

The Relationship between Subclinical Hypothyroidism and Chronic Kidney Disease in Type Two Diabetes Mellitus in Al-Nasria City South of Iraq.

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Abstract— The association between subclinical hypothyroidism (SCH) and chronic kidney disease (CKD) in type 2 diabetes mellitus is unclear. We examined whether SCH is associated with CKD in type 2 diabetic patients in Al-Nasria city. Data from 207 patients who visited Al-Nasria diabetic clinic and Al-Hussain teaching hospital between July 2013-October 2014 were analyzed in cross-section study.

All patients with type 2 diabetes mellitus were evaluated for glycaemic control, thyroid function and chronic kidney disease (CKD). CKD estimated by calculation of GFR from serum creatinine levels according to National Kidney Foundation. GFR levels were classified into five stages. CKD was defined as $eGFR < 60 \text{ mL/min/1.73 m}^2$. The prevalence of SCH was 9.6% (n=20) among patients with type 2 diabetes mellitus. The SCH group had a higher prevalence of dyslipidemia (p=0.009) and CKD (decline in GFR) (p=0.034) than the euthyroid group.

After adjustment for potential risk factors of diabetes mellitus by multivariate logistic regression analysis, SCH remained significantly associated with CKD (odds ratio 2.086 (95% CI 1.10-4.307, p=0.047), duration of diabetes (odds ratio 2.89 (95% CI 0.0-1.00 P=0.032), Dyslipidemia (odds ratio 4.849 (95% CI 0.0-0.1.20 p=0.009). These results suggest that SCH was independently associated with CKD in type 2 diabetes mellitus.

Keywords— subclinical hypothyroidism, type 2 diabetes mellitus, chronic kidney disease.

I. THE OBJECTIVES

1. The idea behind this study is to find the frequency of subclinical hypothyroidism in type 2 diabetic patients in Al-Nasria population.
2. To examine if there is any association between SCH and CKD (decline in GFR) within the type 2 diabetic patients and any difference between SCH and euthyroid patients regarding other demographic and clinical characters of diabetes mellitus.

II. INTRODUCTION

Diabetes mellitus on long term is associated with vascular complications that are responsible for increased morbidity and mortality among diabetic subjects (10). New addition to these complications is the thyroid dysfunction which is indicated by recent studies (32) thyroid dysfunction is increasingly found in the diabetes mellitus patients, the prevalence of which is around 13.4% (19). Diabetes may be affect the thyroid function to variable extent and unrecognized thyroid dysfunction not only worsens the metabolic control but also impede the management of diabetes (18).

Subclinical hypothyroidism (SCH) occurs when serum TSH levels are elevated but free T4 (FT4) concentration remain within the normal range. Although SCH is usually asymptomatic, it has associated with hyperlipidemia (8), atherosclerosis (28,3), cardiac dysfunction (4). An association between type 2 diabetes mellitus and subclinical hypothyroidism is not uncommon, with an SCH prevalence of 2.2 -17 % reported in previous studies (10,22). Previous studies have also shown a close interrelationship between chronic kidney disease (CKD) and SCH (6,16).

III. CHRONIC KIDNEY DISEASE IN RELATION TO THYROID DYSFUNCTION

CKD affects the hypothalamus-pituitary-thyroid-axis and the peripheral metabolism of thyroid hormone. Low T3 is most common laboratory finding and subclinical hypothyroidism is most common thyroid disorder found in CKD patients (11). Low T3 levels in CKD may not be able to increase TSH levels suggests that in uremia, the sensitivity of thyrotrophs is increased. This may account for the resetting of central thyrostat indicating a low level of the circulating thyroid hormones and in turn, affect the negative feedback inhibition (9). In CKD, physiological compensation for low T3/T4 (with normal TSH levels) causes a reduction in protein catabolism which increases the nitrogen waste overload.

The interplay between thyroid and the kidney in each other's function is known for many years (14). Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. In addition, treatment strategies of one disease may affect those of the other organ. This review focuses on the important and clinically relevant interactions between thyroid function and renal function, which are essential for the clinician to optimally manage the patient (11).

Diabetic nephropathy is now the most common cause of end-stage renal disease (ESRD), which significantly contributes to the high mortality in type 2 diabetic patients (21). It is projected that 30-40% of patients with type 1 diabetes and 5-10% of patients with type 2 diabetes eventually develop ESRD (21, 17). Conventional therapies such as strict glycaemic control and antihypertensive treatment do not completely stop the progression of diabetic nephropathy in diabetic patients, (21).

