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Prevalence of proteinuria and its associated factors in hypertensive diabetic patients

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Abstract. – OBJECTIVE: Hypertensive diabetic patients are at increased risk for chronic kidney disease. Proteinuria is an early sign of kidney damage. Limited research is available on proteinuria and on its associated factors in hypertensive patients with diabetes. This study aimed to assess the prevalence of proteinuria and its associated factors in hypertensive diabetic patients.

PATIENTS AND METHODS: The current retrospective study utilized medical records and hospital computers to collect sociodemographic and medical information about the study patients in two major hospitals in Jordan. Binary regression analysis was used to find the factors that are significantly and independently associated with the presence of proteinuria.

RESULTS: Data from 522 hypertensive diabetic patients were investigated. Factors including age (OR=0.691; 95% CI: 0.930-0.994; $p<0.01$), high-density lipoprotein level (OR=0.450; 95% CI: 0.211-0.960; $p<0.05$), and higher glomerular filtration rate (OR=0.964; 95% CI: 0.950-0.977; $p<0.01$) were associated with proteinuria among the study patients. In contrast to metformin (OR=0.237; 95% CI: 0.098-0.572; $p<0.01$), patients who received insulin (OR=1.992; 95% CI: 1.136-3.492; $p<0.05$), thiazide diuretics (OR=1.848; 95% CI: 1.108-3.083; $p<0.05$), calcium channel blockers (OR=1.833, 95% CI: 1.110-3.028, $p<0.05$), or beta-blockers (BBs) (OR=2.199, 95% CI: 1.257-3.848, $p<0.01$) had a higher likelihood of having proteinuria.

CONCLUSIONS: For preserving kidney function, it is deemed necessary to perform regular checkups for proteinuria among hypertensive diabetic patients, particularly in young patients, patients with low levels of high-density lipoprotein, and those with a lower glomerular filtration rate.

Key Words:
Hypertension, Diabetes, Kidney function, Glomerular filtration rate, Proteinuria.

Introduction

Proteinuria is a term used to describe the presence of elevated amounts of proteins such as albumin, globulins, Bence-Jones proteins, and mucoproteins in urine[1]. The presence of proteinuria secondary to hypertension, diabetes, and other chronic conditions, can lead to kidney damage and end-stage renal disease[2]. Proteinuria has been associated[3] with other complications, including an increased risk of coronary heart disease, cerebrovascular events, and even death. An epidemiological study[4] reported that nearly half of the diabetic patients who developed proteinuria died within seven years after the onset of persistent proteinuria, suggesting a premature death risk associated with proteinuria. Furthermore, a collaborative meta-analysis[5] of general population cohorts reported an increased risk of mortality with a high albumin-to-creatinine ratio and a low estimated glomerular filtration rate in the general population.

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In order to reduce the complications associated with proteinuria, it is crucial to discover the factors that increase the likelihood of developing proteinuria, especially in the high-risk population. In a public survey[6], results showed that patients who had both hypertension and diabetes had a significantly higher risk of developing proteinuria. Moreover, the harmful effects of smoking on kidney health are well documented[7,8], with a clear association established between tobacco use and the onset of proteinuria. In Yemen, hypertension, duration of diabetes, obesity, and living in rural areas were associated with a higher likelihood of developing proteinuria[9,10]. Other factors such as younger age, insulin therapy, serum albumin and hemoglobin levels, and blood pressure were significantly associated with the progression of renal failure in patients with type 2 diabetes[11,12]. Given the wide range of data on the risk factors for proteinuria, further research is required to identify the genuine predictors of proteinuria and renal function impairment, especially in diabetic hypertensive patients, which was the primary goal of the current study. The results of the present study should serve as a reference for the design of future healthcare interventions that aim to decrease the likelihood of developing proteinuria, as well as the difficulties that can arise from it, and to improve the health outcomes in hypertensive patients with diabetes.

Patients and Methods

Study Design and Participants

This is a 1-year observational, retrospective study, which utilized the medical data of hypertensive diabetic patients at King Abdullah University Hospital and the Royal Medical Services Hospital in the period from November 2021 through May 2022.

