Prevalence and Risk Factors of chronic kidney disease among diabetic adult out-patients in 'Ayder' Referral and Teaching Hospital, Northern Ethiopia

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Abstract

Background: Chronic kidney disease (CKD) is one of the most common complications of diabetes mellitus and it is increasingly recognized as a leading global public health issue with an estimated CKD due to diabetes accounting for 30·7% (95% uncertainity interval 27·8 to 34·0), the largest contributionof any cause in 2017.. Furthermore, it has been established that CKD is a risk factor not only for progressive kidney failure, but also for cardiovascular morbidity and mortality. Early screening for CKD is not routinely performed in many diabetic clinics in sub-Saharan Africa due to late presentation of patients and/or limited diagnostic resources.

Objective: to determine the prevalence and risk factors of CKD among adult diabetic outpatients attending the diabetes clinic for routine diabetes care at Ayder referral and teaching hospital. **Methods:**A cross-sectional study was conducted by including 199 study subjects. This study was conducted in the diabetes clinic of Ayder Referral and Teaching Hospital (ARTH) in Mekelle, Ethiopia. A convenience sampling technique was used to select the study participants. Data were collected using structured questionnaires. Fasting blood glucose level was measured. Fresh urine sample was used for a total protein by semi-quantitative urine dipstick test. Serum creatinine level was also measured to estimate glomerular filtration rate (eGFR) using the Cockroft-Gault equation. The collected data were sorted, coded and entered to Excel and finally exported to SPSS Version 20.0 for descriptive and regression analysis.

Results: The mean creatinine clearance (CrCl) of 194 patients was 86.01 ± 31.4 and 40.2% were in stage 2 of CKD. None of the participants were in stage 4 or 5 CKD. The urine dipstick test showed that 8.0% had +2/+3 and 2.5% had +1 and 89.4% were negative for urinary protein. The prevalence of CKD was 60% among 194 study subjects of which 22% had an eGFR<60 mL/min/1.73 m^2. Majority of the study subjects were between 33 and 62 years of age with a high proportion of CKD within 48-62 age groups.Using univariate analysis, the following variables were found to be significantly associated with chronic kidney disease: age, type of DM, BMI, and illiteracy. According to the multivariate analysis, age and BMI were significantly associated with CKD: Age in years 41-55 and >=56 (AOR, 6.3[95%CI, 1.69-23.6]; P=0.006) and (AOR, 91.4[95%CI,14.7-569.3]; P=0.000) respectively and BMI inKg/m^2 19-24.9, 25-29.9 and >=30 with (AOR, 0.24[95%CI, 0.08-0.74]; P=0.013), (AOR, 0.06[95%CI, 0.01-0.24); P=0.000) and (AOR, 0.02[0.002-0.28]; P=0.003) respectively.

Conclusion: The prevalence of CKD was foundto be high and age as well as BMI were significantly associated with CKD among diabetic patients. This alarms the need for timely screening of kidney function among diabetic patients and good management of diabetes mellitus.

Key-words: Diabetes Mellitus, Chronic Kidney disease, fasting blood glucose, serum creatinine, estimated glomerular filtration rate, Ethiopia

Background

Diabetes mellitus (DM) is a chronic, metabolic disease characterized by elevated levels of blood glucose level, if not controlled, over time which leads to serious damages to the heart, blood vessels, eyes, kidneys, and nerves. DM is a steadily growing global epidemic. Globally, an estimated 422 million adults were living with diabetes in 2014 anda prevalence of 8.5% among the adult population and will further increase to 300 million by 2025 with the majority of new cases occurring in Asia and Africa [1, 2]. In sub-Saharan Africa alone, the number of people with diabetes was 7 million in 2000 and expected to be 18 million in 2030, a regional increase of 161% [3]. DM virtually affects every system of the body, mainly due to metabolic disturbances caused by hyperglycemia, especially if diabetes control over a period of time proves to be suboptimal [4]. Complications of DM such as cardiovascular diseases, nephropathy, retinopathy and neuropathy are more prevalent among patients with diabetes in Africa as compared to the developed world due to late presentation, limited screening and diagnostic resources, poor glycemic control, and inadequate treatment of complications at an early stage [5, 6]. Chronic kidney disease (CKD) is one of the most common complications of diabetes mellitus. CKD is most commonly defined by a persistent reduction in kidney function (glomerular filtration rate (GFR) <60 ml/min per 1.73 m2 for ≥3 months) or the presence of proteinuria [7].

