PREVALENCE OF DIABETES MELLITUS AND IMPAIRED FASTING GLUCOSE AMONG HYPOTHYROID PATIENTS

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ABSTRACT

Background: The association between autoimmune thyroid diseases and autoimmune diabetes is well established. However, the association between type 2 Diabetes and thyroid disease is unclear. Studies conducted on this topic worldwide have revealed varying results. The aims of this study were to assess the prevalence of diabetes and impaired fasting glucose in a group of hypothyroid patients in Sri Lanka and to assess the relationship between severity and etiology of hypothyroidism with diabetes and impaired fasting glucose.

Method: This descriptive (prospective) study was conducted at the Endocrine clinic, Teaching Hospital, Ragama over a period of 12 months, where all the new and follow up patients with hypothyroidism (both overt and subclinical hypothyroid patients) attending the clinic during this study period were included until the sample size is achieved. Interviewer-administered questionnaire was used to obtain relevant data from the patient and from the clinic book. Fasting blood sugar was done for all patients. When FBS $\geq 100\text{mg/dl}$, the test was repeated. For patients who had repeatedly elevated FBS $\geq 100\text{mg/dl}$, Urine for micro albumin and serum creatinine were also checked. If the urine micro albumin was elevated, the test was repeated after 3 months. The presence of retinopathy was assessed by the ophthalmology team.

Results: Majority of the study population consisted of females (91%). Mean age of the study population was 44.7 (SD – 12.1). 85.6% of the patients had overt hypothyroidism and 14.4% had subclinical hypothyroidism. The overall prevalence of diabetes mellitus among the study population was 15.6%. Prevalence of impaired fasting glucose was 31%. The prevalence of diabetes, impaired fasting glucose as well as dysglycaemia among patients with overt hypothyroidism and the subclinical hypothyroidism not significantly different ($p=0.905$, $p=0.931$, $p=0.982$). There was no significance difference between the etiology of hypothyroidism and in the prevalence of diabetes and impaired fasting glucose ($p=0.079$, $p=0.182$ respectively). None of the newly diagnosed patients with diabetes had microvascular complications.

Conclusion: Overall prevalence of both overt and subclinical hypothyroidism was not associated with type 2 diabetes mellitus and the severity of hypothyroidism did not have an effect on the development of any form of hyperglycemia. There was no significant association between the etiology of hypothyroidism and in the prevalence of diabetes as well as impaired fasting glucose. Even though the age, the body mass index, the presence of hypertension and the family history were significantly associated with the development of diabetes mellitus, the gender and the sedentary lifestyle did not show a significant association with the development of diabetes in our study population.

Keywords: Type 2 Diabetes mellitus, impaired fasting glucose, dysglycaemia, hypothyroidism, subclinical hypothyroidism.

INTRODUCTION

The association between autoimmune thyroid diseases and autoimmune

diabetes is well established. However, the association between type 2 Diabetes and thyroid disease is unclear. Hypothyroidism has been recognized

as an insulin resistant state by various in-vitro and preclinical studies (1-3). Altered metabolism of leptin and adipokines have been implicated in

such pathology (3). As a result, peripheral muscles become less responsive to insulin, which increases the probability of developing diabetes.

Some studies have documented a higher prevalence of thyroid dysfunction (ranging from 12-16%) among patients with diabetes (4). Similar studies done in Greek, Saudi Arabia and Jordan have shown a prevalence of 12.3%, 16%, 12.5% respectively (6, 7, 8, 9). Another large cross-sectional study concluded that the prevalence of hypothyroidism in patients with type 2 DM was much higher warranting thyroid screening for all the patients with type 2 diabetes (5). One study done in Sri Lanka has shown thyroid dysfunction in 21.1% of patients with type 2 Diabetes and subclinical hypothyroidism (9.4%) as the commonest thyroid dysfunction among this patient population (10).

On the other hand, population-based large Norwegian study revealed no association between type 2 diabetes and hypothyroidism (11). This observation was supported by several other cross-sectional studies (9, 12). One small prospective study done in this area also has failed to show any association with type 2 diabetes and hypothyroidism (11).

