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Variation of Urine Parameters among Diabetic Patients: A Cross-Sectional Study

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ABSTRACT

BACKGROUND: *Diabetic kidney disease is a common and severe microvascular complication of diabetes mellitus (DM). There are limited data regarding alteration of urine parameters other than proteinuria among DM patients.*
METHODS: *Institution based cross-sectional study was conducted from February to May 2017 to assess alteration of urine parameters among DM patients at the University of Gondar Hospital, Northwest Ethiopia. A Systematic random sampling technique was used to recruit adult (≥18 years) diabetic participants. Data were collected after ethical requirements had been fulfilled. The degree of association between variables was evaluated through bivariable and multivariable logistic regression models.*
RESULTS: *The majority (69.4%) of the study participants were type 2 DM patients. The prevalence of altered urine chemical parameters was 11.3% proteinuria, 4.5% ketonuria, 13.6% hematuria, 53.8% glucosuria, 24.9% leukocyturia and 1.7% positive for nitrite. Diastolic blood pressure and poor glycemic control were significantly associated with proteinuria. Male participants were 2.4 times more likely to have leukocyturia than female participants. The prevalence of abnormally increased microscopic findings was red blood cells 3.1%, white blood cells 12.5%, epithelial cells 27.5%, yeast cells 1.7%, bacteria 17.8%, casts 3.7% and crystals 29.2%.*
CONCLUSIONS: *The prevalence of altered urine parameters among DM patients is found to be considerable. These increased prevalences of altered urine parameters are potential indicators for diabetic kidney disease.*
KEYWORDS: *Diabetes mellitus, Diabetic kidney disease, Proteinuria*

INRODUCTION

Diabetes mellitus (DM) represents a cluster of metabolic disorders characterized by increased serum glucose level which is caused by insulin defects in terms of secretion or action (1). The worldwide prevalence and incidence of DM has grown significantly (2). It was estimated that there were 382 million diabetic individuals in 2013,

and DM patients are predicted to reach up to 592 million in 2035 worldwide. Among these, most people with DM are living in developing countries. In Ethiopia, among adults (20–79 years), the estimated prevalence of diabetes was 4.4% in 2013, and it is expected to rise to 5.1% in 2035 (3). In the world, the number of diabetic adults raised from 108 million (1980) to 422 million (2014) (4). The global annual health expense attributable to DM approximately ranged from USD 612 to 1,099 billion (5).

Diabetes associated hyperglycemia causes long-standing damage, dysfunction and collapse of many vital organs; mainly kidneys, eyes, nerves, heart and blood vessels (6). Long-term complications of DM include nephropathy which leads to renal failure, retinopathy which potentially causes loss of vision, autonomic neuropathy which causes gastrointestinal and cardiovascular dysfunction and peripheral neuropathy which causes foot ulcers (7). The majority of type 1 and type 2 DM patients develop such complications through time (8). There is also high prevalence of hypertension, cardiovascular and peripheral vascular diseases in diabetic patients. Diabetes has a psychosocial impact on diabetic individuals and family members because of its social influence and demands of high treatment cost (9). Complications of DM can be prevented or delayed by consistent checkup and management of serum glucose, hypertension or serum lipid levels (10).

Diabetic kidney disease (DKD) is a familiar and serious complication of DM. It is the primary cause of renal failure as well as mortality and morbidity in diabetic patients. DKD is caused by environmental and genetic factor interactions. DKD has an effect on 15–25% of type 1 and 30-40% of type 2 DM patients (11). Sustained serum glucose level drastically reduces DKD incidence and prevalence. DKD progression can be also slowed down effectively by blood pressure management (12).

The diagnosis of DKD at initial stage allows immediate management which improves disease prognosis. It is challenging to identify biomarkers for the management of kidney disorder progress in DM patients (13). Proteinuria is the marker of DKD and a primary indicator of kidney disorder progress (14). Microalbuminuria is a key biomarker of kidney injury (15). It is the predictor of kidney disorder in DM individuals and associates with premature mortality and morbidity in diabetic, hypertensive and healthy people (16). Many research findings have demonstrated that decreasing urine albumin level reduces the risks of adverse kidney problems (17,18).

