

Diabetic Nephropathy and its Risk Factors in Type 2-Diabetic Patients in Sana'a City, Yemen

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Abstract: Diabetic nephropathy (DN) is the leading cause of chronic kidney diseases and end stage renal failure. We had designed this study to find out the prevalence of diabetic nephropathy and its risk factors among Yemeni patients with type 2- diabetes mellitus. *Methods:* This study was carried out in Al-Kuwait University Hospital (KUH), Sana'a City (Yemen), on the period between 4th of November 2011 to 1st of December 2012. Five hundred (500) Type 2 diabetic patients (diagnosed according to ADA criteria for diagnosis of diabetes) were selected. Two overnight urine samples per patient were analyzed. Albumin concentration was measured by an automated immunoturbidity assay. Diabetic nephropathy was defined according to American Diabetic Association when using the random collection technique, normal albumin excretion should be defined as <30 mcg/mg of creatinine; micro albuminuria(MA) 30 to 299 mcg/mg of creatinine, and macro albuminuria(MAA) is >300 mcg/mg of creatinine. Information obtained also included age, diabetes duration, sex, body mass index, blood pressure, serum total high-density and low-density lipoprotein cholesterol, triglycerides, serum creatinine, and glycated hemoglobin (HbA1C). Results revealed that in Five hundred type-2 diabetic patients (280 females and 220 males). 332 patients (66.4%) were normalalbuminuric (NA), 168 (33.5%) had diabetic nephropathy, 106 (21.2%) of them had MA and 62 (12.4%) had MAA. There was significant difference among patients with diabetic nephropathy (DNP) (both MA, and MAA) and those without nephropathy regarding age, male gender, BMI or the time actually elapsed since the diabetes were diagnosed. 38.8% of patients with NA and 75% of patients with DNP had hypertension. DNP patients were more frequently smokers and former smokers, than NA patients (21.9% VS 33.9%). There was significant correlation between NA patients, and DNP patients regarding poor glycemic control (42.7% VS 64.8%), serum (se) TG (19.5% VS 55.9%), se HDL cholesterol(18.6% VS 61.3%) and se LDL cholesterol (19.2% VS 49.4%) ($P \leq 0.005$). In conclusions, Prevalence of DNP is high among type 2-diabetic Yemeni patients and high BP was the commonest co-morbidity. These findings highlight an urgent need to develop strategies for prevention, detection and treatment of DNP that could contribute to decreasing the rising incidence of CVD and CRF.

Key words: Type 2- DM • Diabetic Nephropathy • Dyslipidemia

INTRODUCTION

Throughout the world the number of the people developing type 2-DM is increased dramatically [1]. At the present time the disease involves around 171 million people worldwide and the WHO predicts that this number will rise to 366 million by 2030 [1]. In Yemen the overall prevalence of type II Diabetes Mellitus was 4.6% (7.4% in males and 2% in females).[2]. In the course of diabetes mellitus diabetic nephropathy (DNP) occurs in 30%-40% in patients with type 1-diabetes [3] and in

25%-40% in patients with type 2-diabetes [4]. Screening for diabetic nephropathy must be initiated at the time of diagnosis in the patients with type 2- DM[5], while in patients with type 1- the first screening has been recommended at the first year after diagnosis [5]. It is well known that progression to established diabetic nephropathy occurs through several stages. Early stage is characterized by a small increase in urinary albumin excretion (UAE), also called micro albuminuria or incipient DN [6] More advanced disease is defined by the presence of macro albuminuria or proteinuria. The latter is

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classically named overt DN. In most cases, proteinuria and decreased glomerular filtration rate (GFR) occur in parallel. Traditionally, GFR has been expected to decrease when proteinuria is established, but not before. However, it is clear today that some subjects could have DN without increased UAE [7,8] About 10% of subjects with type 2 diabetes mellitus (DM) will have low GFR without micro- or macro albuminuria [9]. This was also observed among patients with type 1 DM and micro albuminuria [10]. It appears that the development of each stage of diabetic nephropathy is determined by somewhat different sets of risk factors. Whereas the level of glycemic control is most likely the dominant factor in the occurrence of micro albuminuria, [11] its progression through the more advanced stages is determined by such risk factors as hypertension, hypercholesterolemia and unidentified genetic factors [11]. Screening for micro albuminuria (MA) can be performed using quantitative methods, including: i) measurement of albumin to creatinine ratios in a random urine sample; ii) a 24-hour collection with creatinine, allowing the simultaneous measurement of creatinine clearance; iii) timed (e.g. 4 hour) overnight urine collection for protein, or by using semi-quantitative reagent dipsticks specifically designed with detection limits suitable for identifying MA, such as the Micral dipsticks [12].

