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Ghada A. Mohamed & Amira M Elsayed

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Original Article

Subclinical hypothyroidism ups the risk of vascular complications in type 2 diabetes ☆

Ghada A. Mohamed [a], Amira M Elsayed [b,*]

[a] Department of Internal Medicine, Assiut Faculty of Medicine, Assiut University, Egypt
[b] Department of Internal Medicine, Benha Faculty of Medicine, Benha University, Egypt

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ABSTRACT

The incidence of thyroid dysfunction in diabetic patients is higher than that of the general population. Undiagnosed thyroid dysfunction may affect the metabolic control and enhance cardiovascular, and other chronic complication risks in diabetic patients. Few studies have examined the relationship between subclinical hypothyroidism (SCH) and vascular complications of type 2 diabetes. *Objectives:* To find out the relationship between SCH and vascular complications in patients with Type 2 diabetes. *Subjects and Methods:* Our cross sectional study included 110 patients with type 2 DM (45 males and 65 females) who were followed at the Diabetes outpatient Clinics in the state of Kuwait during 6 months period. All patients subjected to complete clinical and laboratory data, including thyroid function tests, total cholesterol (TC), triglyceride (TG), HDL-C, LDL-C, urinary albumin, fundus examination, ECG, and Glycosylated hemoglobin. *Results:* Among 110 patients, 21 (19.1%) Patients had SCH. Patients with SCH were more significantly older, with longer duration of diabetes, higher HbA1c, total cholesterol and LDL-C than euthyroid group. However, gender ($p = 0.076$), BMI ($p = 0.092$), and smoking ($P = 0.715$) were not significantly different between the SCH and euthyroid groups. The SCH group had a higher prevalence of dyslipidemia ($p = 0.017$), diabetic nephropathy ($p = 0.003$) diabetic retinopathy ($p = 0.004$) and IHD ($p = 0.011$) than the euthyroid group while no significant difference in the prevalence of diabetic neuropathy ($p = 0.420$). *Conclusions:* SCH is a common endocrine disorder in patients with Type 2 diabetes. It could be associated with a higher prevalence of vascular complications in type 2 diabetes. We could not prove a relation between SCH and diabetic neuropathy.

1. Introduction

Subclinical hypothyroidism (SCH) is defined as an asymptomatic state that is characterized by high serum concentration of thyroid-stimulating hormone (TSH) and a normal serum concentration of thyroxine.[1] The incidence of thyroid dysfunction in diabetic patients is higher than that of the general population and up to a third of patients with type-1 diabetes (T1DM) and 4–17% in type- 2 diabetic patients. Undiagnosed thyroid dysfunction may affect metabolic control and enhance cardiovascular, and other chronic complication risks in diabetic patients.[2] The association between SCH and ischemic heart disease has been noticed in several studies, although the results have been inconsistent[3,4] and very few studies have focused on the population with diabetes. Few studies have examined the relationship between subclinical hypothyroidism and microvascular complications in type 2 diabetic patients. To our knowledge, only three studies have investigated the association between SCH and microvascular complications in Type 2 diabetes. Both Yang et al.[5] and Kim et al.[6] found that SCH was associated with diabetic retinopathy, although not with nephropathy. By contrast, Chen et al.[7] reported that patients with Type 2 diabetes and SCH were at increased risk of nephropathy. Moreover, no study to our knowledge has examined the prevalence of neuropathy in association with subclinical hypothyroidism.

Owing to the paucity of data regarding the prevalence of SCH and its potential association with vascular complications in Type 2 diabetes, this study examined the relationship between SCH and vascular complications patients with Type 2 diabetes.

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* Corresponding author at: Department of Internal Medicine, Benha Faculty of Medicine, Benha University, PO Box 13518, Egypt.
E-mail address: amiramohamady@gmail.com (A.M Elsayed).

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2. Methods

2.1. Patients

Our cross sectional study included 110 patients with type 2 DM (45 males and 65 females) who were followed at the Diabetes outpatient Clinics in the state of Kuwait during 6 months period were subjected to thyroid function test (FT3, FT4, TSH). Patients with known overt hypothyroidism, known overt or subclinical hyperthyroidism and type 1 diabetes mellitus, pregnancy, Postpartum women, patients with pituitary tumor, thyroid carcinoma or severe heart, liver, kidney and brain diseases were excluded from the study.