The complex nature of diabetes needs consistent management through multi-factorial risk reduction approaches (19). A comprehensive management approach including serum glucose and blood pressure control with appropriate treatment integrated to reduced blood lipid level, low protein consumption, reduced salty diet, continuous physical exercise, weight loss and no smoking habit decreases kidney disease progress rate in DM patients (20,21). Thus, this study has presented baseline data regarding alteration of urine parameters among diabetic patients, which will potentially support in DKD assessment and monitoring.

METHODS AND MATERIALS

Study setting and population: An institution based cross-sectional study was conducted from February to May 2017 to assess alteration of urine parameters among DM patients at the University of Gondar Hospital (UoGH), Northwest Ethiopia. Gondar is located 738 kms northwest of Addis Ababa, the capital of Ethiopia. UoGH serves more than 5 million residents in northwestern Ethiopia. Approximately, 8,000 DM patients are registered at Chronic Illness Clinic for medical care service.

Adult DM patients (≥18 years) who attended UoGH Chronic Illness Clinic for diabetes follow-up and volunteered to give informed written consent were included. Critically troubled DM patients who were unable to communicate, catheterized patients and pregnant and menstruating women were excluded from this study.

Sampling procedure: A Systematic random sampling technique was used to recruit adult (≥18 years) DM study participants. The sample size

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was determined based on a single population proportion formula by considering assumptions of 95% level of confidence, 5% margin of error and 50% prevalence of proteinuria. The total calculated sample size was 384. However, the total source population (diabetic patients) was approximately 8,000 (<10,000) and a sample size calculation correction factor (384/8000 =0.048) was used. Therefore, the corrected sample size was 366 (384/1+0.048). Among those, 353 (96.4% response rate) adult DM participants were included in the study. The remaining 3.6% of the population did not volunteer to participate.

Data collection: Prior to the actual data collection, a three-days training and demonstration was given for the data collectors (nurse and medical laboratory professionals) about the study participants' rights, the objectives of the study, confidentiality, the procedure of urine sample collection and measurements, and how to approach and interview participants. Socio-demographic, clinical, behavioral and measurement data of the study subjects were collected by nurses using a pre-tested structured questionnaire. In addition, the urine samples were analyzed by medical laboratory technologist. All aspects of data collection process were supervised by experienced professionals to ensure data quality.

The study participants were communicated early in the morning when they came to UoGH Chronic Illness Clinic for their regular medical follow-up. Primarily, the objective of the study and related issues were explained to study participants by data collectors. Written informed consents were signed by volunteered study participants. Finally, demographic, clinical and measurement data were collected, and at the same time, participants were instructed to collect and transport urine specimen to urinalysis laboratory. Ten ml of urine specimen was collected in a clean, dry and leak-proof urine cap. Chemical parameters of urine were semi-quantitatively assessed by urine dipsticks immediately. Then, the sample was centrifuged at 3,000 rpm for 5 minutes, and the sediment was transferred to clean slide and evaluated microscopically. All the data obtained from chemical and microscopic examination of urine specimen were recorded on registration sheet prepared by authors.

Anthropometric measurements were done by nurses using calibrated equipment and standardized techniques. Every participant's weight was recorded using weight balance. Stadiometer was used for height measurement. Thus, Body Mass Index (BMI) was calculated as weight/height^2 (kg/m^2). BMI was categorized into <18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal), 25–29.9 kg/m^2 (overweight) and ≥30 kg/m^2 (obese). Waist Circumference (WC) was measured midway of lower rib and iliac crest. WC >88 cm for females and >102 cm for males was considered abnormal (22).