Hypothyroidism is accompanied by decrease in GFR and renal blood flow (17). The low level of tri-iodothyronine (T3) is associated with a survival disadvantage of chronic kidney disease (12). Type 2 diabetic patients with subclinical hypothyroidism are associated with an increased risk of diabetic nephropathy (7). In contrast, hyperthyroidism increases GFR and renal blood flow (12)

Clinical studies indicated that serum-free T3 level was about 47% lower in patients with types 2 diabetes compared with non-diabetic patients (13). There were no significant differences in serum levels of free thyroxine (T4) and TSH between the control and the study subjects (13).

A few studies have examined the association between subclinical hypothyroidism and microvascular complications in the type 2 diabetic patients and the association between TSH levels and microvascular complications.

In a study done in Taiwan by chen et al, it was found that there was an increased prevalence of nephropathy in type 2 diabetic patients with subclinical hypothyroidism compared to those who were euthyroid (7).

However in a study done by Yang et al in china, it was reported that there was an increased prevalence of retinopathy in type 2 diabetic patients with subclinical hypothyroidism and patients with a TSH levels in upper normal range (2.0-4.0 uIU/ml) also had a higher prevalence of severe retinopathy compared to those with lower TSH level (30).

According to a study done in Japan by Yausda et al, subclinical hypothyroidism was associated with albuminuria in type 2 diabetic patients and the TSH level was found to be an independent risk factor for the presence of albuminuria (31).

Since the results of those studies were contradictory, it necessary for us to further examine the association of subclinical hypothyroidism and the chronic kidney disease in type 2 diabetic patients to investigate whether subclinical hypothyroidism could influence the severity of decline in GFR in chronic kidney disease in our population, those type 2 diabetic patients attended both AL- Hussan Teaching

Hospital and AL- Nasria diabetic center in AL- Nasria city.

IV. PATIENTS AND METHODS

In this study the diabetic patients were selected patients from those attended the Al-Nasria diabetic center and from patients visited the Al-Hussein teaching hospital .

The study performed from July 2013-october 2014. The study population include 207 subjects with previously diagnosed type 2 diabetes mellitus (median age at recruitment, 63.0years; range, 30-80years; 57% men) .All subjects were fulfilled the WHO criteria of diabetes mellitus.

The WHO criteria for diagnosis of diabetes mellitus.

1-symptoms of diabetes plus random blood glucose concentration ≥ 200 mg/dl.

2. fasting plasma glucose ≥ 126 mg/dl.

3. two-hours plasma glucose ≥ 200 mg/dl during the oral glucose tolerance test.

All patients were subjected to thyroid function test (FT3, FT4, TSH). Patients with known overt hypothyroidism or type 1 diabetes mellitus were excluded from the study. Relevant data about the patients were collected including age, gender, duration of diabetes mellitus, history of hypertension with blood pressure measurement, any history of smoking, Body mass index (BMI kg/m^2), HbA1c, total lipid profile and serum creatinine levels. Also all patients were screened for the chronic diabetic complications (ischemic heart diseases and cerebrovascular accidents) by history and supported by ECG, Echo. Cardiac study and brain CT-scan.

Subclinical hypothyroidism was defined as an elevated TSH level (>4.0 mIU/L) and a normal FT4 level (0.90-1.70 ng/dL). Exclusion criteria included a history of thyroid disease with or without treatment, acute infection, and liver disease.

Body mass index (BMI) was calculated as weight (kg) divided by the square of height in meters (m^2). Patients who smoked ≥ 1 cigarette per day were regarded as current smokers. Blood pressure was measured with a cuff in the sitting position after a rest period of more than 5 minute. Hypertension was defined by a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mm Hg, or both or if the patients was treated already taking ant-hypertensive drugs.

Dyslipidemia was defined by a serum total cholesterol concentration >140 mg/dL, or high density lipoprotein (HDL) cholesterol concentration <40 mg/dL. Or if the patients were already being treated with lipid-lower agents.

V. ASSESSMENT OF ESTIMATED GLOMERULAR FILTRATION RATE AND THE DEFINITION OF CHRONIC KIDNEY DISEASE.

Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine (mg/dL): $194 \times \text{serum Cr}^{1.094} \times \text{age}^{-0.287} \times 0.739$ (if female). CKD was defined as eGFR <60 mL/min/1.73 m^2 .

