Research Article

Clinical Impact of Thyroid Dysfunction in Patients with Diabetes Mellitus

Pravin V Ingle[1]*, Hetalben A Patel[1], PN. Dighore[2] and PH. Patil[1]

[1]Department of Clinical Pharmacy, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur-425 405, Dist: Dhule, Maharashtra, India.
[2]General Physicians, Indira Gandhi Memorial Hospital, Shirpur-425 405, Dist: Dhule, Maharashtra, India.

ABSTRACT

Patients with diabetes mellitus are at increased risk of thyroid disease. The frequency of thyroid dysfunction in diabetic patients is higher than that of the general population and diabetes ultimately develop thyroid dysfunction .Unrecognised thyroid dysfunction may impair metabolic control and add to cardiovascular disease risk in diabetic patients. Our aims were to review the current literature on the association between thyroid dysfunction and diabetes mellitus. The effects of thyroid hormones on various metabolic processes are now better understood. Uncontrolled hyperthyroidism in diabetic patients may trigger hyperglycaemic emergencies while recurrent hypoglycaemic episodes have been reported in diabetic patients with hypothyroidism. Furthermore, thyroid dysfunction may amplify cardiovascular disease risk in diabetic patients through interrelationships with dyslipidemia, insulin resistance and vascular endothelial dysfunction. However, the significance of subclinical degrees of thyroid dysfunction remains to be clarified. While these developments have implications for diabetic patients a consensus is yet to be reached on optimal thyroid screening strategies in diabetes management. The increased frequency of thyroid dysfunction in diabetic patients and its likely deleterious effects on cardiovascular and metabolic functions calls for a systematic approach to thyroid disease screening in diabetes. Routine annual thyroid testing should be targeted at diabetic patients at risk of thyroid dysfunction.

Keywords: Diabetes mellitus, thyroid dysfunction, hypothyroidism, hyperthyroidism.

INTRODUCTION

Diabetes is the most common endocrinal disorder seen in clinical practice. The WHO estimate of diabetes prevalence for all age groups worldwide was 2.8% in 2000 and 4.4% in 2030. The total no. of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030[1]. Factors such as sedentary lifestyle, dietary modifications, ethnicity, hypertension and obesity have led to a dramatic increase in the incidence of diabetes mellitus, especially in the 21st century[2]. The disease has tremendous impact on the quality of life, and morbidity and mortality occur due to complications that affect the small vessels resulting in retinopathy, nephropathy, neuropathy and large vessels resulting in ischemic heart disease and stroke. It is generally believed that both thyroid disorders and diabetes mellitus are common in elder people. Thyroid disorders such as goitre, nodules, and autoimmune thyroid disease and thyroid dysfunction have rarely been investigated in diabetic patients. A number of symptoms and signs are well-established manifestations of thyroid dysfunction. Additional findings in patients, personal and family histories indicate increase risk of developing thyroid dysfunction; diabetes mellitus represent risk factor of developing thyroid dysfunction[3]**.** The prevalence of thyroid dysfunctions in diabetes mellitus population has not received sufficient attention yet. Currently, there are no data on the relation between diabetes mellitus and thyroid dysfunction there is a lack of data concerning this problem. For all these reasons we reviewed thyroid dysfunction and lipid abnormalities among diabetic patients. The analysis of serum lipids has become an important health measurement. Abnormalities of plasma lipids and lipoproteins have been documented in untreated and treated diabetic population by different groups. The hyperlipidemia and the hyperlipoproteinemias have been implicated as risk factors in diabetic population[4]. Hence knowledge of the various aspects of the lipid profile and the significance

of each of the parameters is vital and is essential part of management of coronary heart disease (CHD) and people at risk of CHD[5].

