PREVALENCE AND ASSOCIATED FACTORS OF THYROID DYSFUNCTION AMONG TYPE 2 DIABETIC PATIENTS, KUWAIT

Hessa T Al-Wazzan,[1] Alaa H Daban,[2] Rafaa A Askar,[3] Medhat K El-Shazly[4]

[1]MRCGP(KU). Head of Subah Al-Nasser Center, Primary Health Care, Ministry of Health, Kuwait.
[2]MRCP(UK). North Ardiya Center, Primary Health Care, Kuwait Diabetes program.
[3]MRCGP(KU). Head of Riggae Clinic, Primary Health Care, Ministry of Health, Kuwait.
[4]MD, Department of Medical Statistics, Medical Research Institute, Alexandria University, Egypt. & Department of Health Information and Medical record, Ministry of Health, Kuwait.

Receive: 15 / 4 /2010 - Accepted: 18 / 5 / 2010.

ABSTRACT

Background: *Diabetes mellitus is commonly associated with altered thyroid function. There is much less data about thyroid diseases in patients with type 2 diabetes.*
Objective: *This study was conducted to examine the prevalence and associated factors of the most frequent thyroid dysfunction among type 2 diabetic patients.*
Methods: *The study design can be differentiated into two components. The first was a cross-sectional survey to determine the prevalence of thyroid dysfunction among type 2 diabetic patients. Recruitment efforts resulted in 1580 patients. Thyroid dysfunctions were diagnosed in 204 patients. The second component of the study was a case-control study to identify factors associated with thyroid diseases, whereas patients with thyroid dysfunctions (cases) were compared with a randomly selected similar number of type 2 diabetic patients with euthyroid status*
Results: *The prevalence rate of thyroid dysfunction in type 2 diabetic patients was 12.9%, the most common was subclinical hypothyroidism (45.1%). The multivariate analysis revealed that female gender, Kuwaiti nationality, personal history of autoimmune disease and smoking were significant predictor variables.*
Conclusion:
The prevalence of thyroid dysfunction among diabetic patients in Kuwait is common. Subclinical hypothyroidism is prevailing. All patients with type 2 diabetes should undergo bi-annual screening to detect asymptomatic thyroid dysfunction.
Key words: *Thyroid dysfunction, type 2 DM, prevalence, associated factors.*

INTRODUCTION

Diabetes mellitus (DM) is an important health problem affecting major populations worldwide.[(1)] Despite great strides that have been made in understanding and management of diabetes, the disease and its related complications are increasing unabated.[(2)] The influence of other endocrine and non-endocrine organs other than the pancreas on diabetes is documented.[(3,4)] Occasionally other endocrine disorders such as abnormal thyroid hormones levels are found in DM.[(5)] Diabetes, hypothyroidism and hyperthyroidism are metabolic disorders that affect the levels of carbohydrates, proteins and lipids.[(6)] Mechanisms of interaction between DM and thyroid diseases are complex and still unclear. Clinical relationship between DM and thyroid diseases cannot be explained merely by direct effect of shortage or excess in the thyroid hormones.[(7)]

Thyroid disorders are highly prevalent in the general population; they affect a considerable portion of the population.[(8,9)] Previous studies have demonstrated that diabetes mellitus is commonly associated with altered thyroid function.[(10,11)] The first reports showing the association between diabetes and thyroid dysfunction were published in 1979.[(12,13)] Since then a lot of studies in different countries have tried to estimate the prevalence of thyroid dysfunction among diabetic patients that was varying from 2.2 to 17%.[(14-16)]

Various epidemiological studies showed immunological and genetic base of relationship between DM and thyroid diseases. Type 1 diabetes is often accompanied by other autoimmune diseases. Autoimmune thyroid diseases are among the most common.[(17,18)] There is much less data about thyroid diseases in patients with type 2 diabetes. Recent publications confirm an increased incidence of autoimmune thyroid disease even in type 2 diabetes.[(18,19)] In addition, diabetic women are more frequently affected than men and hypothyroidism is more common than hyperthyroidism.[(16)]

Clinical relevance of thyroid diseases, especially in diabetic patients, significantly increases if it is associated with deteriorated function, which always cause a number of problems with metabolic compensation of diabetes. Most serious consequences are increased frequency of hypoglycaemia in hypothyroidism and development of potentially life-threatening ketoacidosis in thyrotoxicosis. In spite of that, little attention is paid

