The prevalence of subclinical hypothyroidism among patients with diabetes mellitus at the Kalafong Hospital Diabetes Clinic: a cross-sectional study

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Abstract

Objective: The purpose of this study was to determine the prevalence of subclinical hypothyroidism among patients with diabetes mellitus at the Kalafong Diabetes Clinic in Pretoria.

Design: Cross-sectional study.

Setting and subjects: Five hundred and sixty-five patients with diabetes mellitus (type 1, type 2 or unknown), who were following-up at the Kalafong Hospital Diabetes Clinic.

Outcome measures: The thyroid stimulating hormone (TSH) levels of patients were evaluated. Patients with TSH levels > 5.66 IU/ml (upper reference limit of the Kalafong National Health Laboratory Services laboratory) subsequently underwent repeat thyroid function evaluation, including T4 level, to determine the prevalence of subclinical hypothyroidism.

Results: A total of 563 patients met the inclusion criteria for this study and underwent TSH evaluation. The prevalence of subclinical hypothyroidism was found to be 0.9% in the study population, and 1.6% in a subgroup of patients with type 2 diabetes mellitus.

Conclusion: The prevalence of subclinical hypothyroidism in this South African population of patients with diabetes was significantly lower than that stated in the literature. This holds true for both the general population and populations of patients with diabetes mellitus. To our knowledge, there is no data available for the prevalence of subclinical hypothyroidism in the general population in South Africa for comparison with the study group.

Introduction

Diabetes mellitus and its associated complications is a major challenge for both the private and state health sector in South Africa. The number of people with diabetes is increasing because of population growth, ageing, urbanisation and the increasing prevalence of obesity and physical inactivity.

Subclinical hypothyroidism is defined as an elevated serum TSH level, with serum thyroid hormone concentrations within the normal range.[1] According to the literature, subclinical hypothyroidism affects 3-8% of the general Western population.[2] Symptoms may be present or absent. Most patients have TSH levels < 10 IU/ml and are asymptomatic. The cause of subclinical hypothyroidism is usually that of autoimmune thyroid disease.

Patients with diabetes have a higher prevalence of thyroid disorders than people in the normal population (10.8% vs. 6.6% as quoted in one USA study).[3] An

outpatient study of patients with diabetes in Scotland, who were screened for thyroid disease, reported the prevalence to be 13.4%. The most common abnormality was subclinical hypothyroidism.[4]

Patients with one organ-specific, autoimmune disease are at risk of developing other autoimmune disorders. Thyroid disorders are also more common in females, and it was found that up to 40% of female patients with type 1 diabetes had thyroid disease.[5] Eight per cent of these patients had subclinical hypothyroidism.[5]

A number of reports have also indicated a higher-than-normal prevalence of thyroid disorders in patients with type 2 diabetes. Subclinical hypothyroidism was the most common disorder.[3] The prevalence of subclinical hypothyroidism in patients with type 2 diabetes varies in the literature. Some studies stated that subclinical hypothyroidism was found in 10-17% of patients suffering from diabetes mellitus,[4,6-8] while others gave a more conservative prevalence of 5-7%.[9] The latter

is comparable with the prevalence quoted in the general population.

Data that pertain to the prevalence of subclinical hypothyroidism in the South African general population, as well as to South African patients with diabetes mellitus, is lacking.

In a cross-sectional study in Taiwan that reviewed 556 patients with type 2 diabetes and subclinical hypothyroidism, there was an associated higher frequency of nephropathy, after adjustment for age, sex and haemoglobin A_{1c} (HbA$_{1c}$).[10] The prevalence of nephropathy in these patients was 48%. Their data suggest that the higher incidence of cardiovascular events in subclinical hypothyroidism with type 2 diabetes might be mediated by nephropathy.

The endothelial dysfunction that is associated with subclinical hypothyroidism is manifest by thickening of the capillary basement membrane and small vessel dysfunction, leading to retinopathy.[11,12] In a study that compared the prevalence of diabetic retinopathy in patients with type 2 diabetes and subclinical hypothyroidism to their euthyroid counterparts, it was evident that severe retinopathy was significantly more common in the former group.[13] These results were after adjustment for age, sex, duration of diabetes, HbA$_{1c}$, body mass index, hypertension and low-density lipoprotein (LDL) cholesterol. Patients with type 2 diabetes and subclinical hypothyroidism were found to be at an increased risk of sight-threatening diabetic retinopathy.