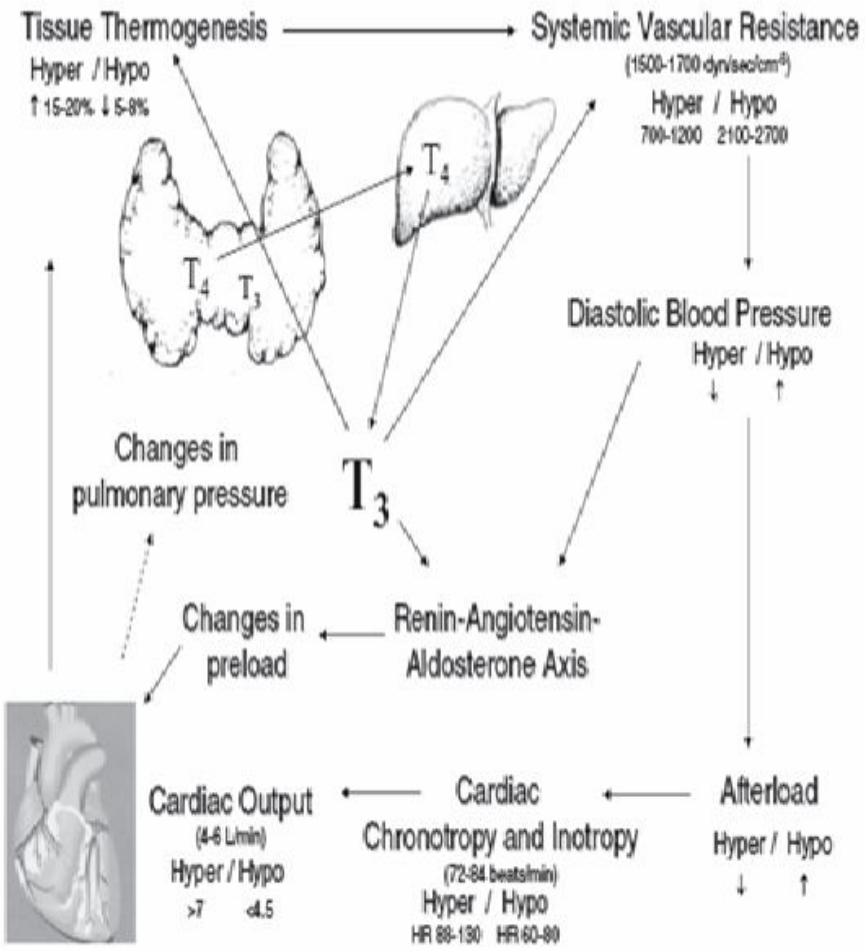

Fig. 1: Effects of thyroid hormone on cardiovascular hemodynamic[6]

Table 1: Changes in Cardiovascular function associated with thyroid disease

Measure	Normal Ranges	Values in Hyperthyroidism	Values in hypothyroidism
Systemic Vascular resistance (dyn.sec.cm-^{5})	1500-1700	700-1200	2100-2700
Heart Rate (beats/min)	72-84	88-130	60-80
Ejection Fraction (%)	50-60	>60	≤60
Cardiac output (liters/min)	4-6	>7.0	<4.5
Isovolumic relaxation Time (msec)	60-80	25-40	>80
Blood Volume (% of normal Value)	100	105.5	84.5

This review suggests that thyroid function should be screened annually in diabetic patients to detect asymptomatic thyroid dysfunction which is increased in frequency in diabetic patient, since progression from subclinical disease to clinical disease has been observed in longitudinal studies.

Prevalence of Thyroid Disorders in the General Population and in Diabetic Patients

Thyroid dysfunction and diabetes mellitus are the two most common endocrine disorders encountered in clinical Practice. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported. On one hand, thyroid hormones contribute to the regulation of carbohydrates metabolism and pancreatic function and on the other hand, diabetes affects thyroid function tests to variable extents[7, 8].