Correspondence to: Prof. Medhat Shazly, Department of Medical Statistics, Medical, Research Institute, Alexandria University, Tel: 00965/66612524, E-mail: medhat_shazly@hotmail.com

pISSN: 1110-0834
eISSN: 2090-2948

to the diagnosis of thyroid diseases in diabetics, as they are diagnosed in only about half of the patients.[19]

To the best of our knowledge no studies have been done to estimate the prevalence of thyroid dysfunction in type 2 diabetic patients in Kuwait. The aim of the present study was to determine the prevalence and factors associated with thyroid dysfunction in patients with type 2 DM attending North Ardiya diabetes clinic.

METHODS.

Setting and design:

The health care system in Kuwait is divided into five regional health authorities. Primary health care is provided by 78 centers served by either family practice physicians (FPs) or general practitioners. (GPs). Mostly in each center, a diabetes clinic is assigned for follow up of diabetic patients and served by either diabetologist or FP. The study design can be differentiated into two phases that was conducted from January to December 2009 in North Ardiya diabetes clinic that serves more than 1800 registered patients of type 1 or type 2 diabetes. The first phase was a cross-sectional survey to determine the prevalence of thyroid dysfunction among type 2 diabetic patients attending the selected center. Subjects having type 1 diabetes, < 18 years old and pregnant females were excluded from this study. Also, patients who were taking drugs for any other disease (e.g. Amiodarone) that influenced the thyroid hormone concentrations in the serum were excluded. All eligible subjects were asked to participate in the study. Recruitment efforts resulted in screening of 1580 type 2 diabetic patients. Among them, 204 patients were diagnosed as having thyroid dysfunction.

The second phase was a case-control study to investigate factors that could be associated with thyroid diseases, whereas all patients with thyroid dysfunction (case group, n = 204) were compared with an equal number of diabetic patients free from any thyroid diseases, chosen randomly from the same clinic (control group, n = 204). Patients were considered eligible as cases if they had type 2 diabetes and any type of thyroid dysfunction as diagnosed by laboratory investigations. Also, patient on any type of thyroid hormone replacement or anti-thyroid medication were identified as having thyroid dysfunction

Patients were considered eligible as control if they had type 2 diabetes proved to be free any type of thyroid dysfunctions.

The study was approved by the Committee of Research Ethics of Kuwait MOH. Verbal consent was taken from all recruited diabetics and control subjects for the purpose of the study.

Study questionnaires

The structured interview method has been adopted to collect data for this study with a specially designed questionnaire. It was derived from other published studies dealing with the same topic as well as from our own experience. It included socio-demographic characteristics (gender, age, nationality, smoking, family history of thyroid disease, personal history of autoimmune disease, BMI) and clinical data (duration since diagnosis of DM, treatment of DM, glycemic state, hypertension, dyslipidemia, microvascular complications, macrovascular complications, peripheral neuritis), in addition biochemical investigations (Hb_{A1c}, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, T3, T4, TSH and auto-antibodies against thyreoperoxidase (anti TPO).

Measurements:

Trained physicians in the chosen centers collected data by interviewing patients and reviewing their medical records. In order to ensure uniformity of data measuring methods that relied on clinical judgment, all participating physicians were trained on data collection and the questionnaire was thoroughly tested for clarity before it was accepted. General physical examination, laboratory investigations, as well as patients' record study were conducted by the trained physicians. Blood samples were drawn after 10-12 hours fasting, for measurement of plasma HbA1c, lipid profile as well as serum levels of thyroid stimulating hormone (TSH), free triiodothyroxine (T3), free thyroxine (T4). However, anti TPO was measured when available.