Although there is a reasonable amount of evidence on the prevalence of hypothyroidism among patients with diabetes, there is only one study that has studied the prevalence of diabetes and impaired glucose tolerance among patients with hypothyroidism. This study done in Bangladesh by Ashrafuzzaman SM et al. has shown a higher prevalence of newly diagnosed diabetes (4.8 vs. 7.01%, $p < 0.01$) and impaired glucose tolerance (IGT) (11% vs. 12.6%) among hypothyroid subjects¹³. Although Sri Lanka is a country with a higher prevalence of diabetes, there is very limited data related to the prevalence of dysglycaemia among patients with hypothyroidism. The objective of our study was to assess the prevalence of diabetes and impaired glucose tolerance in patients with thyroid

dysfunction in Sri Lankan clinical setup.

METHOD

This descriptive (prospective) study was performed at the Endocrine clinic, Teaching Hospital, Ragama over a period of 12 months, where all the new and follow up patients with hypothyroidism (both overt and subclinical hypothyroid patients) attending the clinic during this study period were included. Patients who did not consent to participate in the study, pregnant ladies, children aged < 20 years, patients with other endocrine diseases (other than overt or subclinical hypothyroidism) and patients on diabetogenic drugs were excluded. All patients satisfying the inclusion criteria were recruited and data collection was done until the minimum sample size (sample size of 300) is achieved.

Information was gathered from the patient using an interviewer-administered questionnaire and also from the patient clinic records. Demographic data such as the age, sex, marital status and occupation of the patient as well as the data related thyroid status and blood glucose levels were collected. Patients were categorized into two groups, overt hypothyroidism and subclinical hypothyroidism depending on the thyroid function test at diagnosis. Overt hypothyroidism was defined as having symptoms of hypothyroidism, which was confirmed by TSH above the upper limit of reference range with fT4 below the lower limit of reference range (14). Subclinical hypothyroidism was defined as having TSH above the upper limit of reference range with normal fT4 (14).

Fasting blood sugar was done for all patients. Diagnosis of diabetes and impaired fasting glucose were determined using American Diabetes Association criteria. Data on risk factors for DM (eg. Family history, Sedentary lifestyle) were collected during history taking from the patient. Family history was considered as positive if a participant had a biological member of their family having or had diabetes,

living or deceased. Patients were considered as having a sedentary lifestyle if they spend seating >90 minutes¹⁵.

Anthropometric measurements (height and weight) were measured according to the standard methods using calibrated equipment. All these measurements were done by two specially trained diabetes nursing officers at the clinic. Body mass index was calculated by using the standard formula ($BMI = \text{weight in kgs} / \text{height in meters}^2$). Blood pressure was recorded as the mean of two consecutive measurements in the sitting position taken 10 minutes apart. Blood pressure of $\geq 140/90$ mm Hg or the use of anti-hypertensive drugs were considered as having hypertension.

When FBS ≥ 100 with the 1st report, the tests were repeated and the patients who had persistently elevated ≥ 100 , Urine for microalbumin and serum creatinine were checked. If the urine microalbumin was elevated, it was repeated 3 months apart. Diabetic nephropathy was defined by the following: Persistent albuminuria (>300 mg/d or >200 $\mu\text{g}/\text{min}$) that is confirmed on at least 2 occasions 3-6 months apart, the progressive decline in the glomerular filtration rate (GFR), Elevated arterial blood pressure (15). Eye referral was arranged for retinopathy assessment. Laboratory tests were collected by the investigators.

Data were analyzed by Statistical Package for Social Sciences (SPSS) version 17. Bivariate analysis was done using chi square test. Having done the normality testing, association between the development of diabetes and quantitative variables were analyzed using the Mann Whitney U test.

Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine, the University of Kelaniya and all the patients were recruited after obtaining informed written consent from the patient.

Table 1: Association between Diabetes, impaired fasting glucose (IFG), Dysglycaemia(DG) and hypothyroid status

Thyroid status	Diabetes N (%)	No diabetes N (%)	Total N (%)	Association
Overt hypothyroidism	40 (15.6)	217 (84.4)	257 (100)	X ² = 0.014, df = 1 P value = 0.905 OR = 0.918, CI = 0.39-2.28
Sub-clinical hypothyroidism	7 (16.3)	36 (85.7)	43 (100)	
	IFG N (%)	No IFG N (%)	Total N (%)	Association
Overt hypothyroidism	80 (36.9)	137 (63.1)	217 (100)	X ² = 0.008, df = 1 P value = 0.931 OR = 1.033, CI = 0.5-2.15
Sub-clinical hypothyroidism	13 (36.1)	23 (63.9)	36 (100)	
	DG N (%)	No DG N (%)	Total N (%)	Association
Overt hypothyroidism	120 (46.7)	137 (53.3)	257 (100)	X ² = 0.000, df = 1 P value = 0.982 OR = 1.007, CI = 0.53-1.93
Sub-clinical hypothyroidism	20 (46.5)	23 (53.5)	43 (100)	

RESULTS

There were 300 subjects with overt or sub-clinical hypothyroidism, attending the Endocrine Clinic, North Colombo Teaching Hospital, who were recruited for the study. The majority of the study population consisted of females (91%). Mean age of the study population was 44.7 (SD – 12.1). 91.3% of them were married and 69% were housewives.