The diagnosis of thyroid dysfunction in diabetic patients based solely on clinical 8manifestation can be difficult. Underlying thyroid disorders may go undiagnosed because the signs and symptoms are similar to those of diabetes. Symptoms of hypothyroidism are common in patients with type II diabetes such as severe diabetic nephropathy can be mistaken for hypothyroidism because patients with this condition may have oedema, fatigue, and weight gain. Symptoms of hyperthyroidism may be attributed to poor diabetic control in patients with type1 diabetes as such as weight loss, despite increased appetite and fatigue[9-12] .In a community survey in the UK, the Whickham[13] study recorded an abnormally high serum thyrotropin concentration in 7·5% of women and 2·8% of men. In the NHANES III survey [14] of 17 353 Americans representing US demographics, 4·6% had raised thyrotropin: 0·3% with overt hypothyroidism and 4·3% with mild hypothyroidism. In individuals aged 65 years and older, 1·7% had overt hypothyroidism and 13·7% had mild hypothyroidism. Similarly, in women older than 60 years of age in a Birmingham general medical practice, overt and mild hypothyroidism was present in 2·0% and 9·6%, respectively [15]. In women and men aged older than 74 years screened at a Colorado health fair, the prevalence of hypothyroidism (defined as a serum thyrotropin greater than 10 mU/L) was even higher: 21% and 16%, respectively[16]. In the NHANES III survey, the prevalence of hypothyroidism was higher in whites than in Hispanics and African-Americans (5·1%, 4·1%, and 1·7%, respectively). Special populations with higher risk of developing hypothyroidism include postpartum women[17] individuals with a family history of autoimmune thyroid disorders[18, 19].

Pathophysiology between Diabetes Mellitus and Thyroid Disease

The adverse effect of diabetes on the circulatory, visual, renal, and endocrine function are commonly recognized and have been extensively studied. The effects of decreased insulin secretion or resistance to insulin action on endocrine glands have not been carefully documented. Both clinical and animal research has demonstrated that diabetes mellitus is commonly associated with altered thyroid. The thyroid hormones, 3, 5, 3'-triiodothyronine, T3 and thyroxin, T4 are usually suppressed in both human and experimental animals with diabetes, this effects appears to involve change in hypothalamic thyrotropin–releasing hormone (TRH) secretion as well as change in pituitary thyrotropin, thyroid stimulating hormone, (TSH) and direct effects at the level of thyroid glands[20].

Diabetes mellitus appears to influence thyroid function in at least two sites, one at the level of hypothalamic control of thyroid stimulating hormone (TSH) release and the other at the conversion of thyroxin (T4) to 3,5,3'-triiodothyronine (T3) in the peripheral tissue[21]. Alterations in thyroid hormones indicate the characteristics of low T3 syndrome. Marked hyperglycaemia decreases the activity and concentration of hepatic T4 -5' deiodinase. The characteristic findings include low serum concentrations of T3 elevated levels of reverse T3 (rT3) and low, normal, or high levels of T4. The values return to normal level after correction of hyperglycaemia [22]. Low serum T3 is due to reduced peripheral conversion of thyroxin (T4) to tri-iodothyronine (T3) via 5' monodeiodination reaction and low serum T4 due to decreased protein binding and an inappropriately low serum TSH concentration. Many studies indicate that it may be the long-term diabetic control that determines the plasma T3 levels. Poorly controlled diabetes may also result in impaired TSH response to TRH or loss of normal nocturnal TSH peak. TSH responses and "low T3 state" may normalize with improvement in glycemic status but even with good diabetes control[12, 23].

In euthyroid individuals with diabetes mellitus, the serum T3 levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) may all be strongly influenced by the glycemic status [23]. When hyperthyroidism is also present in a patient with poorly controlled diabetes, the total and even free T4 and T3 concentrations may be inappropriately normal, in which case the diagnosis would be difficult. A suppressed serum basal TSH or an absolutely flat response to TRH would support the diagnosis. In the cases of this type that have been described, serum thyroid hormones rise to

hyperthyroid levels with treatment of the diabetes, and the diagnosis became clear[24].

Effects of Thyroid Hormones On Glucose Homeostasis

Thyroid disorders can have a major impact on glucose control and untreated thyroid disorder can affect the management of diabetes, hypothyroidism can decrease the insulin requirement in patients with diabetes while hyperthyroidism worsens glucose tolerance or control and increase insulin requirement[11, 12].

Hypothyroidism and Glycemic Status

In hypothyroidism, the synthesis and release of insulin is decreased. The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis. In patients utilizing exogenous insulin they may be decrease in insulin requirements from reduced insulin degradation. The net effect is an increased risk of recurrent hypoglycaemia in a diabetic individual[26].

