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Is there Correlation between Subclinical Hypothyroidism and Diabetic Nephropathy?

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Abstract

Background: Diabetic patients have higher prevalence of subclinical hypothyroidism which may be associated with diabetic complications. The aim of this study was to investigate the association of subclinical hypothyroidism with diabetic nephropathy (DN) in type 2 diabetic patients.

Patients and Methods: A total of 150 type 2 diabetic patients were selected. Fasting blood sugar, HbA1C, lipid profile, creatinine, free T4, TSH and urinary albumin to creatinine ratio (UACR) were assessed for all patients. Patients with UACR of ≥30 mg/gr or glomerular filtration rate (GFR) <60 ml/min were defined as diabetic nephropathy (DN). Subclinical hypothyroidism (SCH) was defined as an elevated TSH >4 m IU/L and free thyroxine (FT4) level in normal range.

Results: In our study 7.3% of all patients had subclinical hypothyroidism. No significant difference was found between patients with and without DN in TSH level. There was no significant difference in GFR and rate of albuminuria between subclinical hypothyroid and euthyroid patients. TSH was not correlated with albuminuria and GFR.

Conclusion: Subclinical hypothyroidism is not associated with DN in type 2 diabetes.

Keywords: Hypothyroidism; Diabetes; Diabetic nephropathy; Albuminuria

Introduction

Diabetes mellitus (DM) is the most common chronic metabolic disease which its incidence is increasing rapidly. The prevalence of DM in urban Iranian population aged ≥20 years was 8.1% in 2008 [1]. Diabetic nephropathy (DN) is one of the main chronic complications in type 1 and 2 diabetes and is currently the most common cause for end stage renal disease (ESRD). It is reported that diabetes contributes to approximately 40 percent of newly developed ESRD patients each year [2]. Diabetic nephropathy is likely multi-factorial. Although genetic and environmental factors can involved in diabetic nephropathy, resulted hemodynamic and metabolic changes can not clearly justify the diabetic nephropathy progression.

The prevalence of thyroid disorders is higher in diabetic patients and subclinical hypothyroidism (SCH) being the most disorder [3]. SCH has been associated with endothelial dysfunction and probably atherosclerotic risk factors [4]. Hypothyroidism causes remarkable changes in glomerular filtration rate (GFR), tubular function, water and electrolyte balances but association of SCH and diabetic nephropathy (DN) has not been evaluated so far. The aim of this study was to correlate SCH with DN in Iranian patients with type 2 diabetes.

Methods and Materials

In a cross- sectional study, we recruited 150 patients with type 2 diabetes. Patients with: past history of thyroid disease, taking drugs with effects on thyroid tests and albuminuria and any sever intercurrent illness were excluded. Furthermore, patients with type 1 diabetes, pregnancy, lactation, malignancy and liver failure were also excluded. Patients were informed completely about the study's aims and if they fulfilled the written informed consent, they were entered in the study. We recorded the demographic characteristics including: age, height, weight, blood pressure and body mass index (BMI). BMI was calculated according to this formula: Weight (kg)/ height (m^2). Blood pressure of the right arm was taken in a sitting position after resting for ten minutes. After 8 hours overnight fasting, blood samples were obtained from the brachial vein. Fasting plasma glucose was measured by the glucose oxidase method (Human, Germany). Total cholesterol, triglyceride (TG), and high density lipoprotein (HDL) were measured by enzymatic method (Parsazmon Karaj, Iran). Low density lipoprotein (LDL) was calculated according to Friedwall formula {LDL= total cholesterol-(HDL+TG/5)}. Glycated hemoglobin A1C (HbA1C) was assessed by Column chromatography (Biosource kit, Barcelona, Spain).Urinary albumin was measured as the albumin to creatinine ratio (ACR) in a morning sample. Urine albumin in spot urine was measured by Immunoturbidometry assay (Parsazmon, Karaj, Iran). Urine creatinine was measured by enzymatic colorimetric assay. Urinary microalbumin ≥30 and < 300 mg per gram of creatinine in urine was considered as microalbuminuria and level ≥300 was considered as macroalbumiuria. Estimated GFR (e GFR) (ml/min/1.73 m^2) was calculated according to equation of the Modification of Diet in Renal Disease. DN was defined as an increased ACR of ≥ 30 mg/gr in the absence of other renal abnormalities or e GFR less than 60 ml/min/1.73 m^2according to KDOQI recommendation. Serum thyroid stimulating hormone (TSH) was measured by immunoradiometric assay, and free T4 was determined using radioimmunoassay.