Mercury sphygmomanometer instrument was used to measure blood pressure (BP). BP was taken two times after participants relaxed for at least 15 minutes. Five minutes interval was recommended between the two measurements. In the end, the average of the two measurements was used as the final result. Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or getting histories of taking anti-hypertensive drugs were taken into account to classify hypertension. The current fasting blood glucose (FBG) data were collected from the patients' registration book to group participants into good glycemic control (FBG ≤130 mg/dl) and poor glycemic control (FBG >130 mg/dl) (19).

The chemical parameters of urine (protein, glucose, blood, leukocyte, ketone, nitrite, bilirubin, urobilinogen, pH and specific gravity) were determined and reported semi-quantitatively as normal, 1+, 2+, 3+ and 4+ based on the manufacturer's instruction of urine dipstick test (ALDE Diagnostic Co., Ltd, China). Therefore, the above reports were classified as normal and altered (1+, 2+, 3+ and 4+) for the purpose of this study. The microscopic examination of urine was also performed to evaluate abnormally increased number of urine sediment components (red blood cell (RBC), white blood cell (WBC), yeast cell, epithelial cell, cast, crystal, and parasite). RBCs, WBCs and epithelial cells found >5 cells per high power field were considered as abnormal and any yeast cells, bacteria, cast and crystal observed were defined as abnormal. The study followed

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standard operation procedures (SOPs) to produce reliable results.

Data analysis: The data were cleared, edited and entered into EPI info version 3.5.3 (CDC, USA) and then transferred to SPSS version 20 (IBM, USA) software for statistical analysis. Bivariable and multivariable logistic regression models were used to determine the degree of association between variables. Variables having a p-value of ≤0.2 in the bivariable model were subjected to multivariable analysis to avoid confounding variables' effect. In addition, crude and adjusted odds ratios, with their 95% confidence interval, were used to evaluate the associations between variables. P-value <0.05 was taken as statistically significant.

RESULTS

Socio-demographic and clinical characteristics: The study recruited 353 Diabetic patients. The mean age was 49.3±15.2 (range: 18-85 years). From all participants, 138 (39.1%) had no education, 112 (31.7%) were housewives, 234 (66.3%) were married, 245 (69.4%) were type 2 DM patients and 122 (34.6%) were hypertensive (Table 1).

Table 1: Socio-demographic and clinical characteristics of DM patients attending at University of Gondar Hospital, Gondar, Northwest Ethiopia, 2017 (n= 353)

Variable	Category	Number	Percent
Sex	Male	168	47.6
	Female	185	52.4
Age	≤49	155	43.9
	>49	198	56.1
Marital status	Single	39	11.0
	Married	234	66.3
	Divorced	39	11.0
	Widowed	41	11.6
Occupation	Employed	96	27.2
	Housewife	112	31.7
	Farmer	52	14.7
	Private	61	17.3
	Other	32	9.1
Educational status	No education	138	39.1
	Primary	76	21.5
	Secondary	61	17.3
	Higher	78	22.1
Type of diabetes	Type 1	108	30.6
	Type 2	245	69.4
Family history of DM	Yes	40	11.3
	No	313	88.7
Hypertension	Present	122	34.6
	Absent	231	65.4
Waist circumference	Low risk	230	65.2
	High risk	123	34.8
Blood glucose	≤130	111	31.4
	>130	242	68.6
Body mass index	<25	218	61.8
	25-29.9	94	26.6
	≥30	41	11.6
Total		353	100

Prevalence of altered urine chemical parameters: The 259 (73.4%) study participants had at least one altered chemical parameter. Mixed alteration was: 59.8% (155/259) single,

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30.9% (80/259) double, 8.9% (23/259) triple and 0.4% (1/259) quadruple. The prevalence of altered urine chemical parameters was 11.3% (95% CI: 8.2-15) proteinuria, 4.5% (95% CI: 2.5-6.8) ketonuria, 13.6% (95% CI: 10.2-17.3) hematuria, 53.8% (95% CI: 48.4-58.9) glucosuria, 24.9% (95% CI: 20.7-29.5) leukocyturia and 1.7% (95% CI: 0.6-3.1) positive for nitrite (Figure 1).