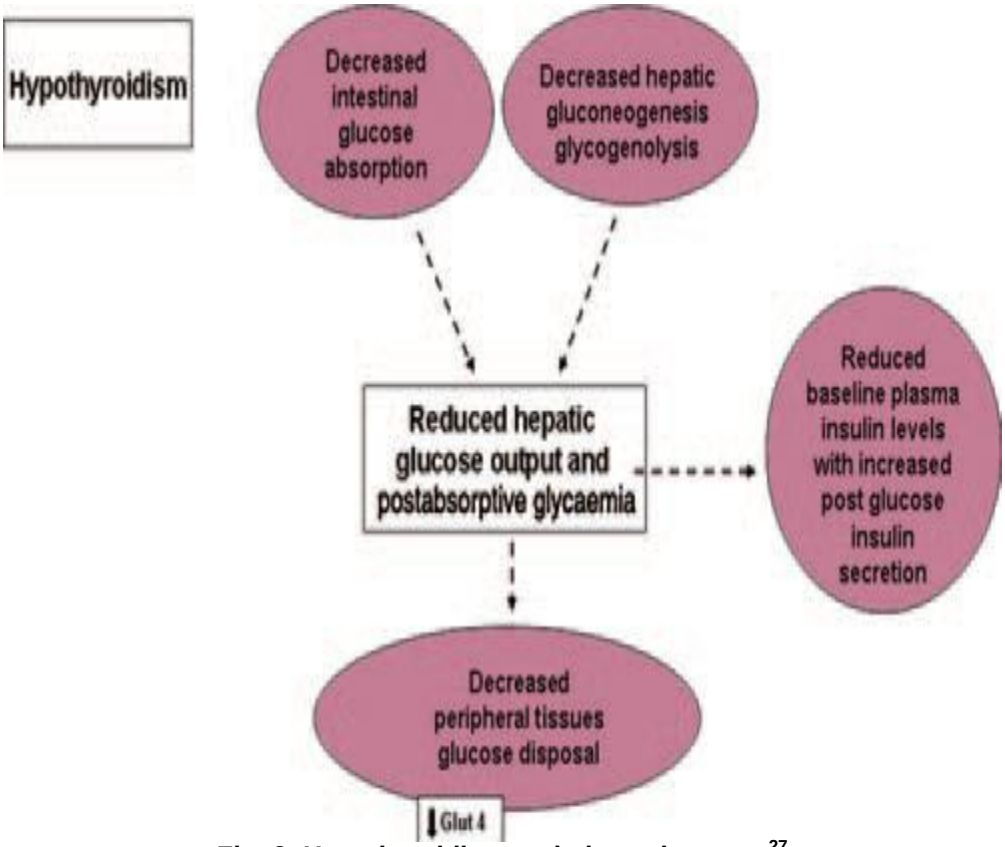

Fig. 2: Hypothyroidism and glycemic status[27]

Hyperthyroidism

Over-activity of thyroid gland is a clinical syndrome produced by sustained high plasma concentrations of thyroid hormones, may be easy to diagnose clinically or may remain unsuspected for a long time[28].

Sub clinical hyperthyroidism

Subclinical hyperthyroidism is defined as persistently suppressed serum TSH with normal thyroxin and triiodothyronine in patients who do not have symptoms[29]. While the diagnostic criteria and treatment modalities for overt hyperthyroidism are well known.

Hyperthyroidism and glycemic status

Varied metabolic changes may occur as a result of hyperthyroidism and contribute to the deterioration of glycemic control status[23].