Subclinical hypothyroidism can elevate serum LDL cholesterol and worsen pre-existing dyslipidaemia, further increasing the risk of atherosclerosis in patients with type 2 diabetes.[3]

Insulin resistance and its associated disorders is more common in patients with subclinical hypothyroidism.[14] The other effects of subclinical hypothyroidism include reductions in hepatic glucose output, gluconeogenesis and peripheral glucose utilisation (because of impaired translocation of the glucose transporter receptor). The net effect of these processes is a predisposition to hypoglycaemia. Frequent hypoglycaemic episodes were documented in children and adolescents with diabetes and subclinical hypothyroidism. Treatment led to an improvement in hypoglycaemic symptoms in this patient group.[15]

In the general population, there is a clear association with an increase in coronary heart disease and subclinical hypothyroidism, especially in persons < 65 years of age. Re-analysis of the Whickham Survey Cohort (which evaluated vascular events over 20 years in community-dwelling subjects, stratified by thyroid function and thyroid auto-antibody status) confirmed that the incidence of ischaemic heart disease was significantly higher in patients with subclinical hypothyroidism, as was ischaemic heart disease-related mortality.[16]

Data from the Rotterdam Cohort indicate that subclinical hypothyroidism is a strong, independent risk factor for cardiovascular disease, particularly in elderly women.[17] Subclinical hypothyroidism was associated with a greater prevalence of aortic atherosclerosis [odds ratio (OR)1.7] and myocardial infarction (OR 2.3).

The above refers to patients with subclinical hypothyroidism in the general population. It is suggested that subclinical hypothyroidism is a co-mediator for cardiovascular risk, in association with nephropathy, in patients with diabetes. However, it has not been shown to be an independent risk factor for cardiovascular disease in patients with diabetes mellitus.[10]

There is a significant correlation between HbA$_{1c}$ and TSH levels. There is an improvement of metabolic control after treatment of subclinical hypothyroidism.[18]

Of patients with subclinical hypothyroidism, 2-5% per year will progress to overt hypothyroidism, while 5% will spontaneously revert to normal thyroid functions.[14] Since overt hypothyroidism is an established indication for replacement therapy with T4, patients who are identified as suffering from subclinical hypothyroidism should be monitored intermittently for progression.

Method

Setting

This cross-sectional study was conducted on adult patients with diabetes mellitus and receiving routine care at the Kalafong Hospital Diabetes Clinic. All patients underwent TSH testing as part of annual investigations carried out at the clinic.

Patient selection

All patients on the clinic's database who were seen during 2010 were included in the study, provided they had signed informed consent for their information to be used, and that they did not meet any of the following exclusion criteria:

- Age < 18 years.
- History of thyroid disease or thyroid hormone replacement therapy.
- Hospitalisation or severe illness at the time of evaluation or preceding month (which could be associated with nonthyroidal illness that relates to abnormalities in thyroid function tests).

Measurements

TSH, creatinine, LDL cholesterol, HbA$_{1c}$ levels and microalbuminuria levels were determined by the National Health Laboratory Service at Kalafong Hospital.

In this study:

- An elevated TSH level was defined as ≥ 5.66 IU/ml.
- A LDL cholesterol level > 2.5 mmol/l was considered to be elevated.

- Microalbuminuria was defined as a urinary albumin to creatinine ratio of 3.3-30 mg/mmol in a spot urine sample.
- Macroalbuminuria was defined as a urinary albumin to creatinine ratio of > 30 mg/mmol.
- Nephropathy was defined as a urine albumin to creatinine ratio of > 3.3 mg/mmol or serum creatinine > 176.8 μmol/l.
- Glycaemic control was documented by HbA$_{1c}$.
- Retinopathy was classified into three categories: no retinopathy, preproliferative diabetic retinopathy and proliferative diabetic retinopathy. Fundoscopy was performed in the diabetic clinic as part of the standard care by the physicians who were treating the patients. Any retinopathy defined as equal to or greater than preproliferative retinopathy was considered to be relevant.

