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RESEARCH ARTICLE

Evaluation of Thyroid Profile in Ghanaian Patients with Type 2 Diabetes

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Abstract

Introduction: Type 2 diabetic patients show thyroid disorders that may aggravate the metabolic imbalance. This study evaluated the prevalence of thyroid dysfunction in type 2 diabetic patients and the effect of altered hormones level on clinical and biochemical outcomes.

Method: Type 2 diabetic patients (60) were age-matched with 58 non-diabetic controls. Thyroid stimulating hormone (TSH), free triidothyronine (FT3) and free thyroxine (FT4) were measured. Serum lipid profile, fasting plasma glucose and clinical parameters were also measured. Two-hour oral glucose tolerance test was performed for the controls.

Results: The levels of TSH and FT3 were significantly lower in diabetic patients than in controls ($p < 0.01$). Mean difference of FT4 levels was not significant ($p > 0.05$). Prevalence of thyroid disorder in diabetic patients was 10.1% (1.7% hypothyroidism and 8.4% hyperthyroidism) while 5.1% of hypothyroidism was found in the non-diabetic controls. The mean duration of diabetes was 9.23 years. Body mass index (BMI), waist-to-hip ratio (WHR), diastolic (DBP) and systolic (SBP) blood pressure between the groups were not statistically significant ($p > 0.05$). The plasma glucose levels and serum lipids exception of high density lipoprotein were significantly raised in the type 2 diabetic patients than controls ($p < 0.05$).

Conclusion: Prevalence of thyroid dysfunction in the studied type 2 diabetic patients was 10.1%. Prevalence of hypothyroidism and hyperthyroidism were 1.7%and 8.4% respectively. Sub-clinical hyperthyroidism was the most common disorder and was higher in females.

Introduction

Diabetes mellitus (DM) is increasingly becoming a major health problem affecting numerous populations worldwide. It is characterized by impaired insulin-mediated glucose disposal as a result of absence of insulin, or the inability of the human body to respond to insulin present (Alberti *et al*., 1998). WHO estimation of global diabetes prevalence for all age groups was 2.8% in 2000, and is expected to rise to 4.4% by 2030 (Wild *et al*., 2004). The incidence of type 2 diabetes mellitus is increasing worldwide, including developing countries like Ghana due to an increase in sedentary lifestyles, urbanization, obesity as well as a shift in dietary habits (Wild *et al*., 2004; Tuomilehto *et al*., 2001). Consequently, the likely expectation is that these new trends may lead to increased incidence of type 2 diabetes. The first reports showing the association between diabetes and thyroid dysfunction were published in 1979 (Feely and Isles, 1979; Gray *et al.,* 1979). Since then studies in different countries have tried to estimate the prevalence of thyroid dysfunction among diabetic patients (Feely and Isles, 1979; Gray *et al.*,

1979; Perros *et al.*, 1995; Celani *et al.*, 1994). The co-existence of both type 2 diabetes and thyroid dysfunction may have an influence on diabetic management. Though the benefits of treating evident thyroid dysfunction are apparent, the management of sub-clinical thyroid dysfunction is unclear and conclusive intervention studies are required. Thyroid dysfunction, comprising hypothyroidism and hyperthyroidism represents what can be described as an altered thyroid profile. This manifests as deviation from normal, in the levels of thyroid stimulating hormone (TSH), free thyroxine (FT4) and free tri-iodothyronine (FT3). Studies have shown reduced TSH levels, in combination with either elevated FT3, FT4 or lowered FT3, FT4 levels in thyroid dysfunction (Roos *et al.*, 2007). Thyroid hormones exert both insulin agonistic and antagonistic actions in different organs, which occurs in a fine balance necessary for normal glucose metabolism (Brenta, 2011). An overload or deficiency of thyroid hormones can alter this balance, and lead to alterations in carbohydrate metabolism. New pathways implicating the involvement of thyroid hormones in glucose homeostasis have been uncovered. These novel findings include stimulation of hepatic glucose production by thyroid hormones, acting through a sympathetic pathway from the hypothalamus (Klieverik *et al.* 2009), and the discovery of transcriptional regulators of metabolic and mitochondrial genes which, if influenced by intracellular T3 levels, may contribute to the development of insulin resistance (Crunkhorn & Patti, 2008). Whilst the therapeutic impact of normalizing thyroid profile (hypothyroidism and hyperthyroidism) is not in doubt, the information available about the benefit of treating sub-clinical thyroid disease which is not overt in diabetes remains insufficient. There is scanty information on thyroid dysfunction in patients with type 2 diabetes, and much less data is available on the thyroid status of Ghanaian patients with type 2 diabetes. A number of studies have provided sufficient evidence indicating a contribution of thyroid hormones to type 2 diabetes. (Celani *et al.*, 1994; Udong *et al.*, 2007). The aim of this study was therefore to assess the level of thyroid dysfunction in Ghanaian type 2 diabetic patients attending clinic at National Diabetes Management and Research Centre at Korle Bu Teaching Hospital.