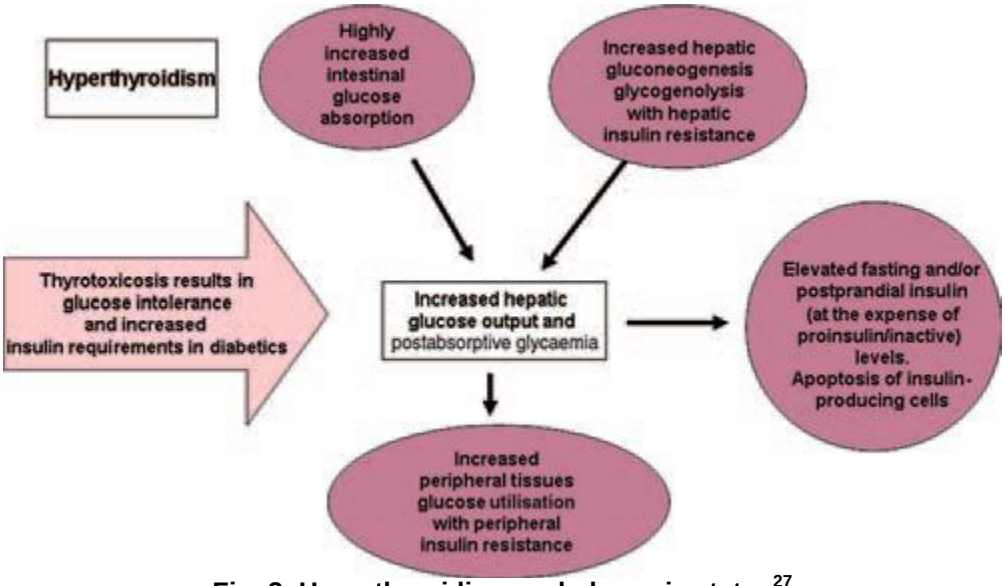

Fig. 3: Hyperthyroidism and glycemic status[27]

Type1 Diabetes Mellitus and Thyroid Dysfunction

Type I diabetes is associated with a number of polyglandular autoimmune syndromes[31]. Commonly affected endocrine organs are the thyroid, parathyroid, adrenals and gonads[32].

The high prevalence of thyroid autoimmunity and thyroid dysfunction in young adults with type 1diabetes was twenty-five of 176 patients (14.2%) were TPO-Ab positive, eighteen of these 25 patients developed thyroid dysfunction at follow up (17 had Primary Hypothyroidism, 1 had hyperthyroidism)[33]

The occurrence of autoantibodies to thyroid peroxidise and autoimmune thyroid disease in type 1 diabetes mellitus be originate positive anti TPO antibodies in 34 (23.4%) diabetic patients out of 145 diabetic patients[34].

A later survey at the same centre randomly selected 1310 patients with either Type I or Type II diabetes, but no previously diagnosed thyroid pathology, the prevalence of thyroid dysfunction (sub- or clinical hypo- or hyperthyroidism) was 31.4% in women and 12.4% in men. The annual incidence of clinical thyroid dysfunction in women was 3.2% approximately six times that calculated in the Whickham survey, whilst in men the figure of 1.6% was more than 10 times the corresponding calculated value[35].

Type II Diabetes Mellitus and Thyroid Dysfunction

Recently, a prevalence of 12.3% was reported among Greek diabetic patients and 16% of Saudi patients with type 2 diabetes were found to have thyroid dysfunction In Jordan, a study reported that thyroid dysfunction was present in 12.5% of type 2 diabetic patients[36, 37, 38].

Among a diabetic clinic population of 5,000 there were 113 patients (1.1%) with concurrent clinical thyroid dysfunction (56 hyperthyroid, 57 hypothyroid). Seventy-one (62.8%) of these patients were insulin-dependent and diabetes preceded thyroid disease in 85 (75.2%). The value of screening diabetic patients for evidence of thyroid dysfunction is important[39].

The combination of diabetes mellitus and primary hypothyroidism is not as rare as generally believed. Nine hypothyroid patients were found among 530 diabetic's patients a prevalence of 1.7%. In 5 patients the diabetes occurs first[40].

Smithson reported an analysis of 206 patients with diabetes managed in primary care. Screening revealed 11 with previously undiagnosed thyroid dysfunction in addition to eight with previously known disease, making an overall prevalence of thyroid dysfunction of 10.8%, and an undiagnosed disease prevalence of 5.5% (9.5% in women). Those findings led the author to advocate screening for people with community managed diabetes[41]. A larger study in secondary care included 904 patients with Type II diabetes. The prevalence of thyroid dysfunction was 10.9% in women and 6.9% in men. The incidence of clinically significant disease in women was 1.1%, twice that calculated from the Whickham survey. In men, the annual incidence was 0.8%, eight times that in the general population[35].