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Table 1: Baseline characteristic of patients (n= 150).

Characteristics	Mean ± SD
Male (%)	28.0%
Age (years)	55.6 ± 9.3
Body mass index (kg/m^2)	27.6 ± 4.6
Duration of diabetes (years)	7.52 ± 6.1
Waist circumference(cm)	98.4 ± 12.7
Systolic blood pressure(mm Hg)	124.8 ± 20.0
Diastolic blood pressure(mm Hg)	77.0 ± 11.9
FBS (mg/dl)	173.4± 68.3
HbA1C (%)	8.5 ± 1.79
Total cholesterol(mg/dl)	177.1 ± 39.4
Triglyceride(mg/dl)	168.1 ± 115.4
HDL cholesterol(mg/dl)	41.9 ± 7.8
LDL cholesterol(mg/dl)	103.8 ± 30.5
Creatinine(mg/dl)	0.98 ± 0.2
Urine albumin to creatinine ratio (mg/gr)	47.1±62.3
TSH(m IU / L)	2.5±1.4

Table 2: Comparison of clinical and paraclinical characteristics between non CKD and CKD patients.

variable	Non-CKD	CKD	P
Age (year)	53.6± 8.8	64.3± 8.5	0.70
Duration of diabetes more than 5 years (%)	42.3	67.7	0.01
Body mass index (kg/m^2)	28.2± 4.4	24.8± 3.3	0.60
Systolic blood pressure(mm Hg)	122.9± 20.7	133.0± 19.7	0.86
Diastolic blood pressure(mm Hg)	75.9±12.1	78.8±12.6	0.71
Cholesterol (mg/dl)	172.3± 35.5	196.1±48.8	0.01
Triglyceride (mg/dl)	177.7± 130.6	154.4± 89.4	0.27
LDL (mg/dl)	98.8± 27.1	122.8± 36.4	0.01
HDL (mg/dl)	42.1± 8.0	42.6± 8.5	0.63
FBS (mg/dl)	177.1 ± 67.5	160.5± 73.2	0.96
HbA1C (%)	8.6±1.7	8.3±1.6	0.71
Creatinine (mg/dl)	0.9± 0.2	1.2 ± 0.3	<0.001
Urine albumin to creatinine ratio (mg/gr)	40. 5± 44.7	70.7± 112.6	<0.001
TSH(m IU/L)	2.5±1.6	2.4±1.1	0.12

Subclinical hypothyroidism (SCH) was defined as an elevated TSH >4 m IU / L and free thyroxine (FT4) level in normal range (0.7-1.8 ng/ dl). Only Type 2 diabetic patients who were euthyroid or subclinically hypothyroid were included in the analyses.

Statistics

We used SPSS (SPSS 21.0 for Windows; SPSS Inc. Chicago, Illinois) for data analysis. Quantitative data was shown as mean ± SD. Student T-Test or ANOVA was used for variables with normal distribution between DN groups with patients without DN. Quantitative variables with non-normal distribution were compared with Mann-Whitney test. Qualitative variables between the groups were analyzed by Chi-square test.

Ethical statement

The study protocol was approved by the local Ethics Committee (The research ethics committee of Mashhad University of Medical Sciences), and was conducted according to the principles of Helsinki Declaration.

Results

Baseline clinical and Para clinical characteristic of 150 participants is shown in Table 1.

There was a significant difference in duration of diabetes, cholesterol and LDL levels and urine albumin to creatinine ratio between patients with and without CKD. TSH level and other variables were not significant different between two groups. Comparison of laboratory and clinical parameters between patients without CKD and CKD is shown in Table 2.

According to Urine albumin to creatinine ratio, we stratified patients to normal and patients with albuminuria and all parameters compared with other in these two groups (Table 3). TSH level was not significant different between patients with and without albuminuria.

7.3% of all patients had subclinical hypothyroidism. We divided patients to euthyroid patients and patients with subclinical hypothyroidism. There was no significant difference in parameters between two groups. Only triglyceride level was significantly higher in hypothyroid patients (Table 4).