Follow-up

Any patient with an abnormally elevated TSH level underwent further evaluation with T4 levels to exclude the presence of primary hypothyroidism.

Statistical analysis

Microsoft® Access® 2003 was used to capture data. Statistical analysis was carried out with IBM SPSS® (version 19, 2010).

Statistical analysis consisted of descriptive statistics. Normally distributed data ere compared with the t-test and skewed data with the Mann-Whitney U test. Categorical data were compared with the chi-square test and the Fisher exact test.

Proportions were compared using Medcalc® (version 11.3.1.0, 2010).

Results

Five hundred and ninety patients were reviewed on the diabetes clinic database, of which 563 patients met inclusion criteria for this study and underwent TSH testing. Of the patients who were included in the study, two were found to have primary hypothyroidism and they were excluded from further analysis.

The study population consisted of 563 patients, of which 347 (62%) were female and 216 (38%) were male. Five hundred and twenty-one (93%) of the study population were of black ethnicity, 19 (3%) patients were white, 18 (3%) were Indian, while the remaining 5 (1%) represented patients of coloured ethnicity.

The average age of the studied population was 56.9 ± 14.8 years, with the mean duration of diabetes being 11.9 ± 8.3 years.

The study population included 182 (32%) patients with type 1 diabetes, 361 (65%) patients with type 2 diabetes and 14 (3%) patients in whom the type of diabetes was unknown. Patient characteristics are shown in Table I.

Table I: Characteristics of diabetic patients evaluated for subclinical hypothyroidism (n = 563)

Age (years, SD)	56.9 ± 14.8
Gender	
Male	216 (38%)
Female	347 (62%)
Race	
Black	521 (93%)
White	19 (3%)
Indian	18 (3%)
Coloured	5 (1%)
Type 1	182 (32%)
Type 2	361 (65%)
Unknown	16 (3%)
Duration of diabetes (years, SD)	14.7 ± 8.3
Co-morbid hypertension	439 (78%)
Current use of statin	289 (51.3%)
TSH level (IU/ml), median (IQR)	1.59 (1.05-2.35)
HbA$_{1c}$%, median (IQR)	7.7 (6.5-9.7)
Total cholesterol (mmol/l), mean, SD	4.5 ± 1.02
LDL (mmol/l), mean, SD	2.53 ± 0.89
HDL (mmol/l), mean, SD	1.19 ± 0.34
TG (mmol/l), median (IQR)	1.5 (1-2.2)
Serum creatinine (μmol/l) median (IQR)	83.0 (70-104.8)
Urine albumin/creatinine ratio, median (IQR)	1.0 (0.4-4.13)

HbA$_{1c}$: haemoglobin A$_{1c}$, HDL: high-density lipoprotein, IQR = interquartile range; LDL: low-density lipoprotein, SD = standard deviation, TG: triglycerides, TSH: thyroid-stimulating hormone

The prevalence of subclinical hypothyroidism in the studied population of patients with diabetes mellitus was 0.9% [confidence interval (CI): 0.296-2.077] for the group as a whole, and 1.4% (CI: 0.45-3.259) in the subgroup of patients with type 2 diabetes.

Five of the 563 screened patients were found to have subclinical hypothyroidism. All five patients were of African descent and suffered from type 2 diabetes. Three of the patients were female and two were male. Four of these patients suffered from concomitant hypertension and dyslipidaemia.

Subgroups within the study population were compared in terms of gender, race and type of diabetes. Compared variables included TSH levels, cholesterol profiles (total cholesterol, LDL, high-density lipoprotein and triglycerides), microalbuminuria and HbA$_{1c}$. The only statistically significant differences between male and female groups were found in HDL cholesterol, as well as LDL cholesterol. Both were increased in females more so than in males, with a mean difference in LDL cholesterol of 0.417 mmol/l (p-value < 0.001) and HDL cholesterol of 0.212 mmol/l (p-value < 0.001).