One important caveat is that poor diabetic control may interfere with the thyroid axis. Evidence for this came from a study of 290 patients with Type II diabetes who were hospitalized due to poor diabetic control. A high prevalence of abnormal thyroid function

tests was noted in both women (40.9%) and men (19.8%). However, TSH concentrations fell as control of diabetes improved, as judged by decreasing HbA1c values[42, 43]. This led the authors to suggest that diagnosis of thyroid dysfunction should be delayed until glycemic control has been optimized and thyroid function tests at diagnosis of Type II diabetes and further testing if these values are abnormal. The case for routine screening in Type II diabetes is less clear than for Type I, although advocated by some authors.

Diabetes Mellitus and Dyslipidaemia

Both diabetes and thyroid dysfunction are associated with dyslipidemia. Thyroxin replacement reduces both total and LDL cholesterol in people with sub clinical hypothyroidism[44].

Gray and his group studied 49 patients with diabetes and primary thyroid failure and found their mean baseline cholesterol significantly elevated in comparison with age, sex and weight-matched diabetic controls. Treatment of those with low T4 concentrations led to a significant reduction in mean plasma cholesterol. Although no significant differences were noted in triglyceride metabolism, those results prompted the authors to suggest that clinically unrecognized thyroid failure could predispose to ischemic heart disease in the diabetic population. Thus thyroid function tests should be measured in patients with an otherwise inexplicably worsening dyslipidemia[4].

Many people with diabetes remain uncontrolled for dyslipidemia. Population – based studies have consistently demonstrated that patients with diabetes have an increased risk of cardiovascular disease (CVD) and low density lipoprotein cholesterol (LDL-C) has been noted to be the strongest predicator of coronary heart disease (CHD) events. Clinical trials have provided evidence that treatment of dyslipidemia reduces mortality and prevents or delays the incidence of micro vascular and macro vascular complications in persons with diabetes. Premature atherosclerosis is often found in patients with diabetes mellitus (DM) type1 and alteration in lipid metabolism seems to play an important role in the development of this complication. The accumulation of triglyceride – rich lipoprotein particles like very low density lipoproteins (VLDL) in insulin – deficient patient occurs because lipoprotein lipase activity is depressed without sufficient insulin for adequate tissue levels[45].

Type II diabetes mellitus (DM) is a well known risk factor for the development of cardiovascular disease due to alteration in lipid and lipoprotein profile[46]. The most frequent alternations of lipid and lipoprotein profiles were the combination of elevated TG (VLDL-TG), decrease clearance of TG- rich lipoproteins, and decreased high – density lipoprotein (HDL)[47] most likely due to a low lipoprotein lipase activity well known in diabetic patients[48].

Effects of Thyroid on Lipid Metabolism

Alterations of the lipid profile are well known phenomena in thyroid dysfunction. Thyroid hormones regulate lipid metabolism through various mechanism. Increased thyroid hormone levels stimulate fat mobilization, leading to increased concentration of fatty acids in plasma. They also enhance oxidation of fatty acids in many tissues. Finally, plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels[49-52]. Even sub-clinical hypothyroidism can exacerbate the coexisting dyslipidemia commonly found in type II diabetes and further increase the risk of cardiovascular disease[46]. Subclinical hypothyroidism can elevate LDL cholesterol and worsen pre-existing dyslipidemia. Since diabetic patients are at high risk for cardiovascular disease, the diagnosis and treatment of sub clinical thyroid disease is important[35].

REFERENCES

1. Wild S, Roglic SG, Green A, Sicree R and King H. Global prevalence of diabetes. Diabetes Care. 2004;27:1047-1053.
2. Zimmat P, Alberti KG AND Shaw J. Global and societal implications of the diabetesepidemic. Nature. 2001;414(6865):782-7.
3. Paul W, Ladenson PA, Singer KB, Nandala BS, Thomas B, Elliot G, Levy Steven A and Smith H. American Thyroid Association Guide-lines for Detection of Thyroid Dysfunction. J Arch Intern Med. 2000;160:1573-1575.
4. Retnam VJ, Nerurkar SV, Gupte M, Bhandarkar S and Taskar SP. Plasma lipids and lipoproteins in treated diabetics. J Postgra Med. 1983;29(4):193-200
5. Johnson JL. Diabetes Control in Thyroid Disease. Diabetes Spectrum. 2006;19:148-153.
6. Klein I and Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001; 344:501–509