Methodology

Study Design

This was a cross-sectional study that involved 60 diagnosed type 2 diabetic patients who reported for treatment at the outpatient unit of National Diabetes Management and Research Centre, Korle Bu Teaching Hospital. They were age-matched with 58 apparent healthy control individuals. Patients were made to understand that opting out from the study would not affect their routine medical care. Participants consented by endorsing a written consent form before samples were collected. Demographic data including age, sex, duration of diabetes, weight, height and waist-hip ratio were collected using standard questionnaire at recruitment. Blood pressure (BP) was measured by first allowing the participant to rest for 15 minutes prior to measurement. The study was approved by the Ethical and Protocol Review Committee of School of Allied Health Sciences, University of Ghana.

Blood sample collection and laboratory procedure

Fasting venous blood (5ml) collected was divided into fluoride and plain tubes. Samples in plain tubes were processed for total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and the thyroid hormone profile (TSH, FT3 and FT4). Samples in fluoride tubes were used for fasting plasma glucose. Fasting plasma glucose, TC, TG, were assayed using kits purchased from Centronic GMbH (Kleinfeld, Germany). HDL-C was determined using kit from Biosystems (Barcelona, Spain). LDL-C, VLDL-C and cardiovascular risk (CVR) were calculated. All tests were carried out using the respective protocols of the manufacturers. Vital Scientific Microlab 300M (VSM 300) automated analyser was used to determine serum lipid and plasma glucose levels. The thyroid profile was determined by enzyme-linked immunosorbent assay (ELISA), (Human, Germany) and Labsystems Multiscan-352 plate reader (Finland).

Statistical Analysis

Descriptive statistics (mean ± standard deviation) was used to summarize all quantitative variables. Student *t*-test was used to test for the mean difference between the two groups and test for proportions was used for categorical data. Graph pad 3.0 was used for t-test analysis and $p < 0.05$ was considered statistically significant for all analyses.

Results

Table 1 shows the comparison of demographic and clinical parameters of the studied populations. Sex distribution showed lower percentage of males among the patients (35%) than controls (50%) ($p < 0.0159$). The mean age

difference between the diabetic patients (52.42 ± 11.57) and the apparently healthy controls (51.21 ± 12.06) was not statistically significant ($p > 0.05$; 95% CI = -3.099 - 5.519). Body mass index and waist-to-hip ratio showed no significant difference between the patients and controls ($p > 0.05$). The mean differences of both systolic blood ($p > 0.05$; 95% CI = -1.025 - 14.705) and diastolic blood pressures ($p > 0.05$; 95% CI = -1.815 - 7.635) were not statistically significant. The mean duration of diabetes was 9.23 years.

