albumin status. A) SBP, and B) DBP. Values were presented on albuminuria as mean±SD.

The results in Figure 7 reveal that only 3.6% (microalbuminuria) and 4.4% (macroalbuminuria) of patients had co-existing CAD. The percentage of patients with microalbuminuria and macroalbuminuria who had a history of stroke was 4.4% and 2.9%, respectively (Figure 8).

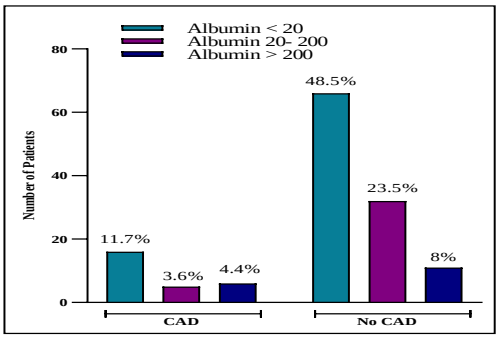

Figure 7: Incidence of albuminuria in association with co-existing CAD.

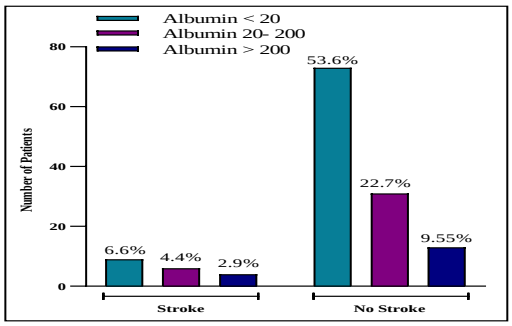

Figure 8: Incidence of albuminuria in association with history of stroke.

Meanwhile, the percentage of patients with microalbuminuria and macroalbuminuria who take ACEI/ARBS was 18.3% and 6.6%, respectively (Figure 9). There was no significant difference in serum cholesterol, LDL, HDL, and TG in patients with microalbuminuria and macroalbuminuria compared to patients with normoalbuminuria (p>0.05). However, serum TG was significantly higher in patients with microalbuminuria than those with macroalbuminuria (p< 0.05) (Figure 10).

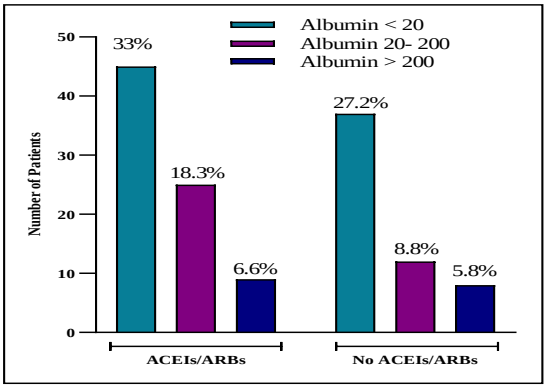

Figure 9: Incidence of albuminuria in patients who were taking ACEI/ARBS.

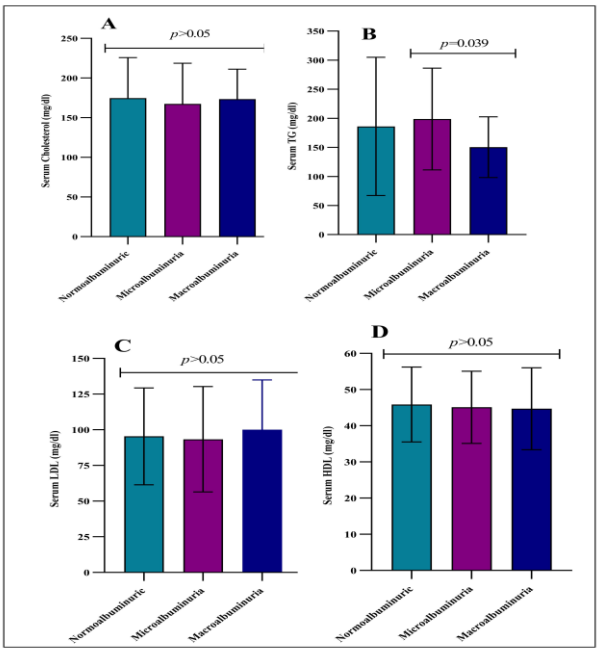

Figure 10: Differences in lipid profile among T2DM patients based on albuminuria status. A) Serum cholesterol, B) Serum TG, C) Serum LDL, and D) Serum HDL. Values were presented mean±SD.