7. Hage M, Zantout MS and Azar ST. Thyroid disorders and Diabetes Mellitus. J Thyroid Research. 2010;1-7
8. Udoing CEJA, Udoh E and Etukudoh ME. Evaluation of thyroid function in diabetes mellitus in Calabar, Nigeria. Indian J Clin Biochem. 2007;22:74-78
9. Skaria LK, Sarkar PD, Agnihotram G, Thakur AS and Pamidamarri G. Thyroid Dysfunctions in Tribal Women of the Bastar Region of Chattisgharh, India. Thyroid science. 2011;6(6):1-5.
10. Oromcan BW and Okello S. Thyroid function among diabetic patients at Mengo Hospital Kampala. Afri J Anim Biomed Sci. 2010;5 (1):42-55
11. Yasmin T, Ghafoor F, Malik T, Ruhy NS and Khan A. Pattern of thyroid Autoimmunity in Type 1 and type II Diabetes. JCPSP. 2006;16(12):751-754.
12. Patricia W. Thyroid Disease and diabetes. J. Clinical Diabetes. 2000;18(1):38.
13. Tunbridge WM, Evered DC and Hall R. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf). 1977;7:115–125.
14. Al-Wazzan HT. Prevalence and associated factors of thyroid dysfunction among type 2 diabetics, Kuwait. Bull Alex Fac Med. 2010;46(2):141-148.
15. Parle JV, Franklyn JA, Cross KW, Jones SC and Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol. 1991;34:77–83.
16. Canaris GJ, Manowitz NR, Mayor G and Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526-534.
17. Muller AF, Drexhage HA and Berghout A.. Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antenatal and postnatal care. Endocr Rev. 2001;22:605–630.
18. Tamai H, Ohsako N and Takeno K. Changes in thyroid function in euthyroid subjects with a family history of Graves's disease: a follow-up study of 69 patients. J Clin Endocrinol Metab. 1980; 51;1123–1127.
19. Thakkar NV and Jain SM. The impact of Diabetes on thyroid dysfunction and outcomes in a Native Indian Female Population. Thyroid Science. 2011;6(4):1-9.
20. Steger R and Rabe M. The effect of diabetes mellitus on endocrine and reproductive function. J. Experimental biology and Medicine. 1997;214:1-11.
21. Engin G Ney, Belgin Aysen, Nur Kebap Y and Esat Erenou. Thyroid Disease in Diabetes Mellitus. J Endocrino Metab. 1999;3:119-122.
22. Gilani BB, Mac Gillivray MH, Voorhess ML, Mills BJ, Riley WJ and Mac Laren NK. Thyroid hormone abnormalities at diagnosis of insulin dependent diabetes mellitus in children. J Pediatr. 1984;105(2):218-222.
23. Sathish R and Mohan V. Diabetes and Thyroid Disease. J. Dia. dev. Countries. 2003;23:120-123.
24. Cavalieri RR. The effects of nonthyroid disease and drugs on thyroid function tests.J. Medical Clinics of North America. 1999;75(1):27-39.
25. Bedone RV, Pimenta WP, Carvalho LR and Mazeto GMFS. TSH and TPOAB as Predictors of Thyroid Disease in Diabetic Patients. The endocrinologist. 2008;18:81-84.
26. Mohn A, Di Michele S, Di Luzio R, Tumini S and Chiarelli F.The effect of subclinical hypothyroidism on metabolic control in children and adolescents with Type 1 diabetes mellitus. J Diab Med. 2001;19:70-3.
27. Brenta G. Diabetes and thyroid disorders, British Journal of Diabetes & Vascular Disease. 2010;10(172):175-177.
28. Vanderpump MP, Tunbridge WM and French JM. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol. 1955;43:55–68.
29. Kek P, HO S and Khoo D. Subclinical Thyroid Disease. Singapore. J Med. 2003;44(11):595-600.
30. Duntas LH, Orgiazzi J and Brabant G. The interface between thyroid and diabetes mellitus. Clinical Endocrinology. 2001;75:1-9
31. Trence DL, Morley JE and Handwerger BS. Polyglandular autoimmune syndromes. Am J Med. 1984;77:107–116.
32. Betterle C, Zanette F, Pedini B, Presotto F, Rapp LB and Monciotti CM. Clinical and subclinical organ-specific autoimmune manifestations in type 1(insulin-dependent) diabetic