VI. STAGE OF CHRONIC KIDNEY DISEASE ACCORDING TO THE NATIONAL KIDNEY FOUNDATION

Stages	Description	(GFR)
I	Kidney damage with normal kidney function	90 or above
II	Kidney damage with mild loss of kidney function	89 to 60
III	Moderate loss kidney function	59 to 30
IV	Severe loss kidney function	29 to 15
V	Kidney failure	Less than 15

VII. STATISTICAL ANALYSIS

All numerical variable are expressed as mean± standard deviation. The statistical significance of an association between two variables was assessed by Chi-square (X²) test of independence. we used mult-variable logistic regression to estimate the odds ratio (OR) for the presence of chronic kidney disease.

An estimate was statistically significant if its calculated value was less than P < 0.05 level of significance with 95% confidence.

VIII. RESULTES

As shown in Figure(1), the prevalence of subclinical hypothyroidism was 9.6% (20/207) among patients with type 2 diabete mellitus. the baseline demographic and clinical characteristics of the study subjects , startified by thyroid status ,were listed in table(1) .Family history of diabetes mellitus(33.0% in euthyroid ,27.9%in SCH and p=0.258), BMI(25.2±4.8 vers 26.1±4.4 and p=0.942), HbA1c(8.8±2.0 vers 8.4±1.9 and p=0.161) , smoking(21.7% vers 11.1% and p=0.135) , hypertension(47.0% vers 54.5% and p=0.359) , Ischemic heart disease(10.0% vers 6.6% and p=0.451) and cerebral infarction(5.8% vers 8.3% and p=0.601) were not significantly differ between the euthyroid and subclinical hypothyroid group in type2 diabetic patients. ,

While SCH group had a higher prevalence of dyslipidemia (40.5% in euthyroid vs 63.9% in SCH and p=0.009) and the prevalence of SCH was higher in elderly diabetic patients (57.8 ±11.8 in euthyroid vs 61.7±9.8 in SCH with P=0.024) and SCH was most common in diabetic female patients than male in compared with euthyroid diabetic patients (51.4% in euthyroid vs 75.4% in SCH with p=0.002).

The frequency of SCH was increased with increased in duration of diabete mellitus in compared with euthyroid diabetic patients (6.7±5.6 years in euthyroid vs 8.9±7.0 years in SCH with p=0.050).

The eGFR in the SCH group was lower than that in the euthyroid group (76.3±20 in euthyroid vers 68±20 in SCH with p=0.034).

In table 2 ,shown that the type 2 diabetic patients with subclinical hypothyroidism had a significantly lower glomerular filtration rate (p=0.0387). and this association was increased with increasing the degree of the declined of GFR (increased stages of GFR). as shown in figure 2: (in stage III 7.5% were euthyroid vs 15% were SCH

)while in advance stages (in stage IV 6.5% were euthyroid vs 15% were SCH, while in stage V 12.5% euthyroid vs 20% were SCH).

In table 3)- shown the Logistic regression analysis of association of Chronic kidney disease (declined in GFR) with the studied characters in SCH patients.

We examine the independent risk factors of diabetes mellitus, a binary logistic regression analysis was performed .The variables which showed an independent association between SCH and CKD (decline of GFR)

SCH remained significantly associated with CKD (odds ratio 2.086 (95% CI1.10-4.307, p=0.047),duration of diabetes (odds ratio 2.89 (95% CI 0.0-1.00 P=0.032),Dyslipidemia (odds ratio 4.849(95% CI 0.0-0.1.20 p=0.009) while the other risk factors like age , gender, smoking, BMI, HbA1c , hypertension and family history of diabetes showed no significant association with declined of GFR in SCH diabetic patients while ischemic heart disease and cerebrovascular accidents were excluded.

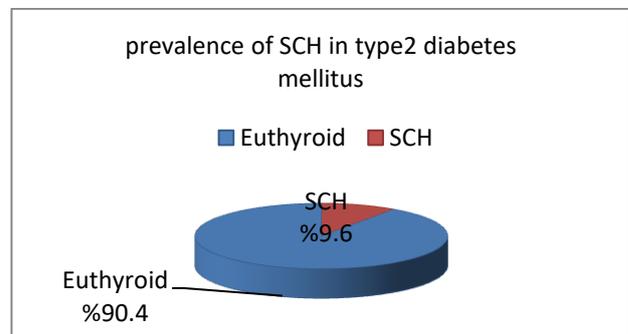


Figure (1) The Distribution of subclinical hypothyroidism(SCH) and euthyroid in type2 diabetic patients.