Inclusion criteria

Data of the patients were collected if they were 18 years or older, diagnosed with hypertension based on the 2017 American College of Cardiology/American Heart Association criteria, and diagnosed with type 2 diabetes according to the American Diabetes Association guidelines[13,14].

Exclusion criteria

Patients who had type 1 diabetes, had a hypertensive crisis, received medication that might increase BP, and pregnant women were excluded from the study.

Study Instruments

The researchers used medical records and hospital computers to collect information about the study patients. The socio-demographic data included age, gender, marital status, employment status, educational level, area of residency, body weight, family history of heart diseases, and family history of type 2 diabetes. The collected medical data included systolic and diastolic blood pressure (BP), glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and the glomerular filtration rate (GFR). The patient was considered to have uncontrolled BP if one of the most recent two BP readings was over 130/80 mmHg. Medical data also included the presence of comorbid diseases and proteinuria, in addition to the prescribed medications.

Statistical Analysis

Data were analyzed using Statistical Software for the Social Sciences version 26 (IBM Corp., Armonk, NY, USA). Means and standard deviations were used to describe continuous variables, whereas frequencies and percentages were used to present categorical variables. Univariate analysis was conducted using Chi-square and Mann-Whitney U tests to determine the variables associated with the presence of proteinuria. Variables with a p-value <0.2 in the univariate analysis were included in the multivariate analysis. Multivariate regression analysis was conducted using a binary regression model to find the variables that are significantly and independently associated with the presence of proteinuria. A p-value <0.05 was considered statistically significant.

Results

We collected data for 522 hypertensive diabetic patients. The mean age of the patients was 62 (± 10) years, ranging from 33 to 89 years. Most of the patients were males (51.2%), married (78.2%), non-obese (68.6%), formerly smokers or non-smokers (68.0%), had a low educational level (72.6%), not physically active (60.5%), retired/non-employed (67.1%), and lived in an urban area (69.6%). The socio-demographic characteristics of the study participants are presented in Table I.

Metformin (87.0%), angiotensin receptor blockers (ARBs) (57.1%), and beta-blockers (BBs) (54.4%) were the most commonly prescribed

Table I. Socio-demographic characteristics of the study patients (n = 522).

		Number (%) or mean (± SD)
Age		62 (± 10)
Gender	Female	255 (48.8%)
	Male	267 (51.2%)
Marital status	Married	408 (78.2%)
	Other	114 (21.8%)
Obesity	Non-obese	358 (68.6%)
	Obese/ overweight	164 (31.4%)
Smoking	Current smoker	167 (32.0%)
	Former/ non-smoking	355 (68.0%)
Educational level*	High	143 (27.4%)
	Low	379 (72.6%)
Performing regular physical activity	No	316 (60.5%)
	Yes	206 (39.5%)
Employment status	Employees	172 (32.9%)
	Retired/ non-employees	350 (67.1%)
Living area	Rural area	159 (30.4%)
	Urban area	363 (69.6%)

*High: Bachelor or postgraduate degree, Low: Secondary/high school.

medications, while sodium-glucose cotransporter-2 (SGLT2) inhibitors (6.1%) and meglitinides (0.6%) were the least commonly prescribed. More details about the medication history of the study patients are presented in Table II.

As shown in Table III, the majority of the patients had no family history of heart disease (88.7%) or type 2 diabetes (83.9%). Most of the patients had uncontrolled BP (63.4%) and uncontrolled blood glucose (51.3%). The most common comorbidity was dyslipidemia (72.0%), followed by microvascular complications (50.6%), with retinopathy being the most commonly recognized microvascular complication (45.2%). The mean systolic BP was 134 (± 17.0) mmHg, while the mean diastolic BP was 79 (± 9.0) mmHg. Concerning biomedical parameters, the mean fasting blood glucose was 170.14 (± 74.4) mg/dl, and the mean HDL and LDL were 1.13 (± 1.8) and 2.58 (± 2.8), respectively. The mean HbA1c = 10.31% (± 49.3), while the mean GFR was 69.85 (± 26.6) ml/min.

Results of the univariate analysis showed that age, HDL, LDL, TG, GFR, duration of hypertension and diabetes, having ischemic heart disease, anxiety, depression, receiving BB, calcium channel blocker (CCB), thiazide diuretics, insulin, metformin, glucagon-like peptide

Table II. Medication history of the study patients (n=522).