CKD is increasingly recognized as a leading global public health issue.In 2017, 697·5 million (95% UI 649·2 to 752·0) cases of all-stage CKD were recorded, for a global prevalence of 9·1% (8·5 to 9·8). CKD due to diabetes accounted for 30·7% (95% UI 27·8 to 34·0) of CKD, the largest contribution in terms of absolute number of any cause in 2017.[8]. CKD is common in diabetes and is a major determinant of adverse outcomes. Over 5% of people with newly diagnosed type 2 diabetes already have CKD, and an estimated 40% of both type 1 and type 2 diabetes will develop CKD during their lifetimes, the majority within 10 years of diagnosis [9]. Furthermore, it has been established that CKD is a risk factor not only for progressive kidney failure, but also for cardiovascular morbidity and mortality. In addition, CKD is a well-known predictor of hospitalization, noncardiac mortality and all-cause mortality [7, 8]. Screening for CKD is not routinely performed in many diabetic clinics in sub-Saharan Africa due to late presentation and limited diagnostic resources such as microalbumin testing which is available in very few centers [5].Many studies showed the prevalence of CKD using

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the Modification of Diet in Renal Disease (MDRD) equations as 15.1% reported in the US National Health and Nutrition Examination Survey (NHANES) III study [10], 27.5% and 31% reported in two UK studies [11, 12], and 33.1% in one Japanese study [13].

In developing countries, such as Ethiopia, chronic disease is a growing problem. Like many other chronic diseases, the incidence of CKD in Ethiopia is rising because of increased risk factors such as high blood pressure and diabetes mellitus [14]. Few studies have described the prevalence of CKD among adults with diabetes in sub-Saharan Africa. In Ethiopia, a study showed 18.2% and 23.8% prevalence of CKD, as defined by eGFR< 60 ml/min/1.73 m^2, according to the MDRD and Cockroft-Gault equations, respectively [15]. Despite evidences are showing high incidence of CKD in diabetic patients, there are limited data on the national prevalence and associated factors of CKD.. Particularly no study is conducted on the prevalence of CKD and associated factors among diabetics in the study area in which there is sociodemographic and life style variations from otherparts of Ethiopia.Therefore, the aim of this study wasto provide supplementaryevidence on the prevalence of CKD among diabetic outpatients and the risk factors to help create more awareness on the diabetic follow up and self care. Methods

Study Area

This study was conducted at the outpatient diabetes clinic of Ayder Referral and Teaching Hospital (ARTH) in Mekelle, Tigray region which is located in the North part of Ethiopia. Mekelle is the capital city of Tigray region, which is 787 kms away from Addis Ababa. According to the Mekelle zonal health bureau profile, the total population of the city in 2013 was estimated to be 301, 642 of which 147, 804 were males and 153,837 were females. Within Mekelle city, there are 7 sub administrative cities and there are 3 government hospitals and 9 public health centers. ARTH is located in Mekelle city. The hospital gives service to a population of approximately 8 million people. The diabetes clinic follows a large number of children and adults for primary diabetes health care.

Study Design and Period

A cross sectional study was conducted at ‘Ayder’ Referral and Teaching Hospital, Northern Ethiopia from December 2015 to August 2016.

Study Population

All out-patients visiting‘Ayder’ Referral and Teaching Hospital during the study period were our source population. All adults (≥18 years old) with known diabetes mellitus who attend the diabetes clinic during this time period were eligible for this study. Only those who gave informed consent and agreed to

provide samples of urine and blood were allowed to participate in the study. Patients <18 years old, pregnancy, acute illness, hospitalization were excluded from the study. A convenience sampling technique was used to include study participants. 199 patients fulfilling the eligibility criteria were included as they presented to the clinic.

Laboratory Analysis

Fasting blood glucose was measured using glucometer. The more fresh urine sample was tested for a total protein using reagent dipsticks (product name "Cromatest") and dipstick readers (DARA trademark) from Linear Chemicals (Spain) were used. The urine dipstick reading was used to predict microalbuminuria by a negative as A1, trace to +1 as A2 and at least +2 as A3 [18]. Serum creatinine was also measured using "pentra 400" to estimate GFR.

Calculationfor Creatinine Clearance (CrCl)

Estimated glomerular filtration rate (eGFR) was calculated using the Cockroft-Gault equation:

$$\boldsymbol{CrCl(mL/minute)} = \frac{\boldsymbol{(140 - age(years)) * Weight}}{\boldsymbol{72 * Scr(\frac{mg}{dl})}} * \boldsymbol{(0.85, iffemale)}$$

After calculating the eGFR, patients were classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) system [16]. The KDIGO guidelines also state that a total urine protein-to-creatinine ratio (TPCR) of 150 mg/g of creatinine (15 mg/mmol) is equal to a urine albumin-to-creatinine ratio (ACR) of 30 mg/g of creatinine (3 mg/mmol) [17] but such test was not available during the study period.