From the study population, 85.6% had overt hypothyroidism and 14.4% had

subclinical hypothyroidism. The overall prevalence of diabetes mellitus among the study population was 15.6%. Diabetes prevalence among females were 14.3% (43 patients) in females and 1.3%(4 patients) in males and this difference was not statistically significant. Only 6% of them were newly diagnosed as having diabetes mellitus during the study and rests of them were already diagnosed patients with Diabetes. Prevalence of impaired fasting glucose was 31%. Therefore, the prevalence of any form of hyper-

-glycemia was 46.6%. The large majority (42) of them had signs of Insulin resistance and had BMI > 23 and the. Rest of the patients did not have signs of insulin resistance or a positive family history for Diabetes. All the patients diagnosed as having Diabetes were well controlled on oral hypoglycemic.

Overall prevalence of both overt and subclinical hypothyroidism was not associated with diabetes mellitus and there was no statistically significant

Table 2: Association between Diabetes, impaired fasting glucose (IFG) and hypothyroid etiology

Hypothyroid etiology	Diabetes N (%)	No diabetes N (%)	Total N (%)	Association
Primary hypothyroidism	36 (15.7)	193 (84.3)	229 (100)	X ² = 5.083, df = 2 P value = 0.079
Secondary to ¹³¹ I therapy	6 (31.6)	13 (68.4)	19 (100)	
Secondary to thyroidectomy	5 (8.7)	47 (91.3)	52 (100)	
	IFG N (%)	No IFG N (%)	Total N (%)	Association
Primary hypothyroidism	75 (38.8)	118 (61.2)	193 (100)	X ² = 3.409, df = 2 P value = 0.182
Secondary to ¹³¹ I therapy	6 (46.2)	7 (53.8)	13 (100)	
Secondary to thyroidectomy	12 (25.5)	35 (74.5)	47 (100)	

difference in the prevalence of diabetes ($p = 0.905$), impaired fasting glucose ($p = 0.931$) or dysglycemia ($p=0.982$) in patients with hypothyroidism and in patients with subclinical hypothyroidism (Table 1).

In hypothyroid patients with diabetes, 76.5% of them had primary hypothyroidism, 12.8% had hypothyroidism secondary to radioiodine therapy and 10.6% had primary hypothyroidism, 12.8% had hypothyroidism secondary to radioiodine therapy and 10.6% had developed hypothyroidism following total thyroidectomy. There was no statistical significance difference between the etiology of hypothyroidism (primary, post radioiodine, post thyroidectomy) and the prevalence of diabetes ($p= 0.079$) among the patients with hypothyroidism (Table 2). Similarly, there was no statistical significance difference between the etiology of hypothyroidism (Primary, post radio iodine, post thyroidectomy) and the prevalence of impaired fasting glucose ($p= 0.182$) among the patients with hypothyroidism (Table 2).

Table 3 shows the bivariate analysis between selected associated factors with the development of diabetes among patients with overt and subclinical hypothyroidism. A family history ($p=0.019$), presence of hypertension ($p<0.001$), BMI ($p=0.011$) and age ($p=0.001$) were significantly associated with the diabetes at 5% significant level.

None of the newly diagnosed patients with diabetes had microvascular complications (retinopathy or nephropathy) at the time of diagnosis of diabetes. Only one patient with pre-existing diabetes had microalbuminuria and background retinopathy.