Medicines used by the patients	Number (%)	
	No	Yes
ACEI*	391 (74.9%)	131 (25.1%)
ARB*	224 (42.9%)	298 (57.1%)
BB*	238 (45.6%)	284 (54.4%)
CCB	303 (58.0%)	219 (42.0%)
Metformin	68 (13.0%)	454 (87.0%)
Insulin	237 (45.4%)	285 (54.6%)
Thiazide diuretics	330 (63.2%)	192 (36.8%)
DPP4 inhibitors*	359 (68.8%)	163 (31.2%)
GLP1 receptor agonist*	269 (51.5%)	253 (48.5%)
Meglitinides	519 (99.4%)	3 (0.6%)
Sulfonylurea	328 (62.8%)	194 (37.2%)
SGLT2 inhibitors*	490 (93.9%)	32 (6.1%)

*ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, BB: beta-blocker, CCB: calcium channel blocker, DPP4: dipeptidyl-peptidase 4, GLP1: glucagon-like peptide 1, SGLT2: sodium-glucose cotransporter-2.

Table III. Medical profile and biomedical data of the study patients (n=522).

		Number (%) or mean (± SD)
Duration of hypertension (years)		34.31(22.94)
Duration of diabetes (years)		23.22 (24.54)
Family history of cardiac problems	No	463 (88.7%)
	Yes	59 (11.3%)
Family history of type 2 diabetes	No	438 (83.9%)
	Yes	84 (16.1%)
Dyslipidemia	No	146 (28.0%)
	Yes	376 (72.0%)
Microvascular complications	No	258 (49.4%)
	Yes	264 (50.6%)
Peripheral artery disease	No	504 (96.6%)
	Yes	18 (3.4%)
Heart failure	No	490 (93.9%)
	Yes	32 (6.1%)
cerebrovascular disease	No	454 (87.0%)
	Yes	68 (13.0%)
Ischemic heart disease	No	308 (59.0%)
	Yes	214 (41.0%)
Renal failure	No	460 (88.1%)
	Yes	62 (11.9%)
Presence of proteinuria on urine analysis	No	375 (71.8%)
	Yes	147 (28.2%)
Retinopathy	No	286 (54.8%)
	Yes	236 (45.2%)
Neuropathy	No	428 (82.0%)
	Yes	94 (18.0%)
Foot damage	No	455 (87.2%)
	Yes	67 (12.8%)
Anxiety	No	407 (78.0%)
	Yes	115 (22.0%)
Depression	No	466 (89.3%)
	Yes	56 (10.7%)
Asthma	No	499 (95.6%)
	Yes	23 (4.4%)
Chronic obstructive pulmonary disease	No	510 (97.7%)
	Yes	12 (2.3%)
Blood glucose control	Controlled	254 (48.7%)
	Uncontrolled	268 (51.3%)
Blood pressure control	Controlled	189 (36.6%)
	Uncontrolled	327 (63.4%)
Systolic BP		134 (± 17)
Diastolic BP		79 (± 9)
Biomedical tests HbA1c		10.31 (± 49.32)
Fasting serum glucose (mg/dl)		170.14 (± 74.40)
Total cholesterol (mmol/l)		4.76 (± 8.21)
TG (mmol/l)		3.46 (± 25.64)
HDL (mmol/l)		1.13 (± 1.83)
LDL (mmol/l)		2.58 (± 2.82)
GFR (ml/min)		69.85 (± 26.58)

*BP: blood pressure, HbA1c: glycosylated hemoglobin, TG: triglycerides, HDL: high-density lipoprotein, LDL: low-density lipoprotein, GFR: glomerular filtration rate.

1 (GLP1) receptor agonist, and sulfonylurea (SU) were significantly associated with proteinuria. Results of the binary regression (Table IV) revealed that increased age was associated with decreased odds of having proteinuria (OR=0.691; 95% CI: 0.930-0.994; $p<0.01$). Increased HDL (OR=0.450; 95% CI: 0.211-0.960; $p<0.05$) and GFR (OR=0.964; 95% CI: 0.950-0.977; $p<0.01$) were also associated with decreased odds of having proteinuria. Patients who received metformin had a lower likelihood of developing proteinuria (OR=0.237; 95% CI:

Table IV. Medication history of the study patients (n=522).

