The prevalence of metabolic syndrome in Yemeni patients with hypothyroidism

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Abstract

Background: Yemen faces major challenges in improving the health status of its population as it is entering an epidemiological transition with rising non-communicable diseases e.g. obesity, diabetes and cardiovascular diseases (CVDs). We designed this study to find out the prevalence of Metabolic Syndrome (MS) and its components among Yemeni patients with hypothyroidism.

Methods: 350 patients with past history or newly diagnosed hypothyroidism (diagnosed as having high TSH, and or low FT4 and FT3) (patients group) and 100 healthy euthyroid volunteers as (control group) attending the outpatients medical clinics at Al-Kuwait University hospital in Sana'a city. The patients and control groups underwent complete history and clinical examination including measurement of blood pressure and waist circumference. The laboratory parameters that were analyzed included fasting samples of plasma glucose, triglycerides, and HDL cholesterol The diagnosis of MS was based on the Adult Treatment Panel III criteria as the presence of at least 3 of the following: systolic BP >130 mm Hg and/or diastolic BP >85 mm Hg or on treatment for high BP, waist circumference >102 cm for men and >88 cm for women, fasting glucose >110 mg/dl or on diabetes treatment, triglycerides ?150 mg/dl, and HDL cholesterol <40 mg/dl in men and <50 mg/dl in women.

Results: from 350 hypothyroid patients and 100 euthyroid volunteers included in this study 233 (66.6%) of hypothyroid patients had subclinical and 117 (33.4%) had overt hypothyroidism. MS was significantly higher in hypothyroid (37.4%), (76.3%) in patients with subclinical and 31 (23.6%) in patients with overt hypothyroidism, than in the euthyroid group (17%). The commonest occurring metabolic syndrome defined criterion in hypothyroid patients was central obesity 89 (67.9%), high blood pressure 88 (67.1%), reduced high density lipoprotein (61%), high serum triglyceride (59.5%) and raised fasting blood glucose (54.9%).

Conclusion: Prevalence of MS is high among Yemeni patients with hypothyroidism and central obesity was the commonest co-morbidity. These findings highlight an urgent need to develop strategies for prevention, detection, and treatment of MS that could contribute to decreasing the prevalence of cardiovascular morbidity and mortality in hypothyroid patients.

Key words: hypothyroidism, metabolic syndrome , dyslipidemia

Introduction

Worldwide prevalence of Metabolic syndrome (MS) ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used (1,2). In general, the IDF estimates that one-quarter of the world's adult population has the MS (3). Higher socioeconomic status, sedentary lifestyle, and high body mass index (BMI) were significantly associated with MS. Cameron et al. have concluded that the differences in genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education all influence the prevalence of the MS and its components (4). The observed prevalence of the MS in National Health and Nutrition Examination Survey (NHANES) was 5% among the subjects of normal weight, 22% among the overweight, and 60% among the obese (6). It further increases with age (10% in individuals aged 20-29, 20% in individuals aged 40-49, and 45% in individuals aged 60-69) (6). The prevalence of MS (based on NCEP-ATP III criteria, 2001) varied from 8% to 43% in men and from 7% to 56% in women around the world (4). Park et al. (5) noticed that there is an increase in the prevalence of MS from 20 years old through to the sixth and seventh decade of life for males and females, respectively. Ponholzer et al. reported that there is high prevalence of MS among postmenopausal women, which varies from 32.6% to 41.5% (7). A Framingham Heart Study report indicated that a weight increase of >2.25kg over a period of 16 years was associated with an up to 45% increased risk of developing the MS (8), and it has been shown by Palaniappan et al. that each 11cm increase in waist circumference (WC) is associated with an adjusted 80% increased risk of developing the syndrome within 5 years (9). The metabolic alterations occur simultaneously more frequently than would be expected by chance and the concurrence of several factors increases cardiovascular risk over and above the risk associated with the individual factors alone (10).

MS is defined by a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes mellitus (T2DM), and all-cause mortality (11,12). This collection of unhealthy body measurements and abnormal laboratory test results include atherogenic dyslipidemia, hypertension, glucose intolerance, pro inflammatory state, and a pro thrombotic state. There have been several definitions of MS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO) (13), the European Group for the study of Insulin Resistance (EGIR) (14), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (15), American Association of Clinical Endocrinologists (AACE) (16), and the International Diabetes Federation (IDF) (3). Under current guidelines, revised in 2005 by the National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) (16) metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions

• Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia)
• Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension)
• Triglycerides >150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
• HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
• Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women (The international diabetes federation [IDF] criteria allow the use of a body mass index [BMI] >30 kg/m² in lieu of the waist circumference criterion.)