According to the American Diabetes Association (ADA), when using the random collection technique, normal albumin excretion should be defined as <30 mcg/mg of creatinine; micro albuminuria 30 to 299 mcg/mg of creatinine, and macro albuminuria is >300 mcg/mg of creatinine [13]. In the 24-hour collection technique, albumin excretion <30 mg per 24 hours is considered normal, 30 to 299 mg per 24 hours indicates micro albuminuria, and 300 mg or higher indicates macro albuminuria [13]. When using the timed collection technique, normal albumin excretion is defined as <20 mcg/min, micro albuminuria is defined as 20 to 199 mcg/min, and macro albuminuria as >200 mcg/min [13].

In Yemen there is no previous published studies that investigate the prevalence of DNP among patients with Type 2 Diabetes.

We designed this study to obtain the prevalence of DNP and associated risk factors among Yemeni patients with type 2-DM in order to stimulate further research on its actual prevalence both among the general population as well as among similar risk groups.

MATERIAL AND METHODS

The study population was type 2- diabetic patients defined according to ADA 2011 [14], as the following, A1C = 6.5%. The test should be performed in a laboratory using a method has the National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complication Trial (DCCT) assay. Or FPG =126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing. Or 2-h plasma glucose =200 mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing. Or In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose = 200 mg/dl (11.1mmol | l), taking hypoglycemic drugs or insulin, or physical exercise therapy for diabetes and not having any episodes of ketosis) who attended the medical clinic of AL-Kuwait University Hospital (KUH) in Sana'a City, Yemen during the study period between the 4th of November 2011 to the 1st of December 2012.

Exclusion Criteria:

- Type 1- DM
- Any one of the participants who suffered from any of the following conditions that increase the urinary albumin excretion such as urinary tract infection, hematuria, acute febrile illness, vigorous exercise, uncontrolled hypertension and heart failure [15].

All subjects were interviewed about their age, habits, occupation, and past history of diabetes and hypertension, as well as their drug intake. Subjects underwent a physical examination consisting of the determination BMI and systolic and diastolic blood pressure. Height was measured without shoes and weight was recorded while wearing indoor clothing. Body mass index (BMI) (weight in Kg, divided by height in meters squared) was calculated. The WHO (2012) classification for BMI was used to estimate the degree of obesity [16].

Blood pressure was recorded with the same mercury manometer in the sitting position after 10-15 minutes rest. Each subject had two measurements of blood pressure at 5 minutes intervals.

Venous blood sampling was performed in the morning after an overnight fast for determination of plasma glucose, triglyceride, High Density Lipoprotein (HDL) cholesterol, LDL cholesterol (LDL) and serum creatinine. Laboratory techniques for biochemical analysis were glucose oxides for blood glucose, and the enzymatic method for triglyceride, HDL cholesterol and LDL cholesterol. Urinary albumin and creatinine levels were determined in a random spot urine specimen (Tina-Quant, Roche Diagnostics for the measurement of urinary albumin and creatinine). Serum creatinine was determined using a KREA Flex, Dade-Behring, for the measurement of urinary modified Jaffe test (KREA Flex, Dade-Behring),

Target Definitions: Type 2- diabetes mellitus was defined according to the American Diabetes Association [14], Obesity was defined according WHO definition based on estimation of BMI [16] which is defined as a person's weight (in kilograms) divided by the square of his or her height (in meters). A person with a BMI of 30 or more is generally considered obese. A person with a BMI equal to or more than 25 is considered overweight.