2.2. Thyroid function tests and definition

Serum thyrotropin (TSH) levels and free thyroxine levels were measured by chemiluminescent immunoassay. Subclinical hypothyroidism was defined as an elevated TSH level (>4.2 mIU/L) and a normal FT4 level (10–23 pmol/L). Euthyroidism was defined as normal levels of all three parameters: free triiodothyronine, free thyroxine and TSH.

2.3. Clinical examination and laboratory measurements

Relevant data about the patients were collected, including age, gender, duration of diabetes, history of hypertension, BMI, systolic and diastolic blood pressure, total cholesterol (TC), triglyceride (TG), HDL and LDL cholesterol. Glycosylated hemoglobin was measured using an ion-exchange HPLC (Merck-Hitachi9100).

2.4. Assessment of diabetic microvascular and macrovascular complication

The patients were diagnosed as having CAD if they had ischemic changes on a resting electrocardiogram (e.g., abnormal Q waves, ST segment depression or inverted T waves), a history of angina, myocardial infarction, or coronary angiography. Diabetic retinopathy was assessed by ophthalmologists and graded according to the International Clinical Classification of Diabetic Retinopathy.[8] Diabetic nephropathy was defined as history of diabetes with the presence of albuminuria, impaired glomerular filtration rate, or both.[9] A single morning urine sample for albuminuria was taken from subjects and albuminuria defined if equal to or more than 30 mcg/mg Creatinine (mcg/mg Cr).[10] Diabetic neuropathy was diagnosed based on abnormalities detected during neuropathic screening test (vibration sense testing, temperature sense, pain perception, monofilament testing and examination of reflexes).

2.5. Statistical analyses

Statistical analyses were performed using SPSS software version 16.0, and results were expressed as mean ± SD. To compare the means between two groups, Student's *t*-test was used for normally distributed data and the Mann–Whitney test was used for non-normally distributed data. For categorical comparisons, the chi-square test was used. A P-value < 0.05 was considered to be statistically significant.

3. Result

Our cross sectional study include 110 patients (45 males and 65 females) with type 2 DM were enrolled in our study with the following characteristics, age, 58.9 ± 10.6 (mean ± SD) years; duration of DM, 17.7 ± 10.02 years; BMI, 31.8 ± 6.5 kg/m^2; HbA1c, 8.4 ± 1.8%; TC, 4.08 ± 0.93 mmol/l; triglycerides (TG), 1.55 ± 0.76 mmol/l; HDL-C, 1.22 ± 0.38 mmol/l; LDL-C, 2.09 ± 0.75 mmol/l; TSH, 3.02 ± 1.93 mU/l;T4 (15.28 ± 2.07) pmol/l; urinary albumin creatinine ratio (185.27 ± 379.66) mcg/mg Cr. It was found that (105, 95.5%) of patients had dyslipidemia, (43, 39.1%) had diabetic retinopathy, (47, 42.7%) had diabetic nephropathy, (29, 26.4%) had diabetic neuropathy, (37, 33.6%) had IHD, (82, 74.5%) were hypertensive and (28, 25.5%) were smoker. Among 110 patients, 21 (19.1%) had SCH. Patients with SCH were significantly older, with longer duration of diabetes, higher HbA1c, total cholesterol and LDL-C than euthyroid group. However, gender ($p = 0.076$), BMI ($p = 0.092$), and smoking (P = 0.715) were not significantly different between the SCH and euthyroid groups (Table 1). The SCH group had a higher prevalence of dyslipidemia ($p = 0.017$), diabetic nephropathy ($p = 0.003$) diabetic retinopathy ($p = 0.004$) and IHD ($p = 0.011$) than the euthyroid group while no significant difference in the prevalence of diabetic neuropathy ($p = 0.420$) (Table 2 & Fig. 1).

4. Discussion

Vascular endothelial dysfunction is supposed to be an important factor in the pathogenesis of microvascular and macrovascular complications in diabetes. Endothelial dysfunction has also been described in subclinical hypothyroidism as well as in those with upper normal TSH values.[11,12] The association between microvascular complications and subclinical hypothyroidism and TSH values has not been comprehensively studied. Among the few studies done on the subject, the findings have been opposing. This is a cross-sectional study with a case control analysis which revealed that The prevalence of subclinical hypothyroidism in type 2 diabetic patients was 19.1%, and this is higher than data reported from another study done by Gao et al.[13] Our present data revealed that the prevalence of subclinical hypothyroidism was 4.5% in males and 14.5% in females with Type 2 diabetes. NHANES III, a population study, reported that the prevalence of subclinical hypothyroidism was 3.4% in males and 5.8% in females.[14] Perros et al. found that the occurrence of subclinical hypothyroidism was 3.3% in men and 4.6% in women with Type 2 diabetes.[15] The incidence of subclinical hypothyroidism in our study was greater than those of both these studies and revealed a dominance of females. The patients with SCH had a significant longer duration of diabetes in comparison to the euthyroid group (p = 0.007). In contrast, Kim et al. didn't found any significant difference in the duration of diabetes between euthyroid and SCH patients.[6] Although obesity affects hypothalamic-pituitary-thyroid axis directly or indirectly leading to variations in thyroid function