Patients were considered as having type 2 diabetes if they had fasting plasma glucose $\geq$ 7.1mmol/L, random plasma glucose $\geq$ 11.1 mmol/L and absence of islet autoantibodies.[20] Three blood pressure measurements were obtained by trained physicians using a standardized sphygmomanometer after a 5-minute sitting rest. Hypertension was considered on the basis of clinical judgment and confirmed by history of receiving anti-hypertensive drugs and/or the presence of systolic blood pressure value > 140 mmHg and/or diastolic pressure > 90 mmHg.[20]

Patients were classified as having microvascualr complications (diabetic retinopathy, nephropathy, neuropathy), macrovascular complications, and organ specific autoimmune diseases other than type 1 DM (vitiligo, alopecia, celiac disease, addison disease) on the basis of the presence of clinical symptoms and signs and confirmed or available medical reports in their records. The glycemic state of patient referred to the last value of Hb_{A1c} and it was considered adequate if < 7%. Normal levels for blood lipids were identified as 5.6 mmol/L for total cholesterol, 2.1 mmol/l for triglycerides, 3.4 mmol/L

for LDL, and 0.91 mmol/L for HDL. Reference ranges of TSH and T4 were defined as 0.27 – 4.2 mIU/L and 12 – 22 pmol/L.respectively. Thyroid dysfunction was identified and classified on the following criteria shown in table I.[21]

Table I: Test results and their potential meaning

Thyroid state	TSH	T4
-Normal	Normal	Normal
-Sick euthyroid	Normal	Low
-Subclinical hypothyroidism	High	Normal
-Hypothyroidism	High	Low
-Subclinical hyperthyroidism	Low	Normal
-Hyperthyroidism	Low	High

Weight was measured with calibrated digital scale while height was recorded with a wall mounted stadiometer. Body mass index (weight/height^2) was used as a measure of obesity Individuals with a BMI between 25 and 29.9 were considered as overweight, while individuals with a BMI of more than 30 were considered obese.

Statistical Analysis

Analysis was initially carried out based on a series of univariate comparisons. In order to control simultaneously for possible confounding effect of the variables, multiple logistic regression was used for the final analysis. In the univariate analysis Chi-square test was used to detect the association between thyroid dysfunction and explanatory variables. In multiple logistic regression analysis, the association between exposure and outcome was expressed in terms of odds ratio (OR) together with their 95% confidence intervals (95% CI).

All the explanatory variables included in the logistic model were categorized into two or more levels (R = reference category): gender: male^R, female; age (years): < 40^R, 40 – 49, 50 – 59, ≥ 60; nationality: non-Kuwaiti^R, Kuwaiti; smoking^R: non-smoker, Ex-smoker, smoker; family history of thyroid disease: no^R, yes; personal history of autoimmune disease: no^R, yes; BMI: < 25^R, 25 - , ≥ 30; duration of diabetes (years): < 5^R, 5 – 9, 10 – 14, ≥ 15; treatment of diabetes: oral^R, insulin, oral + insulin; glycemic state: good control^R, poor control; dyslipidemia: no^R, yes; hypertension: no^R, yes; microvascular diabetic complications: no^R, yes; macrovascular diabetic complications: no^R, yes. Analysis was performed using SPSS package.

RESULTS

Among 1580 type 2 diabetic patients screened in the study, 204 were diagnosed as having thyroid dysfunction with an overall 12.9% prevalence rate. Within patients with thyroid dysfunction, sick euthyroid state was diagnosed in 32 patients (15.7%). The most common dysfunction was subclinical hypothyroidism that was diagnosed in 92 patients (45.1%), followed by hypothyroidism in 41 patients (20.1%), subclinical hyperthyroidism in 27 patients (13.2%), and hyperthyroidism in 12 patients (5.9%) (Figure 1). Only 59 patients with thyroid dysfunction (28.9%) were diagnosed before conducting the study, whereas the majority of them (71.1%) were undiagnosed during the screening process. Also, 92 patients (45.1%) showed symptoms and signs of thyroid dysfunction, whereas in 54.9% of them the disease was silent. Within 65 patients with thyroid dysfunction anti TPO was investigated, 38 cases (58.5%) were positive.

A total of 204 type 2 diabetic patients with thyroid dysfunctions (cases) were compared with 204 type 2 diabetic patients free from thyroid dysfunctions (controls). Personal and clinical characteristics together with the results of unvariate analyses were presented in tables II and III. Regarding personal characteristics, statistically significant higher proportions of females, Kuwaiti nationality, smokers, and patients with personal history of autoimmune diseases were found in cases than in controls. No significant differences between cases and control could be detected regarding clinical variables

The results of the final analysis using multiple logistic regression are summarized in table IV. Gender, nationality, smoking, and history of autoimmune diseases were significantly associated with outcome of interest. Females patients with type 2 diabetes had an increased risk of thyroid dysfunction as compared with males (OR = 1.7, 95% CI: 1.2 – 2.9). Kuwaiti patients had more than double the risk as compared with non-Kuwaiti patients (OR = 2.3, 95% CI: 1.3 – 4.1). Ex-smokers and current smoker patients were more liable for thyroid dysfunctions (OR = 18.1, 95% CI: 10.1 – 32.5) and (OR = 7.8, 95% CI: 3.5 – 17.7) respectively. Patients with history of autoimmune disease had more than triple risk of thyroid dysfunction (OR = 3.8, 95% CI: 1.9 – 13.3).