Table(1) clinical characteristic of type 2 diabetic patients with or without subclinical hypothyroidism (SCH).

	Euthyroid (N=187)	SCH (n=20)	p.value
Age	57.8±11,8	61.7±9.8	0.024
Gender (male%)	48.6	24.6	0.002
DoDM (year)	6.7±5.6	8.9±7.0	0.050
Family history of diabetes	33.0	27.9	0.258
BMI(Kg/m ²)	25.2±4.8	26.1±4.4	0.094
HbA1c(%)	8.8±2.0	8.4±1.9	0.161
Smoking(%)	21.7	11.1	0.135
Hypertension(%)	47.0	54.5	0.359
Dyslipidemia(%)	40.5	63.9	0.009
IHD(%)	10.0	6.6	0.451
CVA(%)	5.8	8.3	0.601
GFR(ml/min./7.75ml)	20.0	76.3± 68.3±20.0	0.034

(DODM) Duration of diabetes mellitus, (BMI)Body mass index, (HT) Hypertension (SCH) subclinical hypothyroidism (IHD)Ischemic heart disease(CVA) Cerebrovascular accidence .

Table (1) Shows the list of baseline demographic and clinical characteristics of the study subjects , startified by thyroid status and shows that these is a significance increase in Dyslipidemia (p=0.009), and declines of GFR (p=0.034) with increase of SCH patients with increasing the duration

of diabetes ($p=0.05$) and SCH was common in females ($p=0.002$).

Table (2)- the prevalence of Renal impairment(stages of GFR) in type 2 diabetic patients with and without subclinical hypothyroidism

GFR	Euthyroid(n=187)	SCH(n=20)	p.value
1-stage I	112(59.8%)	8(40%)	0.036
2-stage II	26 (13.9%)	2(10%)	
3-stage III	14 (7.5%)	3(15%)	
4-stage IV	12(6.4%)	3 (15%)	
5-stage V	23 (12.3%)	4 (20.0%)	

the type 2 diabetic patients with subclinical hypothyroidism had a significantly lower glomerular filtration rate ($p=0.0387$), and this association was increased with increasing the degree of the declined of GFR (increased stages of GFR).

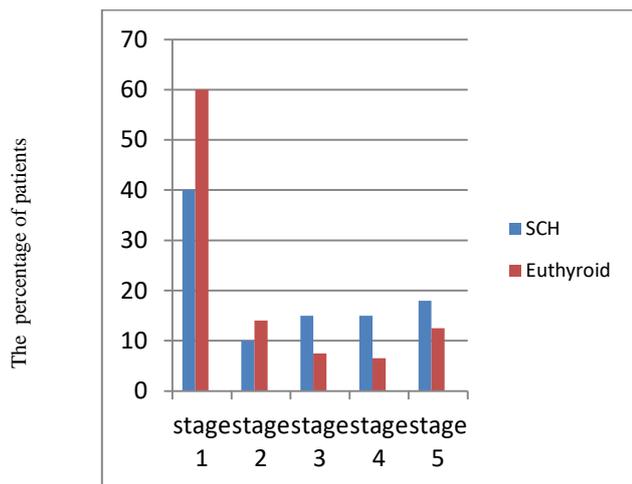


Figure (2)-Distribution of Renal impairment(stages of GFR) in type 2 diabetic patients with and without subclinical hypothyroidism .

Table (3)- Logistic regression analysis of association of Chronic kidney disease (declined in GFR) with the studied characters in SCH patients with type2 diabetes mellitus.

	Variables	β	Significant (P-value)	Expected B	95 % CI for expected B
Significant	DODM	41.952	0.032	2.459	0.0 - 1
	Dyslipidemia	9.729	0.009	4.849	0.0 -1.2
	SCH	20.721	0.047	2.086	1.10-4.307
Insignificant	BMI	0.159	0,060	1.16	0.99
	HT	-11.955	1.000	6.426	-----
	Smoking	26.360	0.872	2.028	-----
	Age	-20.649	0.999	1.077	-----
	Family history of hypertension	-21.718	0.921	3.699E-10	----
	Sex	13.309	0.999	1.100	-----
Excluded variables	IHD	Non significant			
	C.V.A	Non significant			

(DODM) Duration of diabetes mellitus, (BMI)Body mass index, (HT) Hypertension (SCH) subclinical hypothyroidism (IHD)Ischemic heart disease(CVA) Cerebrovascular accident .