Table 1
Comparison between the participants with Euthyroid and SCH in type 2 diabetic patients regarding the different clinical parameters.

	Euthyroid (n = 89)	SCH (n = 21)	P value
Age (years)	57.78 ± 11.045	63.43 ± 6.95	0.027
Sex (M/F)	40/49	5/16	0.076
Duration of DM(years)	16.64 ± 10.245	22.10 ± 7.77	0.007
BMI (kg/m^2)	31.27 ± 6.19	34.2143 ± 7.36	0.092
HbA1c (%)	8.17 ± 1.72	9.15 ± 1.78	0.025
Total cholesterol (mmol/l)	3.85 ± 0.79	5.05 ± 0.83	<0.001
Triglycerides (TG) (mmol/l)	1.54 ± 0.81	1.57 ± 0.50	0.322
LDL cholesterol (mmol/l)	1.89 ± 0.61	2.93 ± 0.73	<0.001
HDL cholesterol (mmol/l)	1.17 ± 0.39	1.41 ± 0.27	0.001
TSH (mU/l)	2.24 ± 0.74	6.37 ± 1.88	<0.001
T4 (pmol/l)	15.49 ± 2.11	14.38 ± 1.66	0.027
UAE	126.43 ± 303.67	434.63 ± 546.92	0.011
Dyslipidemia (%)	97.8	85.7	0.017
HTN (%)	76.4	66.7	0.357
Smoking (%)	24.7	28.6	0.715

Table 2
The prevalence of vascular complications in type 2 diabetic patients with and without SCH.

	Euthyroid (n = 89)	SCH (n = 21)	P value
Retinopathy (%)	32.6	66.7	0.004
Nephropathy (%)	36	71.4	0.003
Neuropathy (%)	24.7	33.3	0.420
IHD (%)	28.1	57.1	0.011

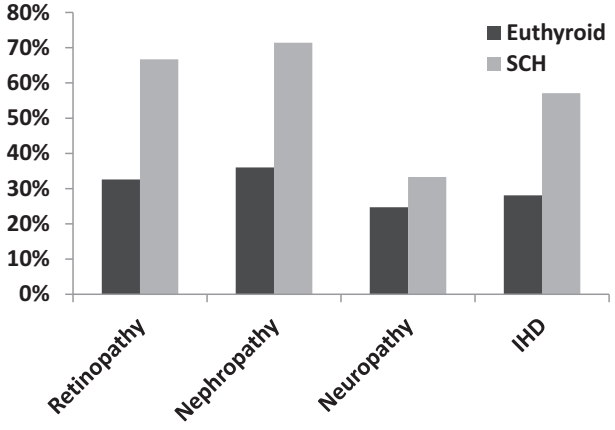

Figure 1. The prevalence of vascular complications in type 2 diabetes patients with and without subclinical hypothyroidism (SCH).