Biochemical parameters of the diabetic patients compared with controls is shown in Table 2. The mean 2Hr OGTT in the non-diabetics was 6.11mmol/l. FPG ($p < 0.001$; 95% CI = 3.481 - 5.979), TC ($p < 0.05$; 95% CI =1.247 - 2.453), TG ($p < 0.001$; 95% CI = 0.199 - 0.582), LDL-C ($p< 0.05$; 95% CI= 0.027 - 1.153) and VLDL-C ($p < 0.01$; 95% CI = 0.093 - 0.268) were significantly elevated in the diabetic patients than the controls with increased risk of cardiovascular disease ($p < 0.01$; 95% CI= 0.814 - 2.406). The mean difference of HDL-C between the diabetic patients and the control group was not significant ($p > 0.05$; 95% CI = -0.119 - 0.079).

Comparison of thyroid hormone levels between type 2 diabetic patients and healthy controls is shown in Table 3. In the diabetic patients, TSH ($p < 0.01$; 95% CI = -1.172-(-0.247) and FT3 ($p < 0.001$; 95% CI = -1.011-(-0.429) were significantly reduced as compared to the apparently healthy controls. The ratio FT3/FT4 was significantly lower in the patients than in controls ($p < 0.001$; 95% CI = -1.078-(-0.502). The mean difference of FT4 level between diabetic patients and controls was not statistically significant ($p > 0.05$; 95% CI = -0.128 - 0.068).

Thyroid disorder pattern according to gender in the studied population is shown in table 4. Among the diabetic patients, prevalence of thyroid dysfunction was 10.1% (1.7% hypothyroidism and 8.4% hyperthyroidism) as against 5.1% hypothyroidism in the apparent healthy non-diabetic controls. Thyroid dysfunction in female patients (66.7%) was higher than male counterparts (33.3%).

Table 1 Demographic and clinical parameters of the studied population

Parameter	Type 2 Diabetic Patients (N= 60)	Non-Diabetic Control (N = 58)	95% CI of Mean Difference	p-value
Sex: n (%) Male	21 (35)	29 (50)	-2.412[§]	0.0159[ŧ]
Female	39 (65)	29 (50)	0.752[§]	0.4521[ŧ]
Age (years)	52.42 ± 11.57	51.21 ± 12.06	-3.099 - 5.519	0.5791
BMI (Kg/m^2)	28.13 ± 6.68	28.11 ± 8.21	-2.705 - 2.745	0.9884
WHR	1.10 ± 0.23	1.13 ± 0.24	-0.116 - 0.056	0.4895
SBP (mmHg)	128.54 ± 20.83	121.70 ± 22.30	-1.025 - 14.705	0.0876
DBP (mmHg)	74.03 ± 10.07	71.12 ± 15.38	-1.815 - 7.635	0.2250
DD (years)	9.23 ± 6.73	-	-	-

n = number of subjects. , BMI = Body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, DD= Duration of diabetes, WHR = waist –to-hip ratio, Categorical values were presented as n (%), § and ŧ is for Z-score and p-value respectively.

Table 2 Biochemical parameters of the studied population

Parameter	Type 2 Diabetic Patients (N= 60)	Non-Diabetic Control (N = 58)	95% CI of mean	p-value (t-test)
2 Hr OGTT (mmol/l)	-	6.11 ± 1.08	-	-
FPG (mmol/l)	9.85 ± 4.76	5.12 ± 0.65	3.481 - 5.979	0.0001*
TC (mmol/l)	6.03 ± 2.00	4.81 ± 1.19	1.247 - 2.453	0.0001*
TG (mmol/l)	1.44 ± 0.53	1.05 ± 0.52	0.199 - 0.582	0.0001*
HDL-C (mmol/l)	1.21 ± 0.38	1.25 ± 0.23	-0.155 - 0.075	0.4923
LDL-C (mmol/l)	3.65 ± 1.88	3.06 ± 1.09	0.027 - 1.153	0.0401*
VLDL-C	0.66 ± 0.24	0.48 ± 0.24	0.093 - 0.268	0.0001*
CVR	5.53 ± 2.91	3.92 ± 0.96	0.814 - 2.406	0.0001*

n = number of subjects. FPG = fasting plasma glucose, TC = total cholesterol, TG = triglyceride, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, VLDL-C =.Very low density lipoprotein and CVR (TC/HDL-C) = cardiovascular risk. 2Hr OG = Two-hour Oral Glucose Tolerance Test. Values are presented as mean ± standard deviation.