Data Collection

Data were collected using questionnaires that include sociodemographic and clinical characteristics related to diabetes mellitus by nurses of the diabetic clinic. A patient history review was done forprior diagnoses of hypertension or renal disease. Patients were labeled as hypertensive if they had

documented diagnosis and/or treatment ofhypertension. For those attending the clinic for the first time on the day of study enrollment, the diagnosis of hypertension was made when systolic blood pressure was >140 mmHg and diastolic blood pressure was >90 mm Hg. Completeness of the questionnaire was being asserted through periodic checking.Atleast three consecutive monthly data were used for calculation and analysis.

Data Processing and Analysis

Data were sorted, coded and entered into Excel then transferred to SPSS Version 20.0 software for analysis. Data were summarized

by their number and percentages. In the univariate and multivariate analyses, chi-squared tests were used and their corresponding 95% confidence levels (CI) were used to describe the association of risk factors with CKD.

Ethics approval and Consent to participate

Ethical clearance was obtained both from the Research and Community Service office of Mekelle University, College of Health Sciences and the Institutional Review Board of BMI. The purpose of the study was explained to each participant to get verbal consent of participation. All research activities were done after the facility had signed a consent paper justifying to participate in the study.

Results

Socio-demographic and Clinical Characteristics of Participants

Of the 199 study participants, 57% were males and 73% were from Mekelle City. The mean age was 46.3 ± 15.4 and the majority was in the age range of 33-62 years. The mean BMI was 22.6 ± 3.94 and the BMI of 52.8%subjectswas in the range 19–24.9 kg/m2. 66.8% had type 2 diabetes mellitus. Among these diabetic adults, 20.1% had Comorbid hypertension. 54.3% were on insulin alone treatment and 43.2% were on oral hypoglycemic agents (OHGA). The mean fasting blood glucose level was 166.0 ± 72.5 and 63.4% had sugar levels ≥126 [Table 1].

Table1. Socio-demographic and clinical characteristics of study subjects at Ayder referral and teaching hospital

Variables		Category	Frequency	Percent	Mean ± SD
Age Groups in years		18-40	65	32.7	46.3 ± 15.4
		41-55	79	39.7	
		>=56	55	27.6	
		Total	199	100.0	
Gender		Female	86	43.2	
		Male	113	56.8	
		Total	199	100.0	
Residence		Mekelle	146	73.4	
		Other	53	26.6	
		Total	199	100.0	
Educational level		Diploma and above	67	33.7	
		Up to secondary	88	44.2	
		Illiterate	44	22.1	
		Total	199	100.0	
Occupation		Employed	75	37.7	
		Others	91	45.7	
		Peasant	33	16.6	
		Total	199	100.0	
Household income in ETB		<1500	95	47.7	
		>=1500	104	52.3	
		Total	199	100.0	
Body Mass Index (BMI)		<19	44	22.1	22.6 ± 3.94
		19-24.9	105	52.8	
		25-29.9	42	21.1	
		>=30	8	4.0	
		Total	199	100.0	
Types of Diabetes Mellitus (DM)		Type 1	132	33.2	
		Type 2	266	66.8	
		Total	398	100.0	
Duration of diabetes in years		<=5	134	68.0	5.6±5.7
		>5	63	32.0	
		Total	197	100.0	
Medication to DM		Insulin + Oral HGA	5	2.5	
		Insulin alone	108	54.3	
		Oral HGA	86	43.2	
		Total	199	100.0	
Hypertension (HTN)		No	159	79.9	
		Yes	40	20.1	
		Total	199	100.0	
Blood Pressure (BP)	**Systolic**	<120	90	45.5	129.5 ± 20.574
		120-139	45	22.7	
		>139	63	31.8	
		Total	198	100.0	
	Diastolic	<=79	97	48.7	75.42 ± 9.408
		80-89	73	36.7	
		>=90	29	14.6	
		Total	199	100.0	
		ACE-I	34	85.0	

Medication to HTN	ACEI+ARB	6	15.0	
	Total	40	100.0	
Smoking	No	196	98.5	
	Yes	3	1.5	
	Total	199	100.0	
Alcohol consumption	No	188	94.5	
	Yes	11	5.5	
	Total	199	100.0	
Family history of KD	Yes	2	1.0	
	No	197	99.0	
	Total	199	100.0	
Fasting Blood Glucose level in mg/dl	<126	71	36.6	166.0 ± 72.5
	>=126	123	63.4	
	Total	194	100.0	

Renal Assessment

The meancreatinine clearance(CrCl)of 194 patientswas 86.01 ± 31.4 and 40.2% were in stage 2 of CKD. None of the participants were in stage 4 or 5 CKD. The urine dipstick test showed that 8.0% had +2/+3 and 2.5% had +1 and 89.4% were negative for urinary protein. The prediction of the urine micro albumin level of 199 participants showed that 89.4% were in A1 while 8% were in A3 [Table 2].