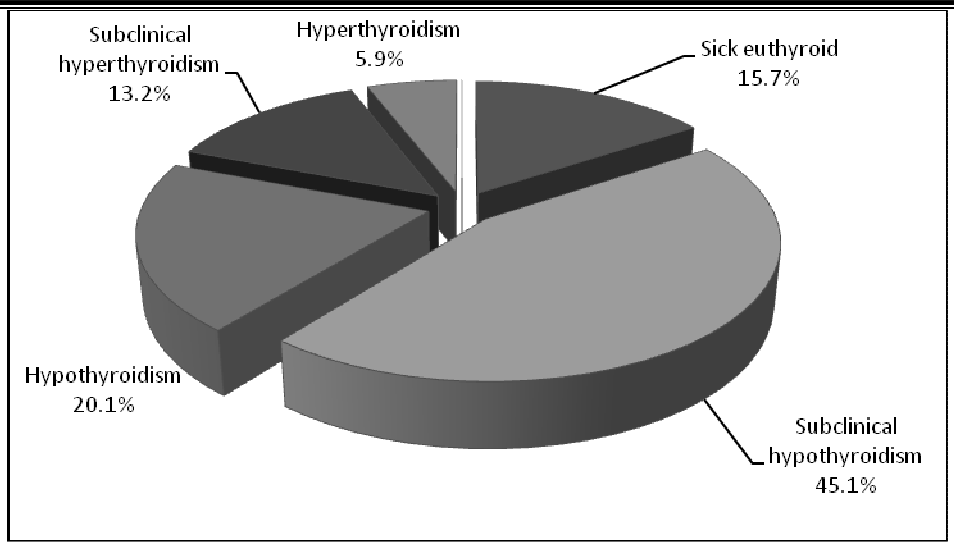

Fig 1: Types of thyroid dysfunctions diagnosed in type 2 diabetic patients

Table II: Personal characteristics of cases and controls

Variables	Thyroid dysfunction				Significance
	No (n = 204)		Yes (n = 204)		
	No.	%	No.	%	
Gender					
Male	102	*50.0*	67	*32.8*	$X^2 = 12.37$
Female	102	*50.0*	137	*67.2*	P < 0.001
Age (years)					
< 40 y	24	*11.8*	18	*8.8*	$X^2 = 1.42$
40 - 49	44	*21.6*	40	*19.6*	P = *0.70*
50 - 59	65	*31.9*	71	*34.8*	
≥ 60	61	*34.8*	75	*36.8*	
Nationality					
NK	81	*39.7*	42	*20.6*	X^2 = 17.70
K	123	*60.3*	162	*79.4*	P < 0.001
Smoking status					
Non smokers	123	*60.3*	24	*11.8*	X^2 =123.13
Ex smoker	48	*23.5*	154	*75.5*	P < 0.001
Current smokers	33	*16.2*	26	*12.7*	
Family history of thyroid disease					
No	168	*82.4*	165	*80.9*	$X^2 = 0.15$
Yes	36	*17.6*	39	*19.1*	P = *0.70*
Personal history of autoimmune disease					
No	200	*98.0*	189	*92.8*	X^2 = 6.68
Yes	4	*2.0*	15	*7.4*	P = 0.01
BMI					
< 25	32	*15.7*	23	*11.3*	X^2 = 4.56
25 -	73	*35.8*	61	*29.9*	P = 0.10
≥ 30	99	*48.5*	120	*58.8*	