DISCUSSION

The current investigation found that more than a quarter of the patients had microalbuminuria, which is consistent with the findings of earlier studies [21,25-29]. Furthermore, the prevalence of microalbuminuria in the current study is lower than in earlier studies [14,16,22,23,30-32], but greater than in other studies [17,33-36]. According to Iqbal Ayesha's study [25], which found that 14% of patients had macroalbuminuria, the current study found that 12.5% of patients had this disease. The incidence rate of macroalbuminuria, on the other hand, is higher when compared to other research [26,27,29,33,34] and lower when compared to other earlier investigations [30,31]. The discrepancy in microalbuminuria and macroalbuminuria rates could be attributed to the fact that all of the patients are older (≥ years), had poor glucose control, long-term diabetes, and high blood pressure. It could also be due to population differences, how urine is collected, or how albuminuria is measured. Male gender has been identified as a risk factor for DN in type 2 diabetes [37,38]. Females made up the bulk of the study sample in the current investigation, and they were the majority of individuals with microalbuminuria (19.1%) and macroalbuminuria (6.6%). In contrast, studies from Rawalpindi, Sindh, and the United Arab Emirates (UAE) found that the majority of albuminuric patients were men [21, 25, 32]. Other research has found no link between gender and albuminuria in T2DM [17,20,28,34,37,39]. This variance could be attributed to the fact that roughly two-thirds of the patients in our study were female. In diabetics, glycosylated hemoglobin (HbA1c) is used as the gold standard for glycemic control. For every 1% increase in HbA1c, the risk of having microalbuminuria increased by 23% [28]. Higher HbA1c values indicate chronic hyperglycemia, which causes excessive protein glycosylation and stores these advanced glycated end products in the glomerulus. This may assist in explaining the situation. As a result, the glomerular basement membrane swells, causing glomerular hypertrophy and, eventually, protein leakage [31]. In patients with T2DM, strict blood glucose control at the start and prior to the onset of DN may help to prevent the development of diabetic nephropathy. [29,33] Currently, studies show that the majority of individuals with albuminuria have elevated HbA1c [25], and a substantial association between albuminuria and elevated HbA1c in T2DM patients has been observed [4,14,16,20,22,23,28-31,33,39]. In contrast, several studies [32,36] revealed no significant link between albuminuria and elevated HbA1c. Furthermore, diabetes duration, particularly 15 years or more, was determined to be the most significant risk factor for developing nephropathy in many ethnic groups [30]. According to the current study, the majority of patients with microalbuminuria had diabetes for a longer period of time: 5-10 years (13.9%) and >10 years (11.7%). Furthermore, the majority of patients with macroalbuminuria had diabetes for a longer period of time: 5-10 years (5.1%) and more than 10 years (5.8%). According to Tandon *et al*. and Bamahel, the majority of patients with microalbuminuria or macroalbuminuria had a longer period of diabetes (5-10 years) [31,37]. Prior research has also discovered a link between albuminuria and the duration of diabetes [16,20-22,26,30,33,36,40]. However, Al-Maskari *et al*. discovered no link between albuminuria and the duration of diabetes [32]. According to the findings of this study, the majority of albuminuric patients (21.3% had microalbuminuria and 10.2% had macroalbuminuria) had comorbidities. This is consistent with the findings of a study conducted in Saudi Arabia by Atalla *et al*. [40]. Hypertension has been linked to the development of kidney disease [16,28]. It is typical for the proximal tubular cells of the kidney to filter blood albumin from the renal tubular lumen so that it can enter the peritubular blood microcirculation. When the proximal tubular cells do not take up the filtered albumin, lysosomes break it down into minute peptide fragments. When the aortic pulse pressure rises, so does peripheral resistance, and the kidneys are subjected to greater pressure and volume demands. These hemodynamic alterations may harm the tiny blood arteries in the kidneys. As a result, more albumin is filtered than the proximal tubules are capable of retrieving. Furthermore, the increased levels of transforming growth factor-b1 and angiotensin II associated with high blood pressure may disrupt the lysosomal breakdown route, leading to albuminuria.