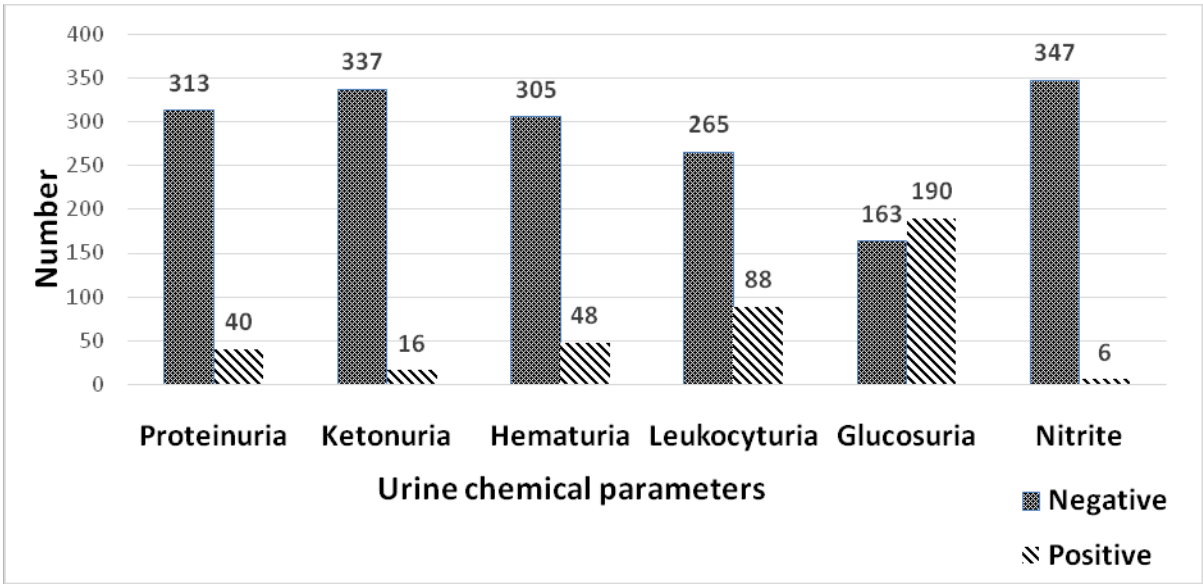

Figure 1*: Alteration of urine chemical parameters of DM patients attending at University of Gondar Hospital, Gondar, Northwest Ethiopia, 2017 (n= 353)*

Risk factors associated with altered urine chemical parameters: Elevated diastolic blood pressure and poor glycemic control were significantly associated with proteinuria. The odds of hematuria was 2.4 times higher among female participants compared to their male counterparts. On the other hand, male participants were 2.4 times more likely to have leukocyturia than female participants. Furthermore, the odds of glucosuria was 3.4 times higher among study participants with poor glycemic control than good glycemic control (Table 2).

Alteration of urine microscopic parameters*:* The study participants, 217 (61.5%), had at least one urine microscopic parameter abnormality. Mixed abnormality was: 60% (130/217) single, 27.6% (60/217) double, 9.7% (21/217) triple and 2.7% (6/217) quadruple. Observed casts were 13: 9 casts were granular and 3 casts were cellular (RBC, WBC or epithelial cell) and 1 was hyaline cast. The frequently reported crystals were calcium oxalate (87/103) and uric acid (13/103) (Figure 2).

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Table 2: Factors associated with altered urine parameters of DM patients attending at University of Gondar Hospital, Gondar, Northwest Ethiopia, 2017 (n= 353)