Nonparametric testing was carried out to compare the group of patients with subclinical hypothyroidism (defined by the TSH cut-off of 5.66 IU/ml) with the remaining patients in the study group. There was

a statistically significant difference in the serum creatinine values, which were higher in the group with subclinical hypothyroidism by a mean of 4.3 µmol/l (p-value = 0.017).

An attempt was made to build a logistic regression model in order to evaluate the difference in nephropathy, retinopathy and lipid profile between those patients with normal thyroid function and those with subclinical hypothyroidism. Unfortunately, the latter group was too small to obtain any covariates which were statistically significant.

Discussion

The purpose of this study was to determine the prevalence of subclinical hypothyroidism among patients with diabetes mellitus in a South African context. We found the prevalence to be 0.9% in the study population and 1.6% in the subgroup of patients with type 2 diabetes.

To the best of our knowledge, this is the first report on the prevalence of subclinical hypothyroidism among patients with diabetes mellitus in a South African context. Data is also lacking on the prevalence of subclinical hypothyroidism in the population as a whole.

The prevalence of subclinical hypothyroidism that was found in this study was much lower than that published in the international literature. This statistically significant difference was found when comparing the prevalence of subclinical hypothyroidism in our study population with the prevalence that was quoted in both the general population and the diabetic population. The difference holds true for our cut-off reference TSH of 5.66 IU/ml, as well as the 4.2 IU/ml that was used in many of the international studies. Table II compares the prevalence of subclinical hypothyroidism in our study population with that that was published.[4,6-7]

Many of the published studies used laboratory tests with an upper limit of normal for TSH of 4.2 IU/ml. A subanalysis of the data was carried out using this reference range, and it was found that if this cut-off was used, 4.2% (CI: 2.459-5.848) of the study population would be classified as having subclinical hypothyroidism, while 4.1% (CI: 2.281-6.738) of patients with type 2 diabetes would be classified as such.

If the TSH cut-off of 4.2 IU/ml is used, 22 (3.9%) patients were identified as suffering from subclinical hypothyroidism. Of these, 7 (1.2%) had type 1 diabetes and 15(2.6%) type 2. Four patients in this group were Indian, one was white and the remaining 17 were of black ethnicity. The prevalence of concomitant dyslipidaemia in this group was 54.5%.

Most of the studies that were performed on the prevalence and significance of subclinical hypothyroidism were carried out in a context of

Table II: Prevalence of subclinical hypothyroidism in this study compared to that that was published

Published %	TSH cut-off	Study population (%), n	CI	p-value
General population prevalence of subclinical hypothyroidism (3-8%)				
3	5.66	0.9, 563	0.26 to 2.08	0.0034
	4.2	3.9, 563	2.46 to 5.85	0.2160
8	5.66	0.9, 563	0.26 to 2.08	< 0.0001
	4.2	3.9, 563	2.46 to 5.84	0.0003
Diabetes population prevalence of subclinical hypothyroidism (10-17%)				
10	5.66	0.9, 563	0.26 to 2.08	< 0.0001
	4.2	3.9	2.46 to 5.85	< 0.0001
13	5.66	0.9, 563	0.26 to 2.08	< 0.0001
	4.2	3.9	2.46 to 5.85	< 0.0001
17	5.66	0.9, 563	0.26 to 2.08	< 0.0001
	4.2	3.9	2.46 to 5.85	< 0.0001
Diabetes type 2 population prevalence of subclinical hypothyroidism (10-17%)				
10	5.66	1.4, 361	0.45 to 3.26	< 0.0001
	4.2	4.1	2.28 to 6.74	< 0.0001
13	5.66	1.4, 361	0.45 to 3.26	< 0.0001
	4.2	4.1	2.28 to 6.74	< 0.0001
17	5.66	1.4, 361	0.45 to 3.26	< 0.0001
	4.2	4.1	2.28 to 6.74	< 0.0001

CI: confidence interval, TSH: thyroid-stimulating hormone

European and Eastern population groups. Very few, if any, black patients were included in these studies. The largest proportion of our population comprises patients of black ethnicity. The results of our study raise the question of whether reference ranges, which were determined in a Western population, can be extrapolated to a demographically different South African population. As with many of the laboratory tests that are used in South Africa, the reference range for the thyroid function tests employed by the National Health Laboratory Services was set based on the normal data of a Western population, rather than on normal values for the local population.