Table III: Clinical characteristics of cases and controls

Variables	Thyroid dysfunction				Significance
	No (n = 204)		Yes (n = 204)		
	No.	%	No.	%	
Duration of DM (years)					
< 5	56	*27.5*	68	*33.3*	$X^2 = 3.70$
5 - 9	58	*28.4*	49	*24.0*	P = 0.27
10 - 14	44	*21.6*	34	*16.7*	
≥ 15y	46	*22.5*	53	*26.0*	
Treatment of DM					
Oral	114	*55.9*	100	*49.0*	X^2 = 3.96
Insulin	12	*5.9*	22	*10.8*	P = 0.14
Oral + insulin	78	*38.2*	82	*40.2*	
Glycemic state					
Good controlled	47	23.0	40	19.6	X^2 = 0.72
Poor controlled	157	*77.0*	164	*80.4*	P = 0.40
Hypertension					
No	74	36.3	57	27.9	X^2 = 3.25
Yes	130	63.7	147	72.1	P = 0.07
Dyslipidemia					
No	34	16.7	42	20.6	X^2 = 1.04
Yes	170	83.3	162	79.4	P = 0.31
Microvascular diabetic complications					
No	97	47.5	103	50.5	X^2 = 0.35
Yes	107	52.5	101	49.5	P = 0.55
Macrovascular diabetic complications					
No	152	74.5	146	71.6	X^2 = 0.45
Yes	52	25.5	58	28.4	P = 0.50

Table IV: Factors associated with thyroid dysfunction among type 2 diabetic patients, results of multivariate logistic regression analysis

Variables	OR	95% CI
Gender		
M [R]	1	
F	1.7	(1.2 - 2.9)
Nationality		
NK [R]	1	
K	2.3	(1.3 - 4.1)
Smoking		
Non smokers [R]	1	
Ex smoker	18.1	(10.1 - 32.5)
Current smokers	7.8	(3.5 - 17.7)
Personal history of autoimmune disease		
No [R]	1	
Yes	3.8	(1.2 - 14.1)

[R] = Reference category, OR = Odds ratio, CI = Confidence interval

DISCUSSION

There is inter-dependence between insulin and thyroid hormones for normal cellular metabolism so that diabetes mellitus and thyroid diseases can mutually influence the other disease process. When diabetes occurs in euthyroid individuals, it results in altered thyroid function tests with no clinical dysfunction. Thyroid diseases affect approximately 10–15% of patients with DM.[6,22,23] In the present study, the prevalence rate of thyroid dysfunction among type 2 diabetic patients attending the selected primary health care center was 12.9%. The above result are in agreement with previous studies showing an association between type 2 DM and thyroid dysfunction.[12-16] A study by Smithson et al.[15] showed a prevalence of 10.8% of thyroid dysfunction in diabetic patients registered in general practice. Another study by Perros et al.[7] in a randomly selected group of 1,310 diabetic adults estimated that the prevalence of thyroid dysfunction was found 13.4%. Also, a study in Jordan showed that the overall prevalence of thyroid dysfunction was 12.5% in type 2 DM patients.[24] A recent study, that was conducted in Saudi Arabia, reported a higher rate (16%) of thyroid dysfunction in Saudi type 2 DM patients.[25]

The present study revealed different grades of thyroid dysfunctions. This goes in accordance with reports of Suzuki et al.[26] and Smithson,[15] who in separate studies found altered thyroid hormone levels of different magnitudes (both low and high) in diabetic patients. The abnormal thyroid hormone levels may be the outcome of the various medications the diabetics were receiving.[27] These factors may explain the findings of low or high thyroid hormone levels in diabetic subjects.[28]

As reported in previous studies, we found that, subclinical hypothyroidism was the most common thyroid dysfunction (45.1%) followed by hypothyroidism (20.1%).[19,24] The thyroid hormones are insulin antagonists that also potentiate the action of insulin indirectly.[27] Thyroid hormones synthesis decreases in diabetes, and this could be responsible for the occurrence of low thyroid hormone levels in diabetics.[26]

Before the current study the majority of patients with thyroid dysfunction (71.1%) were undiagnosed. This suggests that thyroid function should be screened upon reception and then after bi-annually in diabetic patients to detect asymptomatic thyroid dysfunction that is increased in frequency a diabetic population.[21,24] The study revealed that 58.3% of the 72 thyroid dysfunction patients who did the anti-TPO test were positive. The presence of anti-thyroid peroxidase (TPO) antibodies is helpful in predicting the development of autoimmune thyroid disorders, especially hypothyroidism. Patients who have anti-TPO antibodies should be screened for thyroid dysfunction on a regular basis, so early detection and treatment is possible.[22]

Our data showed that several factors were significantly associated with thyroid dysfunction in type 2 diabetes, including gender, nationality, smoking, and autoimmune disease.