Furthermore, albuminuria as a symptom of renal failure may signal vascular damage throughout the body [41]. In this study, 69.1% of patients had hypertension, and the incidence of microalbuminuria and macroalbuminuria in T2DM patients with hypertension was 20.5% and 8.8%, respectively. Although the prevalence of microalbuminuria and macroalbuminuria was 6.6% and 3.6%, respectively, in T2DM individuals without hypertension. This finding is similar with a research by Bamahel, who discovered that the prevalence of diabetic nephropathy was 21.3% in T2DM with hypertension and 12.6% in T2DM without hypertension [37]. Furthermore, earlier research found a link between diabetic nephropathy and hypertension [4,21,26,28-30,35,37,40], which contradicted the findings of other studies [16,20,32,39]. Despite the fact that a high proportion of patients with microalbuminuria and macroalbuminuria had hypertension, we found no significant difference in blood pressure between patients with microalbuminuria and macroalbuminuria and patients with normoalbuminuria. This finding is comparable with the findings of Harahap *et al*., who discovered no discernible change in blood pressure between individuals with microalbuminuria and macroalbuminuria and patients with normoalbuminuria [11]. Other studies [16,23,33] reported a substantial rise in SBP in patients with microalbuminuria compared to individuals with normoalbuminuria. The disparity in these findings could be attributed to our diabetic patients with hypertension who are taking antihypertensive drugs. Endothelial dysfunction or other significant vascular damage is reflected in type 2 diabetes by abnormally elevated albumin excretion rates. Ischemic heart disease is the leading cause of morbidity and death in adults with type 2 diabetes, particularly in those with high levels of urine albumin excretion. [38]. Several explanations have been proposed to explain albuminuria's prognostic importance in the prediction of ischemic heart disease in type 2 diabetic men. Some speculate that this is due to either the damaging effects of androgens in males or the protective effects of estrogen in females. Androgens are known to stimulate the renin-angiotensin system, which can be harmful to endothelial cells. Testosterone, especially in older men, causes salt and water retention, which can lead to edema, hypertension, and vascular damage. Lower testosterone levels following orchiectomy have been shown to reduce oxidative stress and kidney damage after ischemia [38]. Furthermore, we discovered that patients with microalbuminuria (3.6%) and macroalbuminuria (4.4%) had CAD, which is consistent with research done in Saudi Arabia by Atalla *et al*. [40]. Furthermore, Al-Maskari *et al*. discovered that albuminuria was not significantly associated with the presence of CAD [32]. Microalbuminuria has been associated to an increased risk of serious cardiovascular events, including stroke [42]. A stroke history was also documented in 4.4% of microalbuminuria patients and 2.9% of macroalbuminuria patients. Albuminuria was shown to be common in ACEI or ARB users in this study (18.3% microalbuminuria and 6.6% macroalbuminuria). According to previous studies [20,35], the frequency of albuminuria in T2DM was not substantially connected with the usage of ACEI or ARB. However, Makino *et al*. discovered that taking telmisartan inhibits the evolution of microalbuminuria in normotensive Japanese T2DM patients [43]. The difference in our results with the latter could be related to the fact that ACEI or ARBs were utilized in our study's hypertensive diabetic individuals. Dyslipidemia is another key risk factor for the development of diabetic nephropathy [16,22]. The serum cholesterol, LDL, HDL, and TG levels in individuals with microalbuminuria and macroalbuminuria were not significantly different from those in patients with normoalbuminuria. These findings were consistent with previous research [29,35]. Other studies, on the other hand, reported a significant rise in serum TG [16,33,39], LDL [39], and cholesterol [22], as well as a significant drop in serum HDL [33] in patients with microalbuminuria compared to normoalbuminuria.

Study Limitations

The study was carried out in a single outpatient center with a small sample size. As a result, the outcome of the study might not include the whole patient with type 2 diabetes. Additionally, those patients with overt proteinuria might be under the care of a nephrologist.

Conclusion

Albuminuria in elderly patients with T2DM was high in patients with poor glycemic control, a long duration of diabetes, and comorbidity conditions (mainly hypertension). Accordingly, patient education may play a key role in controlling albuminuria risk factors and enhancing early screening of albumin in the urine to prevent further kidney damage.

ACKNOWLEDGEMENT

The authors appreciate the Diabetes and Endocrine Center and the College of Pharmacy, University of Sulaimani for the logistic support.

Conflict of interests

No conflict of interests was declared by the authors.

Funding source

The authors did not receive any source of fund.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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