Table 3. Comparison of thyroid hormone levels between type 2 diabetic patients and controls

Parameter	Type 2 Diabetic Patients (N= 60)	Non-Diabetic Control (N = 58)	95% CI of mean Diff	p-value (t-test)
TSH (mIU/ml)	1.53 ± 1.16	2.24 ± 1.37	-1.172-(-0.247)	0.0029*
FT3 (pg/dL)	1.36 ± 1.01	2.08 ± 0.49	-1.011-(-0.429)	0.0001*
FT4 (ng/dL)	1.05 ± 0.29	1.08 ± 0.25	-0.128 - 0.068	0.5490
FT3/FT4 Ratio	1.27 ± 0.81	2.06 ± 0.77	-1.078-(-0.502)	0.0001*

Values presented as mean ± standard deviation. Thyroid stimulating hormone (TSH), free thyroxine (FT4) and free tri-iodothyronine (FT3)

Table 4 Thyroid disorders in the studied population

Group / Thyroid disorder		Gender	Type 2 Diabetic patients (N = 60)	Non-Diabetic Control (N = 58)
Sub-clinical hypothyroidism	n (%)	Male	1 (1.7)	1 (1.7)
		Female	0 (0.0)	2 (3.4)
Primary hypothyroidism	n (%)	Male	0(0.0)	0 (0.0)
		Female	0 (0.0)	0 (0.0)
Sub-clinical hyperthyroidism	n (%)	Male	1 (1.7)	0 (0.0)
		Female	4 (6.7)	0 (0.0)
Primary hyperthyroidism	n (%)	Male	0 (0.0)	0 (0.0)
		Female	0 (0.0)	0 (0.0)

TSH normal range: 0.3 – 4.0mIU/ml, FT3 normal range: 1.4 – 4.2pg/ml, FT4 normal range: 0.8 – 2.0ng/dl

Subclinical Hypothyroidism: when TSH is more than 5.5 mIU/ml, FT3 and FT4 within normal range.

Primary Hypothyroidism: when TSH more than 5.5mIU/ml, FT3 and FT4 less than normal.

Subclinical Hyperthyroidism: when TSH is less than 0.3 mIU/ml, FT3 and FT4 within normal range.

Primary Hyperthyroidism: when TSH is less than 0.3mIU/ml, FT3 and FT4 more than normal.

Discussion

Thyroid disorders are among the most prevalent medical conditions and its association with diabetes has long been established (Feely and Isles, 1979; Gray *et al.,* 1979). There have been variations in the reports regarding thyroid profile in type 2 diabetic patients. Recent investigations reported high TSH and low thyroid hormones in diabetic patients (Vikram *et al.,* 2013; Singh *et al.,* 2011). Bharat *et al.* (2013), also reported low TSH, high T4 and unchanged T3 levels in diabetic patients compared with non-diabetics. In another study, low TSH, high T3 and non-significant change in T4 levels were reported in type 2 diabetics without complications (Rai *et al.,* 2013). Separate studies also found both high and low levels of thyroid hormones in diabetic patients (Suzuki *et al.,* 1994; Smithson *et al.,* 1998).

The current study showed reduced TSH, FT3 and unchanged FT4 levels in Ghanaian diabetic patients compared to non-diabetic controls. Several attempts have been made to explain the disparity in thyroid dysfunction in type 2 diabetics but information is scanty. Changes in the level of TSH has been attributed to modification of the synthesis and release of thyroid releasing hormone (TRH) (De-Greef *et al.,* 1992). Another possible explanation for thyroid dysfunction in diabetics is the production of thyroid hormone binding inhibitor (THBI) which inactivates 5'-deiodinase, an enzyme responsible for the conversion of T4 to T3 (Suzuki *et al.,* 1994). An important factor suggested to influence the synthesis and release of TRH is glycemic status of patients (Reusch *et al.,* 1999). TRH and TSH are responsible for the production and maintenance of circulating thyroid hormones which regulate glucose homeostasis.