We examine the independent risk factors of diabetes mellitus, a binary logistic regression analysis was performed .The variables which showed an independent association between SCH and CKD (decline of GFR)($p=0.047$).

IX. DISCUSSIONS

The idea behind this study is to find the frequency of subclinical hypothyroidism in type 2 diabetic patients and to examine if there is any association between SCH and chronic kidney disease (declined in GFR) within the type 2 diabetic patients and any different between SCH and euthyroid patients regarding other demographic and clinical characters of diabetic patients.

Our study shows that SCH was associated with chronic kidney disease among 207 patients with type 2 diabetes mellitus . the frequency of SCH was 9.6% among patients with type 2 diabetes mellitus ($n=2.7$),and the prevalence of SCH among patients with chronic kidney disease(GFR <60) was 50% ($n=10$). Our study revealed in multivariate analysis that an independent association between chronic kidney disease and SCH in type2 diabetes mellitus , duration of diabetes mellitus and Dyslipidemia . However, there was no independent association with ischemic heart disease and stroke in multivariate analysis.

Also our study differs from the study by Kim BY, Kim CH , et al. study , was conducted in Korea that failed to show an association between SCH and chronic kidney disease was shown that no significant deferent in declined of GFR between SCH and euthyroid patients in type 2 diabetes mellitus (25/390 (6.4%) in euthyroid vs. 4/59(6.7)in SCH)⁽¹⁵⁾.

In another study was done by Yasuda T, Kaneto H, et al. in Japan reported that serum TSH levels were independently associated albuminuria among Japanese patients with diabetes mellitus. However, chronic kidney disease or GFR was not diagnosed, and the sample size was smaller than other studies and consisted only inpatients⁽³¹⁾.

The results of our study were differ from other previous studies like one obtained by Shinya, F, Shin Y, et al. Who found that the SCH was not independently associated with CKD.⁽²³⁾

Our study was agreement with other studies that shown a strong association between GFR and TSH levels, including negative correlation between GFR and TSH concentration^(1, 24), a close interrelationship between CKD and SCH^(6,16,7,1), a high prevalence of CKD among patients with SCH⁽¹⁾in the general population ,and the efficacy of thyroid replacement therapy in attenuating the rate of GFR decline among patients with CKD that also included patients with diabetes mellitus (38.9%)⁽²⁵⁾..

As well known that hypertension , smoking and family history of diabetes are a risk factors for renal dysfunction among patients with type 2 diabetes mellitus^(26, 29). In our study with multivariate analysis there was no significant difference regarding smoking, hypertension and family history of diabetes between SCH and euthyroid group.

Dyslipidemia also plays a an important role in the progression of kidney dysfunction and had been shown to be an independent risk factor for end stage renal disease in the RENAAL study⁽²⁾.Also in patients with SCH , lipid metabolism is commonly observed⁽²⁷⁾. In our study the prevalence of Dyslipidemia in the SCH group was higher than that in the euthyroid group, and the multivariate analysis resulted in a highly significant association between Dyslipidemia and CKD ($p= 0.009$).

In Shinya, F, Shin, Y, *et al.* Study who found that there was no significant difference regarding the duration of diabetes between the SCH group and euthyroid⁽²³⁾ that differs from our study that revealed significant increased prevalence of SCH with increased duration of diabetes mellitus. Also in multivariate analysis there was a significance independent association of duration of diabetes between SCH and CKD in type 2 diabetes mellitus(p=0.032).

X. CONCLUSION

1. This study provides evidence that SCH in patients with type2 diabetes is associated with high prevalence of CKD (50%).and the frequency of SCH increases with advance stage of CKD (stage V).
2. The duration of diabetes as risk factor is an independently associated with CKD in SCH with type2 diabetes mellitus (p=0.032).
3. There is significant increase in frequency of Dyslipidemia in patients with SCH more than that in euthyroid in type 2 diabetes mellitus. And furthermore, Dyslipidemia is an independently associated with CKD in SCH type2 diabetic patients(p=0.009).
4. There is no significant association of other factors like age, gender, smoking, HbA1c, and hypertension with CKD in patients with SCH have type2 diabetes mellitus.

RECOMMENDATIONS

1. The patients with subclinical hypothyroidism should be diagnosed and treated to prevent the development and progression of renal disease in diabetic patients.
2. Thyroid function screening should be offered to diabetic patients with chronic kidney disease.

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