Variables	*p*-value	EXP(B)-OR	CI	
			Lower	Upper
Age*	0.002	0.961	0.930	0.994
HDL*	0.039	0.450	0.211	0.960
LDL	0.689	0.952	0.748	1.212
TG	0.055	1.060	0.999	1.125
GFR*	0.000	0.964	0.950	0.977
Duration of hypertension	0.612	1.013	0.964	1.064
Duration of diabetes	0.833	0.995	0.950	1.042
Receiving Sulfonylurea	0.195	1.436	0.831	2.482
Receiving GLP1 receptor agonist	0.588	1.161	0.677	1.992
Receiving Metformin*	0.001	0.237	0.098	0.572
Receiving Insulin*	0.016	1.992	1.136	3.492
Receiving Thiazide diuretics*	0.019	1.848	1.108	3.083
Receiving CCB*	0.018	1.833	1.110	3.028
Receiving BB*	0.006	2.199	1.257	3.848
Depression	0.102	1.840	0.886	3.820
Anxiety	0.417	0.780	0.427	1.422
Ischemic heart disease	0.741	1.098	0.630	1.915

BB: beta-blocker, CCB: calcium channel blocker, GLP1: glucagon-like peptide 1, TG: triglycerides, HDL: high-density lipoprotein, LDL: low-density lipoprotein, GFR: glomerular filtration rate. *Significant at $p < 0.05$.

0.098-0.572; $p<0.01$). On the other hand, patients who received insulin, thiazide diuretics, CCB, or BB had higher likelihood to have proteinuria than their counterparts (OR=1.992; 95% CI: 1.136-3.492; $p<0.05$); (OR=1.848; 95% CI: 1.108-3.083; $p<0.05$); (OR=1.833; 95% CI: 1.110-3.028; $p<0.05$); (OR=2.199; 95% CI: 1.257-3.848; $p<0.01$), respectively.

Discussion

Understanding the factors associated with proteinuria in hypertensive diabetic patients is considered a preliminary step in the development of clinical interventions aimed at reducing the likelihood of developing proteinuria in this group of patients. Patients' data revealed that 28.3% of the current study patients had proteinuria. A population of 40,400 individuals was screened by Ong et al[6] for the presence of proteinuria and the results showed that 1.4% had positive results. The study also reported that the coexistence of both high blood pressure and high blood glucose exerts a synergistic effect, substantially increasing the risk for proteinuria. During the period from 2013 to 2016, a community-based mobile health check-up service called the Portable Health Clinic (PHC) was conducted in Bangladesh[15]. The findings from the data of this service revealed that among individuals with both hypertension and diabetes, the prevalence of proteinuria was 77%. Comparatively, the prevalence of proteinuria was lower in patients with diabetes alone (55.2%) or hypertension alone (37.7%)[15]. Another study[16] reported a 9.4% prevalence of proteinuria among patients with diabetes. Furthermore, other studies in the literature reported a high prevalence of proteinuria among the general population of different countries, including Uganda (13%)[12] and Nigeria (13%)[17]. However, other studies in literature focused solely on patients with either hypertension or type 2 diabetes, whereas the present study specifically targeted patients who had both diseases. This, together with the paucity of research in the field, contributes to a deeper understanding of proteinuria and its associated factors in this group of patients.

The present study revealed that younger age was significantly associated with proteinuria. In a study[12] conducted in Uganda, researchers discovered that individuals in the age range of 18-39 years had significantly higher levels of proteinuria compared to older adults aged 40 years and above. Similarly, in another study[10] involving 10,242 individuals aged 15-69 years in Yemen, it was observed that proteinuria exhibited an inverse relationship with age. Proteinuria detection in younger age groups highlights the urgent need

for more research that is capable of identifying the etiologies behind proteinuria development in such a young, economically productive group of population.