Discussion

This study was undertaken to evaluate relation between thyroid dysfunction and diabetic nephropathy. The study showed that 7.3% of all patients had subclinical hypothyroidism. Other studies showed that diabetic patients have a prevalence of 4.1-8.6% of subclinical hypothyroidism [5]. A population study, NHANES III, demonstrated that the prevalence of subclinical hypothyroidism was 3.4% in males and 5.8% in females [6]. Our result is similar with them but we excluded all patients with known thyroid disease from this study so it seems that subclinical hypothyroidism is more common in our diabetic patients. This difference may be related to preponderance of

Table 3: Comparison of clinical and paraclinical characteristics according to albuminuria.

Variable	No albuminuria	Albuminuria	P
Age (year)	9.4±54.4	57.0±8.9	0.99
Body mass index (kg/m^2)	27.1±4.4	28.3±4.8	0.92
Systolic blood pressure (mm Hg)	122.6±18.4	126.8±21.0	0.19
Diastolic blood pressure (mm Hg)	74.4±11.7	79.2±11.4	0.3
Total cholesterol (mg/dl)	170.8±38.3	182.7±39.5	0.85
Triglyceride (mg/dl)	145.3±97.3	190.5±106.8	0.4
HDL(mg/dl)	43.0±8.3	40.9±7.3	0.94
LDL(mg/dl)	100.8±31.1	106.5±29.9	0.46
FBS(mg/dl)	161.1±64.1	186.0±71.3	0.19
HbA1C (%)	8.2±1.6	8.9±1.7	0.31
GFR (ml/min/1.73 m^2)	82.3±29.6	78.3±22.9	0.03
Creatinine (mg/dl)	0.96±0.21	1.0±0.3	0. 2
TSH(m IU/L)	2.3±1.4	2.6±1.5	0.92

Table 4: comparison of clinical and paraclinical characteristics between eutyroid and subclinical hypothyroid patients.

Variable	Euthyroid	Subclinical hypothyroidism
Age (year)	8.96±56.03	11.44±50.50
Body mass index (kg/m^2)	27.5±4.6	28.1±3.8
Systolic blood pressure (mm Hg)	125.7±19.0	124.0±29.5
Diastolic blood pressure (mm Hg)	77.4±11.5	76.0±16.8
Total cholesterol (mg/dl)	176.3±38.9	186.3±46.1
Triglyceride (mg/dl)	168.2±115.5	219.7±172.4
HDL (mg/dl)	41.6±7.7	45.8±8.3
LDL (mg/dl)	103.8±30.4	104.0±32.9
FBS (mg/dl)	168.8±65.5	225.5±79.6
HbA1C (%)	8.5±1.7	8.6±1.8
GFR (ml/min/1.73 m^2)	79.2±25.8	94.9±32.4
Urine albumin to creatinine ratio (mg/gr)	48.4±64.4	32.4±29.8
Creatinine	0.99±025	0.85±0.17

females in our study, variation in environmental and dietary factors.

In this study, there is no significant difference in the levels of TSH and free T4 among diabetic patients with and without nephropathy. This result is contrary with some other studies [7-9]. We expected that GFR to be lower in hypothyroid than euthyroid patients [10] due to increasing of vascular resistance and intrarenal vasoconstriction in hypothyroidism [11] but in our study GFR was not significant different in hypothyroid patients. In the other hand, subclinical hypothyroidism is associated with endothelial dysfunction through a reduction in nitric oxide (NO) [12]. Endothelial dysfunction is implicated in DN so endothelial dysfunction may be a possible link between DN and SCH.

An epidemiological study has revealed increased prevalence of hypothyroidism in chronic kidney disease [13]. The possible explanation for the difference of our result is due to excluding of patients with overt hypothyroidism from this study.

Some other studies have reported increasing level of albuminuria in hypothyroid patients [14-15]. Hypothyroidism can leads to thickening of glomelular and tubular basement membrane and expansion of mesangial matrix which causes glomerular leakage of proteins similar to early stages of diabetic nephropathy [16]. We did not find significant difference in levels of albuminuria in hypothyroid patients compared with euthyroids. Exclusion of all known previous hypothyroid patients and Lower concentration of TSH in our study may be responsible for this difference.

Similar with other studies, the present study found that duration of diabetes is associated with DN [17,18] but in contrary with other studies age, FBS, HbA1C and blood pressure are not associated with DN.

Our study had some limitations. First, Cross sectional design is a major limitation in our results. Second, excluding of overt hypothyroid patients is another limitation of this study and third, thyroid function test was measured at a single time point. Further prospective studies with inclusion of overt hypothyroid patients should be conducted to confirm these results.

Conclusion

Our results suggest that subclinical hypothyroidism is not associated with diabetic nephropathy.

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