Variable		Proteinuria		COR	P-value	AOR	P-value
		N	P				
SBP	<140	257	26	1	0.013	1	0.338
	≥140	56	14	2.471(1.214-5.032)		1.573(0.623-3.971)	
DBP	<90	276	28	1	0.003	1	0.002
	≥90	37	12	3.197(1.498-6.824)		3.332(1.54-7.209)	
BG	≤130	105	6	1	0.022	1	0.019
	>130	208	34	2.861(1.164-7.029)		2.979(1.199-7.4)	
	Hematuria						
Sex	Male	152	16	1	0.036	1	0.012
	Female	153	32	1.987(1.047-3.771)		2.355(1.209-4.586)	
TDM	Type 1	88	20	1.761(0.943-3.291)	0.076	1.154(1.121-4.137)	0.021
	Type 2	217	28	1		1	
HTN	Present	111	11	0.52(0.255-1.059)	0.072	0.558(0.265-1.175)	0.125
	Absent	194	37	1		1	
	Leukocyturia						
Sex	Male	140	28	1	0.001	2.4(1.442-3.994)	0.001
	Female	125	60	2.4(1.442-3.994)		1	
Age	≤49	122	33	1	0.163	1	0.534
	>49	143	55	1.422(0.867-2.332)		1.19(0.687-2.061)	
ALC	Yes	31	5	0.455(0.171-1.208)	0.114	0.609(0.22-1.682)	0.338
	No	234	83	1		1	
SBP	<140	217	66	1	0.162	1	0.747
	≥140	48	22	1.507(0.848-2.678)		1.127(0.546-2.323)	
DBP	<90	232	72	1	0.181	1	0.2
	≥90	33	16	1.562(0.813-3.002)		1.545(0.794-3.007)	
WC	Low risk	178	52	1	0.169	1	0.277
	High risk	87	36	1.416(0.862-2.327)		0.703(0.373-1.327)	
BMI	<25	173	45	1	0.013	1	0.09
	25-29.9	62	32	1.984(1.158-3.399)		1.623(0.927-2.841)	
	≥30	30	11	1.41(0.656-3.029)	0.379	1.033(0.465-2.297)	0.936
	Glucosuria						
Age	≤49	57	98	1.981(1.289-3.044)	0.002	1.729(1.081-2.764)	0.022
	>49	106	92	1		1	
Sex	Male	71	97	1.352(0.888-2.058)	0.16	1.388(0.879-2.191)	0.159
	Female	92	93	1		1	
TDM	Type 1	40	68	1.714(1.078-2.726)	0.023	1.118(0.59-2.121)	0.732
	Type 2	123	122	1		1	
DDM	<120	133	167	1.638(0.909-2.952)	0.101	1.451(0.776-2.712)	0.243
	≥120	30	23	1		1	
ALC	Yes	12	24	1.819(0.879-3.764)	0.107	1.473(0.658-3.301)	0.346
	No	151	166	1		1	
HTN	Present	70	52	0.501(0.321-0.781)	0.002	0.557(0.343-0.905)	0.018
	Absent	93	138	1		1	
SBP	<140	123	160	1	0.041	1	0.87
	≥140	40	30	0.577(0.34-0.978)		0.948(0.497-1.807)	
BG	≤130	73	38	1	0.000	1	0.000
	>130	90	152	3.244(2.026-5.195)		3.393(2.092-5.502)	
WC	Low risk	98	132	1	0.067	1	0.821
	High risk	65	58	0.662(0.427-1.029)		0.931(0.504-1.722)	
BMI	<25	93	125	1	0.307	1	0.733
	25-29.9	46	48	0.776(0.478-1.261)		0.911(0.532-1.559)	
	≥30	24	17	0.527(0.268-1.037)	0.064	0.717(0.338-1.52)	0.385

ALC: Alcohol consumption, AOR: Adjusted odds ratio, BG: Blood glucose, BMI: Body mass index, COR: Crude odds ratio, DBP: Diastolic blood

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pressure, DDM: Duration of DM (in month), DM: Diabetes mellitus, HTN: Hypertension, N: Negative, P: Positive, SBP: Systolic blood pressure, TDM: Type of DM, WC: Waist circumference