Table 2. Renal outcomes of patients attending the diabetes clinic at Ayder referral and teaching hospital

Stages of CKD according to the CrCl of Cockcroft-Gault equations (n =194).				
KDIGO classification		**N**	**%**	**Mean ± SD**
CrCl in mL/min (GFR)	>=90 (G1)	74	38.1	86.01 ± 31.4
	60-89 (G2)	78	40.2	
	45-59 (G3a)	37	19.1	
	30-44 (G3b)	5	2.6	
	15-29 (G4)	0	0	
	<15 (G5)	0	0	
	Semi quantitative Urine protein level (n=199)			**Predicted Urine Microalbumin level**
Urine Protein (UP)	+1	5	2.5	A2(30-300mg/g)
	+2	13	6.5	A3(>300mg/g)
	+3	3	1.5	
	Negative	178	89.4	A1(<30mg/g)

Prevalence of Chronic Kidney Disease (CKD)

Of the 194 study participants, 120(62%) had eGFR< 90 mL/min; Prior to enrollment, 4 (2.2%) had a prior diagnosis of CKD in their charts [Table 3]. 21.9% had eGFR<60 mL/min/1.73m^2.

Table3. Prevalence of CKD, according eGFR at Ayder referral and teaching hospital (n=194)

CKD by KDIGO Definition considering only CrCl		N	%
Chronic kidney disease (CKD)	No	74	38.0
	Yes	120	62.0
	Total	194	100.0

Characteristics of CKD among different variables

As shown in Table 4, the majority of the study subjects were between 33 and 62 years of age with a high proportion of CKD within 48-62 age groups. 74.8% of the CKD subjects had type 2 diabetes.

A higher percentage of women with DM had CKD compared with males. There was a lower percentage of obese patients with CKD than was noted in non-obese patients.

Table4. Distribution of CKD by a baseline characteristics of DM patients at Ayder Referral and Teaching Hospital

Variables		Chronic kidney disease (CKD)		Total
		No=76	Yes=119	N=195
Age groups in years	18-32	25(32.9%)	16(13.4%)	41(21.0%)
	33-47	35(46.1%)	28(23.5%)	63(32.3%)
	48-62	16(21.1%)	45(37.8%)	61(31.3%)
	>=63	0(0.0%)	30(25.2%)	30(15.4%)
Type of DM	Type 1	32(42.1%)	30(25.2%)	62(31.8%)
	Type 2	44(57.9%)	89(74.8%)	133(68.2%)
Sex	F	27(35.5%)	58(48.7%)	85(43.6%)
	M	49(64.5%)	61(51.3%)	110(56.4%)
Body mass index (BMI)	<19	9(11.8%)	32(26.9%)	41(21.0%)
	19-24.9	40(52.6%)	64(53.8%)	104(53.3%)
	25-29.9	23(30.3%)	19(16.0%)	42(21.5%)
	>=30	4(5.3%)	4(3.4%)	8(4.1%)
Educational level	Above diploma	30(39.5%)	35(29.4%)	65(33.3%)
	Illiterate	6(7.9%)	37(31.1%)	43(22.1%)
	Up to secondary	40(52.6%)	47(39.5%)	87(44.6%)

Factors associated with CKD

Using univariate analysis, the following variables were found to be significantly associated with chronic kidney disease: Age (P=0.000), type of DM (P=0.013), BMI (P=0.003), and illiterate (P=0.001). According to the multivariate analysis, two variables Age (P=0.000) and BMI (P=0.003) were significantly associated with CKD [Table 5].

Table5. Factors associated with CKD, according to univariate and multivariate regression analysis, among diabetic patients at Ayder referral and teaching hospital