Hormonal imbalance may greatly affect mechanisms that control plasma glucose. Modification of circulating insulin levels, intestinal absorption, hepatic production and peripheral tissues uptake of glucose were reported regulatory mechanisms affected by thyroid hormones (Reismann and Somogyi, 2011). Thyroid hormone levels inversely affect the action of insulin, critical for plasma glucose clearance. Effect of thyroid hormones on target cells under normal conditions, is different from the diabetic state. In euthyroidsm, GLUT-4 and phosphoglycerate kinase genes are upregulated to enhance glucose transport and glycolysis respectively. These processes complement insulin action to facilitate glucose utilization by peripheral tissues (Viguerie *et al.,* 2002).

Study revealed that hyperthyroidism increases hepatic endogenous glucose output and decreases hepatic insulin sensitivity (Beylot, 1996). This is explained by the thyroid hormone effect on gene transcription. These include elevated GLUT-2 glucose transporters in the liver plasma membrane, ensuring glucose efflux (Weinberg and Utter, 1979; Mokuno et *al*., 1999) together with increased lipolysis (Saunders *et al.,* 1980) and increased sympathetic action controlled by the hypothalamus (Klieverik *et al.,* 2009). Under such condition, insulin receptors were reported to decrease in isolated adipocytes (Arner *et al.,* 1984). Hyperglycemic associated hypothyroidism is linked to the decreased disposal of plasma glucose (Maratou *et al.,* 2009). The above may explain the association between impaired insulin-induced hyperglycemia in type 2 diabetics and either hyperthyroidism or hypothyroidism (Dimitriadis *et al.,* 2006a; 2006b; Feely and Isles, 1979; Gray *et al.,* 1979).

In the current study, 10.1% of the patients showed abnormal thyroid function as against 5.1% of non-diabetic apparent healthy individuals. Among the patients, thyroid dysfunction was higher in the females than counterpart males. Prevalence of hypothyroidism in the diabetic patients was 1.7%. Similar study has showed 16.3% subclinical hypothyroidism, 11.4% hypothyroidism, 2.0% subclinical hyperthyroidism and 1.5% hyperthyroidism (Demitrost and Ranabir, 2012). Other reports estimated prevalence of thyroid dysfunction among type 2 diabetics to vary between 2.2% to 17% (Smithson, 1998; Perros *et al*., 1995). Separate population studies reported prevalence of thyroid dysfunction as 31.0% and 46.5% (Udong *et al.,* 2007; Celani *et al.,* 1994) respectively. In another study, prevalence of hyperthyroidism was found to be 6.25% in type 2 diabetic patients (Singh *et al.,* 2011). The variation in the pattern of thyroidism in diabetics is said to be influenced by the various medications administered to patients. Oral hypoglycemic agents such as phenylthiourea are found to increased TSH and suppress FT4 and T4 levels (Whitley, 1984).

Metabolic imbalance in diabetic patients with thyroid dysfunction irrespective of hormonal profile type have been reported. High levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL) and low level of high density lipoprotein cholesterol (HDL-C) have been reported in patients showing various thyroid hormones abnormalities (Singh *et al.,* 2011; Zhu and Chang, 2010). The lipid profile parameters of type 2 diabetics in this study were in agreement with the previous studies except HDL-C (Singh *et al.,* 2011; Zhu and Chang, 2010; Sawant *et al.,* 2008). Patients were also found to have high plasma fasting glucose as compared to the control group. A study showed a negative association between FT3/FT4 ratio and impaired glucose tolerance (Jing *et al.,* 2013). This study showed low FT3/FT4 ratio in type 2 diabetic patients together with higher cardiovascular risk than non-diabetic control. Decreased FT3/FT4 ratio was

found to correlate with high mortality in patients with right ventricular enlargement and advanced diastolic dysfunction (Kozdag *et al.,* 2005). On the contrary, the clinical indices of the studied population showed no significant difference between the type 2 diabetics and controls. Increased metabolic abnormalities reported in this present study support earlier findings that changes in thyroid profile in diabetic individuals alter metabolism (Larsen, 2003; Erem *et al.,* 1999).