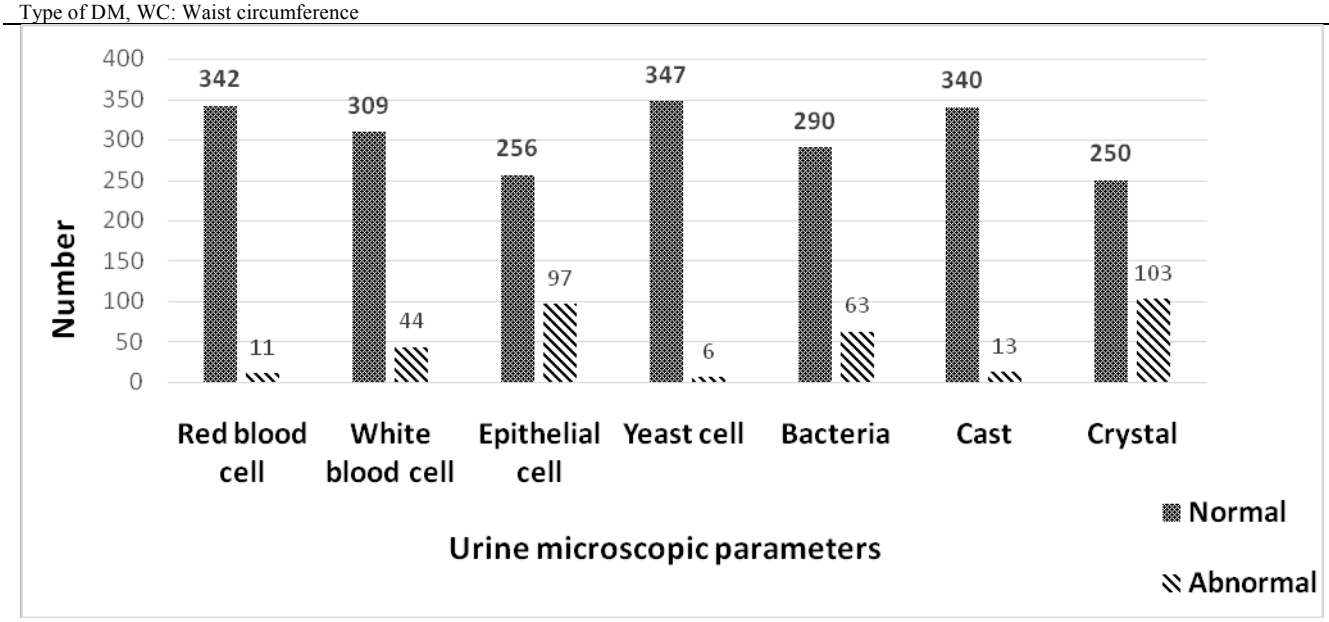

***Figure 2**: Alteration of urine microscopic parameters of DM patients attending at University of Gondar Hospital, Gondar, Northwest Ethiopia, 2017 (n= 353)*

DISCUSSION

This study demonstrated that 242 (68.6%) DM patients had poor glycemic control (FBG >130 mg/dl). DM patients who are unable to control their blood glucose level may develop complications, like diabetes kidney disease, diabetes ketoacidosis, and infection. Therefore, DM patients with proteinuria (11.3%), ketonuria (4.5%) and leukocyturia (24.9%) are at risk of the above-mentioned complications. There is evidence that diabetes is associated with onset and severity of urologic disorders which result in complications, such as bladder, sexual dysfunction and urinary tract infections (23).

The results of this study revealed 11.3% (95% CI: 8.2-15) prevalence of proteinuria which is lower than microalbuminuria findings from the study conducted in India (36.3%) (24) and Saudi Arabia (37.4%) (25) and total albuminuria (macroalbuminuria plus microalbuminuria) prevalence in Tanzania (15.6%) (26). This variation may be due to ethnic variation (27), patient mix (11) and method of determination of urine protein. Studies supported that there are racial/ethnic differences in proteinuria due to DKD among patients with type 2 diabetes (28). Our study population comprised of both type 1 and type 2 DM patients but previous studies used only type 2 DM patients. A study conducted on young Japanese DM patients showed a higher incidence of nephropathy in type 2 than type 1 DM patients; more likely, type 2 DM is the major cause of DKD ([29). The urine dipstick primarily measures albumin, but sensitivity and specificity are relatively lower than quantitative methods. In addition, most dipstick tests are sensitive to albumin but may not detect low concentrations of Bence Jones proteins and γ-globulins (30).