A study that was carried out in Israel by Ishay et al[8] determined the prevalence of subclinical hypothyroidism in women with type 2 diabetes, with that of women in the general population. They found the difference between the two groups to be statistically insignificant (9% in patients with diabetes, compared to 8% in the general population). The prevalence of subclinical hypothyroidism in this study group of patients with diabetes was lower than stated in other studies, and the author concluded that routine screening of thyroid function in patients with type 2 diabetes is unwarranted. However, even this more modest estimation of the prevalence of subclinical hypothyroidism in patients with diabetes was much higher than that found in our population.

The results of our study lend itself to the same conclusion as that of Ishay et al. It may not be cost-effective to routinely screen patients with diabetes mellitus with thyroid function tests, unless it is clinically indicated. However, baseline TSH levels can predict the future development of hypothyroidism in patients with diabetes mellitus. Patients with a baseline TSH of greater than 2.2 IU/ml have an increased risk of developing hypothyroidism.[1] Targeted screening of this subgroup of patients may be more cost-effective than universal annual screening. Patients with positive thyroid autoantibodies, and those at risk of polyglandular autoimmune endocrinopathy, also warrant routine annual screening of thyroid function tests.[14]

The upper limit of the reference range for TSH has been a contentious issue in the literature. A large Dutch population-based survey defined a much narrower range of TSH levels of between 0.3 and 2.5 IU/ml.[17] It is argued that more than 95% of normal individuals have TSH levels below 2.5 IU/ml. Furthermore, the population-based studies in which the reference ranges for TSH were determined previously, featured patients undergoing an initial phase of autoimmune thyroid disease. This could have potentially skewed the upper reference limit.[18]

Using an upper reference limit of 2.5 IU/ml for TSH to define subclinical hypothyroidism, as proposed in the literature, would have increased the prevalence of subclinical hypothyroidism in our population to 21% in the group as a whole, and to 23% in patients with type 2 diabetes. However, none of the studies that described outcomes in patients with subclinical hypothyroidism used such a low threshold to diagnose the condition. Consensus has not been reached about the level of TSH which defines the upper limit of normal. The definition of subclinical hypothyroidism remains related to the assay-specific upper limit of the TSH reference range. Therefore, the upper limit of normal for TSH of 5.66 IU/l, used in our laboratory, was used as the cut-off value.

A shortcoming of this study was the lack of data in the South African general population with which to compare our findings in a diabetic population. The upper limit of normal for TSH at our institution's laboratory has been determined for the specific assay used. However, the reference range was derived from the normal values in the Western population where the test was manufactured, leaving much to be desired in terms of determining what is "normal" in our population.

This study has highlighted the need for further studies to determine the normal reference range of TSH in a South African context, which contains a greater proportion of black patients than that in Western populations.

Once the aforementioned data is available, the definition of subclinical hypothyroidism can be customised to our population, and its prevalence more accurately determined.

Screening for thyroid dysfunction among patients with diabetes mellitus remains a cost versus benefit dilemma. Furthermore, the literature supports treatment of subclinical hypothyroidism only in those with a TSH level >10 IU/l, or those with thyroid antibodies.[14]

One strategy, which is supported in the literature, is to screen all patients with diabetes once with a TSH level, and repeat annual screening only in those with TSH levels that are greater than 2.2 IU/ml, or those which comprise a high risk for subsequent hypothyroidism (patients with the polyglandular autoimmune syndrome and those with positive thyroid antibodies).

Conclusion

The prevalence of subclinical hypothyroidism among a South African population of patients with diabetes mellitus at the Kalafong Diabetes Clinic was 0.9%. The prevalence among the subgroup of patients with type 2 diabetes was 1.6%. Both of these values are statistically significantly lower than the prevalence of subclinical hypothyroidism quoted in the literature for patients with diabetes and for the general population.

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