Conclusion

This study reports for the first time the prevalence (10.1%) of thyroid dysfunction in Ghanaian type 2 diabetic patients. Prevalence of hypothyroidism and hyperthyroidism were 1.7%and 8.4% respectively. Routine assay of thyroid hormones in type 2 diabetics will provide useful information for diabetes management.

Limitations of study

Clinical history on thyroid dysfunction and medications of patients were not considered in the study.

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References

Alberti, K. G. and Zimmetmm, P. Z. (1998): Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet. Med. J., 15: 539-553.

Arner, P., Bolinder, J., Wennlund, A. andOstman, J. (1984): Influence of thyroid hormone level on insulin action in human adipose tissue. Diabetes, 33(4):369-75.

Bharat, H. D., Gangte, D., Lalnunpui, P., Devi, I. and Singh, G.W. (2013): Thyroid Status in Diabetes Mellitus. J Glycomics Lipidomics, 3:1.

Brenta, G. (2011): Why can insulin resistance be a natural consequence of thyroid dysfunction? Journal of Thyroid Research, 2011: 1-9.

Beylot, M. (1996): "Regulation of in vivo ketogenesis: role of free fatty acids and control by epinephrine, thyroid hormones, insulin and glucagon," Diabetes and Metabolism, 22(5); 299–304.

Celani, M. F., Bonati, M. E. and Stucci, N. (1994): Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus. Diabetes Res., 27(1): 15–25.

Crunkhorn, S. and Patti, M. E. (2008): Links between thyroid hormone action, oxidative metabolism, and diabetes risk. Thyroid, 18(2): 227–237.

De-Greef, W. J., Rondeel, J. M., Van-Haasteren, G. A., Klootwij, K. W. and Visser, T. J. (1992): Regulation of TRH production and release in rats. Acta Medica Austriaca, 19(1): 77-79.

Demitrost, L. and Ranabir, S. (2012): Thyroid dysfunction in type 2 diabetes mellitus: A retrospective study. Indian J Endocrinol Metab, 16 (2): S334–S335,

Dimitriadis, G., Mitrou, P., Lambadiari, V. et al., (2006a): Insulin action in adipose tissue and muscle in hypothyroidism. Journal of Clinical Endocrinology and Metabolism, 91: 4930–4937.

Dimitriadis, G., Mitrou, P., Lambadiari, V. et al., (2006b): Glucose and lipid fluxes in the adipose tissue after meal ingestion in hyperthyroidism. Journal of Clinical Endocrinology and Metabolism, 91:1112–1118.

Feely, J. and Isles, T. E. (1979): Screening for thyroid dysfunction in diabetics. Br. Med. J., 1 (6179): 1678.

Gray, R. S., Irvine, W. J. and Clarke, B. F. (1979): Screening for thyroid dysfunction in diabetics. Br Med J., 2(6202):1439.

Jing, S., Xiaoying, D., Ying, X., Rui, L., Mingyu, G., Yuting, C., Yanhua, Y., Yufan, W., Haiyan, S. and Yongde, P. (2013): Different levels of thyroid hormones between impaired fasting glucose and impaired glucose tolerance: free T3 affects the prevalence of impaired fasting glucose and impaired glucose tolerance in opposite ways. Clin Endocrinol, doi: 10.1111/cen.12384.

Klieverik, L. P., Janssen, S. F. and Van, R, et al., (2009): Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. PNAS, 106 (14): 5966–5971.

Kozdag, G., Ural, D., Vural, A., Agacdiken, A., Kahraman, G., Tayfun, S. T., Ural, E. and Komsuoglu, B. (2005). Relation between free triiodothyronine/free thyroxine ratio, echocardiographic parameters and mortality in dilated cardiomyopathy. The European Journal of Heart Failure, 7:113–118.

Maratou, E., Hadjidakis, D. J., Kollias, A., et al., (2009): Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. European Journal of Endocrinology, 160: 785-790.