Proteinuria was significantly associated with elevated DBP and poor glycemic control in this study population. However, it was not significantly associated with age, sex, type of DM and other variables. In Saudi Arabia, microalbuminuria was positively related to BMI, hypertension, duration of DM and fasting plasma glucose. Similar with our study, no statistically significant correlation was found between microalbuminuria and age (25). In India, age, DBP, fasting plasma glucose and duration of DM were found to be associated with microalbuminuria (24). A study in the United Kingdom also identified that male gender and increased WC were the independent risk factors

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of albuminuria (27). Study population diversity and sample size inconsistency may affect associated risk factors for proteinuria.

This study showed 13.6% hematuria and 3.1% abnormally increased number of RBCs. The source of this hematuria might be DKD. Moreover, hematuria can be caused by other kidney diseases, cystitis, pyelonephritis, urinary tract infection, kidney stone and cancer of the urinary tract, which are directly or indirectly related to DM (31). Hematuria was significantly associated with type 1 DM and female sex. In addition to urinary system disease, hematuria can happen physiologically in females who were at menstruation and sexual intercourse prior to the data collection time.

This study depicted 24.9% leukocyturia, 1.7% positive for nitrite, 17.8% bacteriuria and 12.5% abnormally increased WBCs. All of the above figures represent the presence of infection in the urinary system, which is probably considered as the complication of DM. A study conducted in the Netherlands has found that diabetic patients were more at risk for urinary tract infection (UTI) than hypertensive patients without diabetes (32). The prevalences of asymptomatic bacteriuria and incidence of UTIs are more frequent to happen in DM patients than individuals without diabetes (33). UTIs are familiar or serious and can lead to undesirable effects in type 2 DM patients (34). Our study demonstrated that leukocyturia was associated with male sex, and different studies found that UTIs commonly affect diabetic women more than non-diabetic women (35). The defect in urinary cytokine secretion and increased bacterial colonization of uroepithelial cells are the potential mechanisms of increased prevalence of UTIs in such patients (36).

In this study, poor glycemic control, younger age and hypertension were associated with glucosuria**.** If the blood glucose level is above the renal threshold, it will be excreted through urine. Young DM patients may have low awareness and practice regarding blood glucose control, and there is the probability of glucosuria in those patients**.** As various studies documented, hypertension is a common co-morbidity with DM, and hypertension is usually associated with nephropathy (37,38).

The prevalence of altered urine parameters of DM patients was found to be significant. These increased prevalences of altered urine parameters are potential indicators of diabetic kidney disease. Proteinuria was associated with diastolic blood pressure and poor glycemic control. Hematuria was higher among female participants compared to their counterparts. On the other hand, male participants were more likely to have leukocyturia than females. Urine parameters could help in the diagnosis of diabetic kidney disease. Moreover, the result of this study can be used as a baseline data for further longitudinal and multicenter studies in developing countries.

This study was conducted after obtaining ethical approval from the Research and Ethics Review Committee of the School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar. Informed written consent was taken from each of the study participant to participate in the study. The results of this study were based on only one urine sample because of budget limitation. This study was also a cross-sectional study, and it was not possible to assess the alteration of urine parameters repeatedly for a long period.

ABBREVIATIONS

BMI: Body Mass Index; BP: Blood Pressure; CI: Confidence Interval; DBP: Diastolic Blood Pressure; DKD: Diabetic Kidney Disease; DM: Diabetes Mellitus; FBG: Fasting Blood Glucose; RBC: Red Blood Cell; SOPs: Standard Operation Procedures; UoGH: University of Gondar Hospital; UTI: Urinary Tract Infection; WBC: White Blood Cell; WC: Waist Circumference.

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