Hypertension was defined according to the European Society of Hypertension-European Society of Cardiology[17,18] as blood pressure = 130/85 mmHg. Dyslipidemia was defined according to the Joint National Committee VII [19] as the following, = 150 mg/dl for TG, =100 mg/dl for LDL cholesterol, = 200mg/dl for total cholesterol, and = 45mg/dl (men) and = 55 mg/dl (women) for HDL cholesterol.

Micro albuminuria was defined as an albumin-creatinine ratio of 30 to 300 mg/g, and macro albuminuria as an albumin-creatinine ratio of more than 300mg/g [13]. The research protocol was reviewed and approved by the Ethical Committee of the Faculty of Medicine and Health Sciences, Sana'a University. All participants provided informed consent after explaining the study objectives and that the data will be used only for purpose of the research. Health education both verbally and using education materials was provided to all participants and those who were found to have any medical problem were referred to the specialized clinic for proper management and follow up.

Statistical analysis was under taken using the statistical package for the social sciences (windows version 13.0; SPSS, Chicago IL USA).

Differences between groups were tested statistically using the chi square test for categorical and T test for numerical variables. Data were considered statistically significant when the p-value was = 0.05.

RESULTS

In this study 500 type 2-diabetic was studied (280 were females and 220 were males), the overall prevalence of DNP in this study was 33.6%, Micro albuminuria (MA) was in 106 of 500 diabetic persons (21.2%) and macro albuminuria (MAA) was found in 62 of 500 diabetic persons (12.4%).

Table 1: Demographic and clinical char act. Of the study groups

Factors	Total -500	NA=332(66.4%)	DNP=168(33.6%)	P-value
Age in years	56.3±32	58.1±21	62.5±43	0.005
Male sex %	220(44%)	100(31%)	120(71.4%)	0.0001
Smoking %	130(26%)	73(21.9%)	57(33.9%)	0.0056
Duration of DM in years	10.6±54	9.8±54	11.6±32	0.001
BMI kg/m	108(21.6%)	48(14.4%)	50(29.7%)	0.0001
High BP	255(51%)	129(38.8%)	126(75%)	0.0001

Significant difference (p<0.05)

Table 2: Laboratory characteristic of type 2- diabetic patients with and without nephropathy

Factors	Total=500	NA=332(66.4%)	DNP=168(33.6%)	P-value
Se.TG mg/dl	159(31.8%)	65(19.5%)	94(55.9%)	0.0001
Se.HDLmg/dl	165(33%)	62(18.6%)	103(61.3%)	0.0001
Se.LDLmg/dl	147(29.4%)	64(19.2%)	83(49.4%)	0.0001
HbA1C=6.5	251(50.2%)	142(42.7%)	109(64.8%)	0.0001
Se.creatinine	15(3%)	5(1.5%)	10(5.3%)	0.01

Significant difference (p<0.05)

Table 1 showed the demographic and clinical characteristic of the study groups. DNP was more prevalent in males than females, also type 2-diabetic patients with DNP was older, had longer diabetic duration (9.8 ± 54 in NA vs 11.6 ± 32 in DNP) and more frequently smokers (21.9% in NA vs 33.9% in DNP) than type 2-diabetic without DNP. The prevalence of obesity as indicated by BMI was significantly higher in DNP patients (14.4% in NA vs 29.7% in DNP) and hypertension (38.8% in NA vs 75% in DNP) than in type 2-diabetic without DNP.

The laboratory characteristic of type 2-diabetic patients with and without DNP are showed in Table 2.

Type 2-diabetic with DNP had poor glycemic control, HbA1C = 6.5 (42.7% in NA vs 64.8% in DNP), also the prevalence of dyslipidemia (high serum TG, serum LDL and low serum HDL) was more frequently higher in DNP patients (Table 2).

DISCUSSION

The study analyze the prevalence of DNP in type 2-diabetic patients who attended the medical departments in Al-Kuwait University Hospital using the American Diabetic Association (ADA) for diagnosis of DNP [13]. The results of this study provide valuable information in the prevalence of DNP and its associated risk factors in type 2-diabetic Yemeni patients.