tests,[16] there was no significant difference in BMI between SCH diabetic patients and euthyroid group (P = 0.092). In this cross-sectional analysis of type 2 diabetes mellitus, subclinical hypothyroidism was associated with a higher frequency of microvascular (diabetic nephropathy, and retinopathy) and macrovascular complication (IHD). Our result differed from those of Chen et al. study which showed that type 2 diabetic patients with subclinical hypothyroidism are associated with an increased risk of nephropathy and cardiovascular events, but not with retinopathy.[7] While Kim et al. showed that SCH was associated with sight-threatening diabetic retinopathy, but not associated with diabetic nephropathy. However, he did not analyze the relationship between SCH and prevalence of macrovascular complications. kim et al. explained the link between SCH and diabetic retinopathy by insulin resistance that was higher in the SCH than the euthyroid group.[6] In contrast to, Gao et al. concluded that there is no association between subclinical hypothyroidism, and microvascular complications in type 2 diabetes.[17] It is known that thyroid hormone plays an important role in kidney growth and preservation of many of its functions.[18,19] In other words, the glomerular filtration rate in hypothyroid patients is approximately one-third lower than the corresponding values in euthyroid individuals.[20] Suher et al. suggested that subjects with hypothyroidism may have increased urinary albumin excretion rate[21] which came consistence to our result as there was a significant increase in the mean of albuminuria in patients with SCH. Moreover, a study done in Japan by Yasuda 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.[22] In our study, the prevalence of IHD was significantly higher in patients with SCH than in patients without SCH. Jia et al. provides evidence that SCH in patients with Type 2 diabetes is associated with a high prevalence of CHD.[23] This issue can be explained by Overt thyroid hormone deficiency which leads to increases in total cholesterol and LDL–C levels[24] which is evident in our result. Also, thyroid hormone deficiency can also damage vascular function directly.[25,26] Furthermore, several researchers have stated that SCH impairs the relaxation of vascular smooth muscle cells, thereby inducing increased arterial stiffness and systemic vascular resistance[25], as well as changes in endothelial function due to decreased nitric oxide availability.[26,27] Endothelial dysfunction in SCH could be due to inflammation.[28] A higher levels of IL-6, TNF-alpha and high-sensitive C-reactive protein (hs-CRP) in patients with SCH were found. In addition, a low grade chronic inflammation in patients with SCH can also be explained by the autoimmune thyroiditis.[29] Although, Hollander et al. demonstrated that renal function was better in 32 patients with hypothyroidism after thyroxine treatment,[30] our study was observational, and it does not follow the impact of treatment of subclinical hypothyroidism on risk reduction of diabetic vascular complication. Whether the management of patients with subclinical hypothyroidism affects important cardiovascular outcomes remains an unanswered question.[31,32] Chu and Crapo suggested that there was a little or no benefit of thyroxine therapy in most patients with subclinical hypothyroidism.[33] However, they also concluded that thyroxine treatment may be beneficial in selected patients with certain clinical circumstances.[34]

5. Conclusion

SCH is a common endocrine disorder in patients with Type 2 diabetes. It could be associated with a higher prevalence of vascular complication in type 2 diabetes. But, we could not prove a relation between SCH and diabetic neuropathy.

Recommendation

Routine screening of thyroid function in type 2 diabetic patients is necessary; and the treatment of subclinical hypothyroidism might have a considerable effect on the prevention or clinical course of vascular complications in type 2 diabetes.

Limitation of the study

Firstly, our study was observational, and it does not follow the effect of treatment of subclinical hypothyroidism on risk reduction of diabetic vascular complication. Secondly, there is a need for further study with a case matched control to be compared to the major variables like age, duration of DM, glycemic control, and lipid profile. Thirdly, the screening tests for diabetic nephropathy were done once; ideally these should be repeated for confirmation. Finally, we did not evaluate the other macrovascular complications of diabetes such as cerebrovascular and peripheral vascular diseases.

References

1. Helfand M, Redfern CC. Clinical guideline, part 2. Screening for thyroid disease: an update. American College of Physicians. *Ann Intern Med*. 1998;129:144–158.
2. Kadiyala R, Peter R, Okosieme OE. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. *Int J Clin Pract*. 2010;64:1130–1139.
3. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med*. 2000;132:270–278.
4. Cappola AR, Fried LP, Arnold AM, Danese MD, et al.. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295:1033–1041.
5. Yang JK, Liu W, Shi J, Li YB. An association between subclinical hypothyroidism and sight-threatening diabetic retinopathy in type 2 diabetic patients. *Diabetes Care*. 2010;33:1018–1020.
6. Kim BY, Kim CH, Jung CH, Mok JO, Suh KI, Kang SK. Association between subclinical hypothyroidism and severe diabetic retinopathy in Korean patients with type 2 diabetes. *Endocr J*. 2011;58:1065–1070.