DISCUSSION

Although there is a suggestion that hypothyroidism could be associated with type 2 diabetes and dysglycaemia, our study did not find a statistically significant relationship with the occurrence of diabetes among patients with hypothyroidism and subclinical

Table 3: Association between development of Diabetes and predisposing factor

Predisposing factor	Association
Gender	P = 0.961*
Family history	P = 0.019*
Sedentary lifestyle	P = 0.603*
Hypertension	P = <0.001*
Body mass index	P = 0.011+
Age	P = 0.001+

hypothyroidism. The prevalence of diabetes mellitus and impaired fasting glucose among patients with subclinical and overt hypothyroidism patients attending our clinic were 15.6% and 31% respectively. We found no association between the severity of hypothyroidism and the development of hyperglycemia. There was no statistically significance difference between the etiology of hypothyroidism (Primary, post-radioiodine, post thyroidectomy) and in the prevalence of diabetes as well as impaired fasting glucose. Even though Age, sedentary life style and family history were strongly associated with the development of diabetes mellitus, body mass index and hypertension did not show a significant association with the development of diabetes in our study group. Our study did not reveal an increased risk microvascular complications among hypothyroid patients with diabetes.

A study conducted by the University of Kelaniya, the prevalence of diabetes was found to be 20.3% among males, 19.8% among females and the prevalence of impaired fasting glucose was found to be 42.2%¹⁶. Prevalence of diabetes and impaired fasting glucose in our study population (patients with hypothyroidism and subclinical hypothyroidism) was not higher than the latest figures available for population prevalence in that same geographical area and it is even lower than the general population (15.6% and 31% respectively). Several studies including a large population-based study by Hanne F. Fleiner (HUNT study) has also demonstrated similar results where there was a significant association between type 2 diabetes and hypothyroidism (10, 12). However, controversial results were

observed in a study done in Bangladesh by Ashrafuzzaman SM et al. where they observed a higher prevalence of newly diagnosed diabetes (4.8 vs. 7.01%, $p<0.01$) and impaired glucose tolerance (IGT) (11% vs. 12.6%) among hypothyroid subjects (13).

Thyroxine deficiency has a direct and an indirect relationship with the development of insulin resistance. Reduced metabolic rate related to thyroxine deficiency leads to progressive weight gain, increasing the insulin resistance of that individual. It also alters the metabolism of leptin and adipokines leading to insulin resistance. However, our study did not reveal any association between the severity of hypothyroidism and the development of hyperglycemia. In literature, none of the studies done in the past identified a significant association between severity of hypothyroidism and diabetes or IFG.

There was hardly any research done in assessing the relationship between the etiology of hypothyroidism (Primary, post radioiodine, post thyroidectomy) and in the prevalence of type 2 diabetes. Since there is no immune contribution in the development of type 2 diabetes, it can be argued that thyroxine deficiency is common to all 3 etiological conditions and has the similar predisposition in developing diabetes. Supporting this theory, we found no significance difference between the etiology of hypothyroidism and in the prevalence of dysglycaemia in our study population.

Age, positive family history, sedentary life style and obesity are well known

predisposing factors for the development of type 2 diabetes. It is sensible to assume that the excessive weight gain that is associated with hypothyroidism could predispose to diabetes. As expected family history, BMI and age were statistically significantly associated with the development of diabetes mellitus in our study population. In addition, presence of hypertension was also associated with the development of diabetes mellitus. However, sedentary life style, gender and smoking were not associated with the development of diabetes mellitus. Different results were obtained in a Sri Lankan study done by Shyaminda Kahandawa et al, where there was no association identified between body mass index and hypertension and prevalence of thyroid dysfunction in a diabetic population. (10).

There is evidence to suggest that patient with diabetes and hypothyroidism are at a high risk of developing microvascular complications. One Chinese study results indicated that type 2 diabetes patients with proliferative diabetic retinopathy (PDR) had a higher prevalence of subclinical hypothyroidism and suggested routine screening for thyroid function in PDR subjects (17). Another small study done in Netherlands have shown an increased risk of renal impairment among patients with hypothyroidism, which improved with thyroxin replacement therapy (18). However, our study did not reveal any increased risk of retinopathy or renal impairment among hypothyroid patients with diabetes.

CONCLUSION

The overall prevalence of both overt and subclinical hypothyroidism was not associated with type 2 diabetes mellitus and the severity of hypothyroidism did not have an effect on the development of any form of hyperglycemia. Our study did not find any significant association between the etiology of hypothyroidism and the prevalence of diabetes or impaired fasting glucose. Even though the

family history, the presence of hypertension, BMI and age were significantly associated with the development of diabetes mellitus, gender and sedentary life style did not show a significant association with the development of diabetes in our study population.

LIMITATIONS

We made the assumption that all patients who had family a history of diabetes mellitus and well controlled on oral hypoglycemic drugs as having type 2 diabetes mellitus. Rare forms of diabetes such as MODY were not excluded due to unavailability of the genetic test in Sri Lanka.

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