In our study, we reported a higher prevalence of thyroid dysfunction among diabetic females. It is well established that hypothyroidism is more common in diabetic females. In a study by Perros et al. the prevalence of thyroid dysfunction was 10.9% in females and 6.9% in males.[7] The NHANES III study reported that the prevalence of subclinical hypothyroidism was 3.4% in males and 5.8% in females.[29] In addition, a study in 420 adult females with type 2 DM randomly selected from participants in the community-based Fremantle Diabetes Study showed that the prevalence of subclinical hypothyroidism was 8.6%.[23] This finding is probably associated with the higher prevalence of obesity recorded in female diabetics.[30]

Personal history of autoimmune diseases were encountered in a significant higher proportion of cases than controls. This result goes in agreement with recent publications that confirm an increased incidence of autoimmune thyroid disease in type 2 DM.[18,19,22,25] The reason for increased incidence of autoimmune thyroid disease in type 2 DM is unknown. Possible mechanisms are genetic relationships between type 2 DM and thyroid disease. However infections and stress could be a trigger factors.[17,19]

In the current study, smokers and ex-smokers were more liable to cases. Smoking is associated with so many abnormalities of thyroid function. One component of tobacco smoke is cyanide, which is converted to thiocyanate, which inhibits iodide uptake and hormone synthesis. There are many other components of smoke that might have antithyroid action; decrease the binding of triiodothyronine to its receptors or its post-receptor actions in the liver, muscle, or other organs; or both.[31] It was reported that smoking/nicotine creates an artificially high metabolism that masks the fatigue/lethargy commonly seen in hypothyroidism. When the smoker quits, this masking is removed, and the full effects of hypothyroidism on the metabolism and thyroid are felt. And, for smokers with undiagnosed thyroid dysfunction, without proper thyroid hormone treatment, smoking cessation seems to double weight gain whammy, as they lose the appetite suppressant, metabolism-upping effects of nicotine, and experience the full effects of the hypothyroidism.[32]

Kuwaiti patients were more liable for thyroid dysfunction than non Kuwaiti, and this could be explained by the increased rates of marriage between

relatives in Kuwaiti population that increase the effect of genetic factor as a predictor of thyroid dysfunction.[22]

The associations observed in the current study regarding personal history of autoimmune, Kuwaiti nationality and smoking provide evidence for interactions between genetic and environmental / endogenous factors.[25,33]

We apologize some limitations in the present study. The generalization of our results was not confirmed as the survey was conducting in a single primary health care center. However the homogeneity of Kuwaiti population might decrease the effect of this limitation and the present work could be considered as a model for further larger study including the other centers. Another limitation of the study was its cross-sectional nature that create difficulties in ascertaining causality. However, our results are consistent with that from prospective studies. Results concerning smoking should be considered cautiously especially in females due to culture influence.

Conclusion

The prevalence of thyroid dysfunction among type 2 diabetic patients in Kuwait is common. Gender, Kuwaiti nationality, smoking and personal history of autoimmune diseases were associated with thyroid dysfunction. We recommend regular screening for thyroid abnormalities in all type 2 diabetic patients particularly in females with other autoimmune diseases.