7. Chen HS, Wu TE, Jap TS, Lu RA, et al.. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. *Diabetic Med: J Br Diabetic Assoc*. 2007;24:1336–1344.
8. Wilkinson CP, Ferris 3rd FL, Klein RE, Lee PP, et al.. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110:1677–1682.
9. Chen J. Diabetic nephropathy: scope of the problem. In: Lerma EV, Batuman V, editors. *Diabetes and kidney disease*, vol. 2014:9–14.
10. Summary of Revisions for the 2013 Clinical Practice Recommendations Diabetes Care 2013 Jan; 36 (Suppl 1): S3–S3. https://doi.org/10.2337/dc13-S003.
11. La Vignera S, Condorelli R, Vicari E, Calogero AE. Endothelial dysfunction and subclinical hypothyroidism: a brief review. *J Endocrinol Invest*. 2012;35:96–103.
12. Biondi B, Galderisi M, Pagano L, Sidiropulos M, et al.. Endothelial-mediated coronary flow reserve in patients with mild thyroid hormone deficiency. *Eur J Endocrinol/Eur Fed Endocr Soc*. 2009;161:323–329.
13. Gao Feng, Poullé NP, Zafar Mohammad Ishraq, Adeel Shafqat Raja. Association among subclinical hypothyroidism, TSH levels and microvascular complications in Type 2 diabetic patients. *IOSR J Dent Med Sci (IOSR-JDMS)*. 2014;13:01–06. e-ISSN: 2279-0853, p-ISSN: 2279-0861. Ver VI (Mar 2014).
14. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, et al.. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489–499.
15. Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. *Diabetic Med: J Br Diabetic Assoc*. 1995;12:622–627.
16. Bilgin H, Pirgon O. Thyroid function in obese children with non-alcoholic fatty liver disease. *J Clin Res Pediat Endocrinol*. 2014;6:152–157.
17. Gao Feng, Poullé NP, Zafar Mohammad Ishraq, Adeel Shafqat Raja. Association among subclinical hypothyroidism, TSH levels and microvascular complications in Type 2 diabetic patients. *IOSR J Dent Med Sci (IOSR-JDMS)*. 2014;13:01–06. Ver. VI. (Mar.).
18. Katz AI, Emmanouel DS, Lindheimer MD. Thyroid hormone and the kidney. *Nephron*. 1975;15:223–249.
19. Algun E, Topal C, Ozturk M, Sekeroglu MR, Durmus A. Urinary beta-2 microglobulin in renal dysfunction associated with hypothyroidism. *Int J Clin Pract*. 2004;58:240–243.
20. Singer MA. Of mice and men and elephants: metabolic rate sets glomerular filtration rate. *Am J Kidney Dis: Off J Natl Kidney Found*. 2001;37:164–178.
21. Suher M, Koc E, Ata N, Ensari C. Relation of thyroid disfunction, thyroid autoantibodies, and renal function. *Ren Fail*. 2005;27:739–742.
22. Yasuda T, Kaneto H, Kuroda A, Yamamoto T, et al.. Subclinical hypothyroidism is independently associated with albuminuria in people with type 2 diabetes. *Diabetes Res Clin Pract*. 2011;94:e75–e77.
23. Jia F, Tian J, Deng F, Yang G, et al.. Subclinical hypothyroidism and the associations with macrovascular complications and chronic kidney disease in patients with Type 2 diabetes. *Diabetic Med*. 2015. http://dx.doi.org/10.1111/dme.12724.
24. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab*. 2003;88:2438–2444.
25. Owen PJ, Sabit R, Lazarus JH. Thyroid disease and vascular function. *Thyroid: Off J Am Thyroid Assoc*. 2007;17:519–524.
26. Taddei S, Caraccio N, Virdis A, Dardano A, et al.. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab*. 2003;88:3731–3737.
27. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab*. 2007;92:1715–1723.
28. Hingorani AD, Cross J, Kharbanda RK, Mullen MJ, et al.. Acute systemic inflammation impairs endothelium-dependent dilatation in humans. *Circulation*. 2000;102:994–999.
29. Turemen EE, Cetinarslan B, Sahin T, Canturk Z, Tarkun I. Endothelial dysfunction and low grade chronic inflammation in subclinical hypothyroidism due to autoimmune thyroiditis. *Endocr J*. 2011;58:349–354.
30. den Hollander JG, Wulkan RW, Mantel MJ, Berghout A. Correlation between severity of thyroid dysfunction and renal function. *Clin Endocrinol*. 2005;62:423–427.
31. Surks MI, Ortiz E, Daniels GH, Sawin CT, et al.. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004;291:228–238.
32. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab*. 2005;90:581–585. discussion 6–7.
33. Chu JW, Crapo LM. The treatment of subclinical hypothyroidism is seldom necessary. *J Clin Endocrinol Metab*. 2001;86:4591–4599.
34. Chu JW, Crapo LM. Should mild subclinical hypothyroidism be treated? *Am J Med*. 2002;112:422–423.