Mokuno, T., Uchimura, K., Hayashi, R., et al., (1999): "Glucose trans- porter 2 concentrations in hyper- and hypothyroid rat livers," Journal of Endocrinology, 160(2); 285–289.

Perros, P., McCrimmon, R. J., Shaw, G. and Frier, B. M. (1995. Frequency of thyroid dysfunction in diabetic patients: Value of annual screening. Diabet. Med., 12(7): 622–627.

Rai, S., AShoK, K. J., PraJna, K., Shetty, S. K., Rai, T., Shrinidhi, Begum. M, ShaShiKala (2013). Thyroid Function In Type 2 Diabetes Mellitus and in Diabetic Nephropathy. Journal of Clinical and Diagnostic Research. 7(8): 1583-1585.

Reismann, P. and Somogyi, A. (2011): Diabetes and thyroid disorders. OrvosiHetilap, 152, 516–519

Reusch, C.E. and Tomsa, K. (1999): Serum fructosamine concentration in cats with overt hyperthyroidism. J American Vet Med Asso. 215(9): 1297-330.

Roos, A., Bakker, S. J. L., Links, T. P, Gans, R. O. B., and Wolffenbuttel, B. H. R. (2007): Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J. Clin. Endocrinol. Metab., 92:491-496.

Saunders, J., Hall, S. E. H. and Sonksen, P. H. (1980): "Glucose and free fatty acid turnover in thyrotoxicosis and hypothyroidism, before and after treatment," Clinical Endocrinology, 13(1); 33–44.

Sawant, A.M., Shetty, D., Mankeshwar, R. and Ashavaid, T .F. (2008): Prevalence of Dyslipidemia in Young Adult Indian Population. JAPI .56. 99-102.

Singh, G., Gupta, V., Sharma, A. K. and Gupta, N. (2011): Evaluation of Thyroid Dysfunction Among type 2 diabetic Punjabi Population. Adv. Biores., 2(2):3-9.

Smithson, M. J. (1998): Screening for thyroid dysfunction in a community population of diabetic patients. Diabetes Med., 15(2); 148-150.

Suzuki, J., Nanno, M., Gemma, R., Tanaka, I., Tamainato, T. and Yoshimi, T. (1994): The mechanism of thyroid hormone abnormalities in patients with diabetes mellitus. Nippon Niabunpigakki. Zasshi, 7:465-470.

Tunbridge, W. M. G., Evered, D. C., Hall, R., Appleton, D., Brewis, M., Clarke, F., Evans, J. G., Young, E., Bird, T., and Smith, P. A. (1977): The spectrum of thyroid disease in a community: The Whickham survey. Clin. Endocrinol., 7 (6): 481–493.

Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., and Uusitupa, M. (2001): Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N. Engl. J. Med., 344(18): 1343-1350.

Udong, C. E. J. A., Udoh, E., and Etukudoh, M. E. (2007): Evaluation of thyroid dysfunction in diabetes mellitus in Calabar, Nigeria. Ind. J. Clin. Biochem., 22: 74-78.

Viguerie, N., Millet, L., Avizou, S., et al., (200): Regulation of human adipocyte gene expression by thyroid hormone. J Clin. Met., 87; 630-634.

Vikram, B. V., Shubhangi, A. K., Krunal, K. T., Anu, N. G, Meenakshi, K. andRajani, R. (2013): Thyroid dysfunction in patients with type 2 diabetes mellitus at tertiary care centre. National Journal of Medical Research., 3(4); 377-380.

Weinstein, S.P., O'Boyle, E., Fisher, M. and Haber, R.S. (1994): Regulation of GLUT2 glucose transporter expression in liver by thyroid hormone: evidence for hormonal regulation of the hepatic glucose transport system. Endocrinology, 135, 649–654.

Whitley, R. J. (1984): Thyroid functions. In Brurtis C, Ashwood AR editors. Teitz text book of Clinical Chemistry, 3rd Edition.Philadelphia: Saunders and Company pp. 1496-1529.

Wild, S., Roglic, G., Sicree, R., and King, H. (2004): Global prevalence of Diabetes estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053.