Consistent with earlier research findings[18,19], patients with higher HDL levels were less likely to have proteinuria than those with lower HDL levels. In a trial[20] of over 9,000 atorvastatin-treated patients, results showed that higher HDL levels were associated with lower deterioration of kidney function after a 3-month follow-up period of normal GFR at baseline. The Atherosclerosis Risk in Communities study[21], which included more than 12,000 participants, showed that high triglycerides and low HDL levels were associated with an increased risk of kidney dysfunction. These findings imply that dyslipidemia has a deleterious influence on renal function even in healthy individuals, requiring effective management of dyslipidemia, particularly in hypertensive diabetic patients.

Similar to previous research findings[16,22,23], the current study showed that patients with a higher GFR were less likely to have proteinuria. Increased proteinuria and lower GFR have been recognized as significant predictors of mortality and progression to kidney failure in previous research[24,25].

Patients who received metformin had a lower likelihood of developing proteinuria in the present study. Recent studies[26-28] showed that metformin exerted renoprotective effects and reduced proteinuria in hypertensive or diabetic animals. On the other hand, insulin use was associated with a higher risk for proteinuria in the present study. In comparison, a randomized controlled trial[29] was conducted to evaluate and compare the impact of intensive blood glucose control using either sulphonylurea or insulin *vs.* conventional treatment on the occurrence of microvascular and macrovascular complications in individuals with type 2 diabetes. Over a period of 10 years, the study revealed that rigorous blood-glucose control, whether achieved through sulphonylureas or insulin, significantly reduced the risk of microvascular complications, such as nephropathy, in those patients, which contradicts the current study findings. However, studies investigating the relationship between insulin use and the risk of proteinuria in hypertensive diabetic patients are lacking, calling for additional research in this area.

The current study showed that patients who received thiazide diuretics, CCBs, or BBs had a higher likelihood of having proteinuria than their counterparts. In contrast, the use of thiazide diuretics was associated with a significant reduction in proteinuria in several prospective randomized trials conducted among diabetic and non-diabetic patients[30,31]. However, the later studies were conducted under special circumstances of renin-angiotensin-aldosterone system blockade or a low-salt diet. Additionally, the anti-proteinuria effect of diuretics may have been induced by their impact on BP, casting doubt on their purported anti-proteinuria effect[32]. Concerning CCBs, a randomized clinical trial[33] showed that hypertensive diabetic patients who received diltiazem showed a reduction in proteinuria after 21-month follow-up, which was not observed in patients who received nifedipine. β-blockers have also been associated with reduced urinary protein excretion in a meta-analysis[34] of 39 prospective studies conducted among hypertensive patients. The discrepancy between the results of the current study and earlier research studies[30,31,33,34] could be attributed to the variation in study design and in terms of ethnic composition, social structure, and individual traits, prompting additional research in this field to gain a clearer understanding of this association. Further research is required to investigate the association between receiving these medications and proteinuria.

Conclusions

The factors associated with proteinuria in the present study should provide insight for future interventions that aim at decreasing the risk of proteinuria, preserving kidney function, and improving health outcomes in hypertensive diabetic patients. Such interventions should emphasize regular checkups for proteinuria, particularly among young patients and those with low HDL and GFR. Further research is required to investigate the association between receiving BBs, CCBs, thiazide diuretics, insulin, and metformin and the likelihood of having proteinuria in hypertensive diabetic patients.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Authors' Contribution
ASJ conceived and designed the study, validated instruments, wrote the initial and final draft of the article, and supervised the project. WA validated instruments, organized, analyzed, and interpreted data, and wrote the initial and final of the article. KA designed the study, analyzed and interpreted data, and reviewed the final draft of the article. SA collected and organized data and wrote the initial and final draft of the article. SRA validated instruments, analyzed and interpreted data, and wrote the initial and final draft of the article. TM conceived and designed the study and wrote the final draft of the article. YAN conceived and designed the study and reviewed the final draft of the article. SA conceived and designed the study, reviewed the final draft of the article, and provided logistic support. MA conceived and designed the study, reviewed the final draft of the article, and co-supervised the project. All authors have critically reviewed and approved the final draft of the study and agreed to be accountable for all aspects of the work.

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Data Availability
The data generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

Informed Consent
Not applicable due to the retrospective design of the study.

Ethics Approval
This study was conducted according to the Declaration of Helsinki principles. Ethical approval was obtained from the Institutional Review Board (IRB) of King Abdullah University Hospital at Jordan University of Science and Technology (Ref. #25/138/2021).

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