Variables	Category	COR (95%CI)	P-value	AOR (95%CI)	P-value
Age group in years	18-40	1			
	41-55	2.3(1.2-4.6)	0.016*	6.3(1.69-23.6)	0.006*
	>=56	21.6(6.9-67.6)	0.000*	91.4(14.7-569.3)	0.000*
Gender	Female	1.7(0.96-3.12)	0.071	1.51(0.61-3.73)	0.367
	Male	1			
Educational level	Diploma and above	1			
	Illiterate	5.3 (1.96-14.24)	0.001*	2.09(0.44-9.94)	0.353
	Up to Secondary	1.01(0.53-1.92)	0.983	0.66(0.26-1.69)	0.390
Occupation	Employed	1			
	Others	3.15(1.65-6.04)	0.001*	1.26(0.47-3.37)	0.647
	Peasants	3.27(1.33-8.04)	0.010*	1.60(0.37-6.82)	0.528
Income in ETB	<1500	1.32(0.74-2.36)	0.340	1.89(0.87-4.11)	0.109
	>=1500	1			
Type of DM	Type 1	1			
	Type 2	2.16(1.17-3.99)	0.014*	0.64(0.18-2.29)	0.494
Body mass index (BMI) in Kg/m^2	<19	1			
	19-24.9	0.45(0.195-1.04)	0.062	0.24(0.08-0.74)	0.013*
	25-29.9	0.23(0.09-0.61)	0.003*	0.06(0.01-0.24)	0.000*
	>=30	0.28(0.06-1.35)	0.113	0.02(0.002-0.28)	0.003*
Duration of diabetes mellitus in years	<=5	1			
	>5	1.47(0.78-2.75)	0.233	1.19(0.499-2.85)	0.690
Fasting blood glucose in mg/dl	<126	1			
	>=126	0.94(0.52- 1.73)	0.853	0.81(0.37-1.80)	0.611

*statistically significant at 0.05 significance level, R=reference

Discussion

CKD was found to be 62% inthe study participants with eGFR<90 mL/min; and 22% had eGFR<60 mL/min. The mean CrCl was 86.01 ± 31.4. None of the participants were in stage 4 or 5 CKD. The mean fasting blood glucose level was 166.0 ± 72.5 and 63.4% had sugar levels ≥126. This highlights the importance of implementing routine screening for CKD among adult diabetics in Africa [5]. This finding was higher when compared to 15.1% reported in the US [10], 27.5% and 31% in UK studies [11, 12], and 33.1% in Japan [13] and in Ethiopia 18.2% and 23.8% [15].

The mean duration diabetes mellitus in this study was 5.6 years, but around 60% of both type 1 and 2 diabetes were found to have CKD and 2.1% of the study subjects were already diagnosed for CKD. Internationally over 5% of people with newly diagnosed type 2 diabetes already have CKD, and an estimated 40% of both type 1 and type 2 diabetes develop CKD during their lifetimes, the majority within 10 years of diagnosis [9]. This difference may be indicate inadequate

management or it could be due to the late diagnosis for diabetes mellitus.

Older age was significantly associated with CKD in this study. This is consistent with other studies [15]. Other factors such as type of diabetes (P=0.013), BMI (P=0.003), and being illiterate (P=0.001) were significantly associated with CKD by univariate analysis. Only age and obesity were statistically significant by multivariate analysis (P=0.000) and obese (P=0.003) respectively. In contrast to other studies obese individuals were observed at low risk when compared to the non obese subjects for CKD. This is because muscle makes up less percentage of the weight of obese patients, with weight being a factor in CrCl but not in CKD Epi or MDRD equations. In fact, lean body weight is higher in obese patients when heights are compared, indicating likely higher muscle mass for height, just lower percentage of muscle mass. Correcting the weights for lean body weight or ideal body weight might adjust this limitation.

Early screening would allow more aggressive measures to be taken to reverse protinuria and/or prevent further adverse renal and cardiovascular complications. A low eGFR has implications in drug therapy for diabetes mellitus and, if undetected, could lead to complications such as lactic acidosis from metformin or hypoglycemia from sulfonylureas or insulin.

Conclusion

The prevalence of CKD was found to be high among the diabetic patients at Ayder referral and teaching hospital. 62% had CKD and 22% had an eGFR<60 mL/min/1.73 m^2. This indicated the need of timely screening for kidney function in DM patients and management of DM. Early screening and management will prevent the progress to complications especially in developing countries where management of advanced stages of renal diseases is difficult due to limited resources.

List of Abbreviations

ETB = Ethiopian Birr

DM= Diabetes mellitus

CKD = Chronic kidney disease

eGFR = estimated glomerular filtration rate

NHANES = National Health and Nutrition Examination Survey

MDRD=Modification of Diet in Renal Disease

ARTH = Ayder Referral and Teaching Hospital

KDIGO = Kidney Disease: Improving Global Outcomes

CrCl = Creatinine Clearance

Competing of Interests

We declare that we have no competing interests.

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Authors' contributions

GGA designed and Proposedthe study. GGA, AHW,MHN were involved in the designing of the study, data entry, analysis and interpretations. GGA drafted the manuscript and all authors reviewed and approved the manuscript.

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