patients and their first degree relatives. J Diabetologia. 1984;26:431–436.
33. Gonzalez GC, Mauricio D, Capel I, Leiva AD, Rodriguez-Epinosa J and Perez A. Thyroid autoimmunity at onset of type 1 diabetes as a predictor of thyroid dysfunction. Diabetes care. 2007;30:1611-1612.
34. Moayeri H and Rabbani A. Prevalence of autoantibodies to thyroid peroxidise and autoimmune thyroid disease in type 1 Diabetes Mellitus. Acta Medica Iranica. 2004;42(4): 267-271.
35. Perros P, Crimmon R, Shaw G and Frier. Frequency of thyroid dysfunction in diabetic patients. Value of annual screening. J. Diabet Med. 1965;7:622–627.
36. Radaideh AR, Nusier MK, Amari FL, Bateiha AE, El-Khateeb MS, Naser AS and Ajiouni KM. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. Saudi Med J. 2004;25 (8):1046-1050.
37. Papazafiropouloua A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P and Pappas S. Prevalence of Thyroid Dysfunction Among Greek Type 2 Diabetic Patients Attending an Outpatient Clinic. J Clin Med Res. 2010;2(2):75-78.
38. Akbar DH, Ahmed MM, AL-MUGHALES J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. Acta Diabetol. 2006;43(1):14-18.
39. Sugrue DD, Evoy MC and Drury MMI. Thyroid disease in diabetics. J Postgrad Med. 1982;58 (865):680-684.
40. Arthur H and Herbert G. Diabetes mellitus and primary hypothyroidism. science direct. J. Metabolism. 1968;17(2):108- 113.
41. Smithson MJ. Screening for thyroid dysfunction in a community population of diabetic's patients. Diabetic medicine. 1998;15(2):148-150.
42. Celani MF, Bonati ME and Stucci N. Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type II diabetes. J Diabetes Res. 1994;27(1):15–25.
43. Mouradian M and Abourizk N. Diabetes mellitus and thyroid disease. J Diabetes Care. 1983;6:512–520.
44. Franklyn JA, Daykin J, Betteridge J, Hughes EA, Holder R and Jones SR.Thyroxin replacement therapy and circulating lipid concentrations. JClin Endocrinol. 1993;38:451–452.
45. Dzien A, Lechleitner M, Hopferwieiser T, Drexel H, Patsh JR and Braunstecine H. Long –Term Effect of Intensified Insulin Treatment on Lipid parameters in diabetes Mellitus Type1. J Klin Wochenschr. 1991;69:483-485.
46. Hyden JM and Reaven PS. Cardiovascular disease in diabetes mellitus type (2). J Lipid Research. 2000;11:519-528.
47. Smaoui M, Hammami S, Chaaba R, Attia N, Ben Hamda K, Masmoudi AS, Masmoudi S and Mahjoub A. Lipids and lipoprotein concentration in Tunisian typeII diabetic patients. J. diabetes complic. 2004;18:258-263.
48. Taskinen MR. Diabetic dyslipidemia. Atheroscler. Supp. 2002;3:47-51.
49. Danese MD, Ladenson PW, Meinert CL and Powe NR. Effect of thyroxin therapy on serum lipoproteins in patients with mild thyroid failure. J Clin Endocrinol Metab. 2000;85:2993–3001.
50. Singh BM, Goswami B and Mallika V. Association between Insulin Resistance and Hypothyroidism in Females Attending a Tertiary Care Hospital. Indian J of Clinical Biochemistry. 2010;25(2):141-145.
51. Afkhani-Ardekani M, Rashidi M and Shojaoddiny A. Effect of Thyroid Dysfunction on Metabolic Response in Type 2 Diabetic Patients. Iranian J of diabetes & Obesity. 2010;2:20-26.
52. Pasupathi P, Bakthavathsalam G, Saravanan G and Sundaramoorthi R. Screening for Thyroid Dysfunction in the Diabetic/Non-Diabetic Population. Thyroid Science. 2008;3(8):1-6.