REFERENCES

1. World Health Organization. Diabetes mellitus fact sheet no. 312. Geneva: WHO; 2006.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53.
3. Bando U, Ushiogi Y, Toya D, Tahaka N, Fujisawa M. Diabetic nephropathy accompanied by iodine induced non-autoimmune primary hypothyroidism: two cases report. Endocrinol J 1999; 46: 803-10.
4. Hilton CW, Mizuma H, Svec F, Prasad C. Relationship between plasma Clyco (His-Pro), a neuropeptide common to processed protein foods and C-peptide/insulin molar ratio in obese woman. Nutr Neurosci 2001; 4: 469-74.
5. Mayne PD. Carbohydrate metabolism. Clinical chemistry in diagnosis and treatment. 6TH edition. Glasgow, Barth: Colourbooks 1998: 195 -222.
6. Udiong CEJ, Udoh AE, Etukudoh M E. Evaluation of thyroid function in diabetes mellitus in Calabar, Nigeria. IJCB 2007; 22: 74-8.
7. Perros P, McCrimmon RJ, Shaw G. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabet Med 1995; 12: 622–7.
8. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA: The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 1977; 7: 481–93.
9. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC: The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526–34.
10. Sathish R, Mohan V. Diabetes and thyroid disease – A review. Int J Diabetes Dev Ctries 2003; 23: 120-3.
11. Wang SH, Sun ZL, Guo YJ, Wei Q, Yuan Y. Prevalence of subclinical hypothyroidism in older patients with diabetes mellitus with poorly controlled dyslipidemia in China. J Am Geriatr Soc 2009; 57: 1506-7
12. Feely J, Isles TE. Screening for thyroid dysfunction in diabetics. Br Med J 1979; 1: 1678.
13. Gray RS, Irvine WJ, Clarke BF. Screening for thyroid dysfunction in diabetics. Br Med J 1979; 2: 1439.
14. Ganotakis ES, Mandalaki K, Tampakaki M, Malliaraki N, Mandalakis E, Vrentzos G, Melissas J. Subclinical hypothyroidism and lipid abnormalities in older women attending a vascular disease prevention clinic: effect of thyroid replacement therapy. Angiology 2003; 54: 569-76.
15. Smithson MJ. Screening for thyroid dysfunction in a community population of diabetic patients. Diabet Med 1998; 15: 148-50.
16. Celani MF, Bonati ME, Stucci N. Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus. Diabetes Res 1994; 27: 15-25.
17. Vondra K, Zamrazil V. Thyroid diseases in patients with diabetes mellitus. DMEV 2002; 5: 72-84.
18. Krejci H, Perusicova J. Autoimmune thyropathies in patients with diabetes mellitus type 1 and type 2. DMEV 2004; 7: 164.
19. Vondra K, Vrbikova J, Dvorakova K. Thyroid gland diseases in adult patients with diabetes mellitus. Minerva Endocrinol 2005; 30: 217-36.
20. American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines. American Association of Clinical Endocrinologists protocol for Clinical Practice Guidelines. Endocr Pract 2004; 10: 353-61.
21. Pasupathi P, Bakthavathsalam G, Saravana G, Sundarmoorthi R.Screening for thyroid dysfunction in the diabetic/non-diabetic population. Thyroid Science 2008; 3: CLS 1-6.
22. Schroner Z, Lazurova I, Petrovicova J. Autoimmune thyroid disease in patients with diabetes mellitus. Bratisl Lek Listy 2008; 109: 125-9.
23. Chubb SA, Davis WA, Inman Z, Davis TM.

Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the Fremantle Diabetes Study. Clin Endocrinol (Oxf) 2005; 62: 480-6.

24. Radaideh AR, Nusier MK, Amari FL, Bateiha AE, El- Khateeb MS, Naser AS, Ajlouni KM. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. Saudi Med J 2004; 25: 1046-50.
25. Akbar DH, Ahmed MM, Al-Mughales J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. Acta Diabetol 2006; 43: 14-8.
26. Suzuki J, Nanno M, Gemma R, Tanaka I, Taminato T, Yoshimi T: The mechanism of thyroid hormone abnormalities in patients with diabetes mellitus. Nippon Niabunpi Gakki Zasshi 1994; 7: 465-70. (abstract)
27. Johnson JL, Duick DS. Diabetes and thyroid disease: A likely combination. Diabetes Spectrum 2002; 15: 140-2.
28. Bagchi N, Palaniswami N, Desai H, Felicetta J, Brown TR: Decreased thyroidal response to thyrotropin in type II diabetes mellitus. Metabolism 1988; 37: 669-71.
29. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. 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: 489-99.
30. Khandekar S. Therapy related weight gain among non-insulin dependent diabetics in Saudi Arabia. Pract Diabetes Digest 1991; 2: 84-6.
31. Manji N, Carr-Smith JD, Boelaert K, Allahabadia A, Armitage M, Chatterjee VK, Lazarus JH, Pearce SH, Vaidya B, Gough SC, Franklyn JA. Influences of age, gender, smoking, and family history on autoimmune thyroid disease phenotype. J Clin Endocrinol Metab 2006; 91: 4873-80.
32. Utiger RD. Cigarette smoking and the thyroid. N Engl J Med 1995; 333: 1001-2.
33. Vestergaard P. Smoking and thyroid disorders--a meta-analysis. Eur J Endocrinol 2002;146:153-61.