The overall prevalence of DNP among type 2-diabetic patients in this study is 33.6% (21.2% had MA and 12.4% had MAA) which is similar to that in other comparable studies in type 2-diabetic patients [20-24]. The prevalence of MA in our patients with type 2-DM was 21.2% which is similar to the results done in North India (25.5%), Hungary (26.9%) and in Bahrain (25%) [25-27] (respectively), while its lower than the study done in Saudi Arabia (45.6%) and in Pakistan (34%) [28,29]. While the prevalence of MAA in our study was 12.4% which is similar to the result done in Taiwan (12.7%), Bangkok, Thailand (11.2%), Italy (16%) and Germany (9%) [20, 25, 30,31] but its lower than the study done in Hungary (38.5%) [26].

The variation in prevalence rates is most probably attributable to differences in diagnostic criteria, the stage of the disease, the method of assessment and ethnicity [32]. The increased prevalence of DNP in type 2-could be explained by hyperglycemia of diabetes [33,34] in addition to genetic predisposition and other associated risk factors namely male gender, prolonged diabetic duration [34],

smoking habits, hypertension, obesity and dyslipidemia [34,35]. In this study hypertension was most common prevalent risk factor in type 2-diabetic with DNP [31], followed by poor glycemic control [22], dyslipidemia, male gender, smoking and obesity.

High prevalence of hypertension was found in patients with DNP compared with normoalbuminuric patients. Thus our study support the observation that the prevalence of hypertension in people with type 2-DM was 60% (at time of diagnosis) increasing to 80% in the presence of MA and 90% with MAA [36]. Of all of the mechanism contributing to DNP reduction of the blood pressure has been shown to be clearly important and powerful intervention. It shown that reduction of blood pressure is associated with decreased progression of DNP [37].

In the present study as shown in Table 2 DNP has a highly significant correlation with HbA1c ($p < 0.05$), similar to the study reported by S.A. Sheikh *et al.* [34]. The complications of both Type 1 and 2 Diabetes do not develop or progress for 6-9 years when the average HbA1c level is kept at $< 7\%$ [38]. The present study found an increase in HbA1c levels as indicated by a mean value of 9.06. This shows that the population under study had poor glycaemic control.

Part of the cross-sectional studies on type-2 diabetes revealed a significant correlation between the metabolic control and albuminuria [38,39], in this study there was strong association between poor glycemic control and the developments and progression of DNP.

The frequency of microalbuminuria increased with the increase in duration of diabetes.[34, 38] DNP had a highly significant correlation with duration of diabetes $p < 0.001$ as shown in Table-1.

Our study showed that the prevalence of diabetic dyslipidemia (high TG, low serum HDL and high serum LDL) was higher in type 2-DM with DNP than without DNP. This observation is supported by the result of investigation in this field [26,27].

The role of hyperlipidemia in the development of diabetic nephropathy has been described in several studies. In the vast majority of the studies, cholesterol and triglyceride showed a positive correlation with the degree of albuminuria, while HDL-cholesterol was found to have negative correlation with it [36,37]. Mashahiko *et al.* showed that triglyceride, but not total cholesterol or LDL-cholesterol, was a major risk factor for predicting the development of proteinuria.[38] In another prospective study in type 2 diabetes, an elevated

triglycerideto- HDL ratio was shown to be independently associated with the progression of microalbuminuria [39] while hypertriglyceridemia could predict the need for further renal replacement therapy [40] In this study, higher.

CONCLUSION

Our study demonstrates an alarming high prevalence of DNP among type 2-Yemeni diabetic patients that increases the burden on overstrained Yemeni health system with uprising CVDs and other DNP related health problems e.g. CRF. There is an urgent need to develop strategies for prevention, detection, and treatment of DNP that could contribute to decreasing the incidence of grave consequences such cardiovascular disease and CRF. Meanwhile, it is also vital that we obtain reliable prevalence among the whole population, which is currently lacking, in order to obtain more precise estimates of the magnitude of the problem and action needed.

Abbreviations: World Health Organization (WHO), ADA (American diabetic association), Body Mass Index (BMI), Non Communicable Diseases (NCDs), DNP (diabetic nephropathy), MA (micro albuminuria) MAA (macro albuminuria) High Density Lipoprotein (HDL), TG (triglyceride), LDL (low density lipoprotein) Fasting Blood Sugar (FBS), CRF (chronic renal failure).

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