Abundant data suggest that patients meeting these diagnostic criteria have a greater risk of significant clinical consequences, the 2 most prominent of which are the development of diabetes mellitus (17) and of coronary heart disease. Pooled data from 37 studies involving more than 170,000 patients have shown that metabolic syndrome doubles the risk of coronary artery disease(18). It also increases risk of stroke, fatty liver disease, and cancer.(19)

In recent times there has been an increasing global prevalence of two endocrine disorders, thyroid disorders and type 2 DM, with frequency of thyroid disorders being second to type 2DM. About three percent of the general population has hypothyroidism (20). In community surveys, the prevalence of overt hypothyroidism varies from 0.1 to 2 percent (20-22). The prevalence of subclinical hypothyroidism is higher, ranging from 4 to 10 percent of adults, with possibly a higher frequency in older women (23,24,25,26). However, there is an age-related shift towards higher thyroid-stimulating hormone (TSH) concentrations in older patients and, therefore, if age-adjusted normal ranges are used, the prevalence may not increase with old age. Hypothyroidism is five to eight times more common in women than men, and more common in women with small body size at birth and during childhood (24,27)

Almost one-third of the world's population lives in areas of iodine deficiency(28). In areas where the daily iodine intake is <50 υg, goitre is usually endemic, and when the daily intake falls <25 υg, congenital hypothyroidism is seen. The prevalence of goitre in areas of severe iodine deficiency can be as high as 80%. Populations at particular risk tend to be remote and live in mountainous areas in South-East Asia, Latin America and Central Africa. Iodization programs are of proven value in reducing goitre size and in preventing goitre development and cretinism in children. Autonomy can develop in nodular goitres leading occasionally to thyrotoxicosis and iodization programmes can also induce thyrotoxicosis, especially in those aged >40 years with nodular goiters (29). In iodine-replete communities, the prevalence of spontaneous hypothyroidism is between 1 and 2%, and it is more common in older women and 10 times more common in women than in men.(30,31).

Hypothyroidism is a well known cause of hypertension, dyslipidemia, endothelial dysfunction and cardiovascular diseases (32,33). Considerable overlap occurs in the pathogenic mechanism of atherosclerotic cardiovascular diseases by metabolic syndrome and hypothyroidism. Insulin resistance has been studied as a basic mechanism in metabolic syndrome (34,35). Rule of insulin resistance in development of dyslipidemia in hypothyroidism has been suggested in recent studies (36). Recent data have suggested that there may be some association between serum thyroid function and MS (36). Sub-clinical hypothyroidism (SCH) and overt hypothyroidism(OH) are established risk factors for insulin resistance, hyperlipidemia, hypercoagulability and low grade inflammation (37, 38). Several studies have proved the association between insulin resistance and hypothyroidism for overt hypothyroidism, but there is controversy as to whether this association is also present in sub clinical hypothyroidism. In a recent study it was found that insulin resistance was comparable in both SCH and OH (39, 40). It is known that overt hypothyroidism leads to an increase in plasma cholesterol levels (39, 41). Most studies in sub clinical hypothyroidism show comparable but less pronounced associations (42, 43). The prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population (44). This indicates a possible interplay between thyroid status and insulin sensitivity.

Insulin resistance leads to an increased production of hepatic cholesterol and very low density lipoproteins (VLDL) (45) and an increased HDL cholesterol (HDL-C) clearance (46). Insulin resistance augments the deleterious effect of hypothyroidism on the lipid profile as suggested by Bakker et al (46). Complex interplay between thyroid function and insulin resistance has been implicated in diabetic dyslipidemia (47).

Methods

This case control study was conducted in the outpatient department of AL-Kuwait University Hospital Medical Department (Sana'a University ,Yemen) in the period between 21st September 2014 to 11 January 2016. 312 patients with hypothyroidism (both subclinical and overt) (case group) and 100 healthy volunteers with normal thyroid function test (control group) were included. The hypothyroid patients who were selected in this study are those who are newly diagnosed by laboratory tests or who are known to have hypothyroidism on hormonal replacement therapy. A high serum TSH level (range between 4.2 uIU/ml to 10 uIIU/ml) and normal free thyroxine (FT4) level were required for the diagnosis of sub-clinical hypothyroidism (SCH) (44). Patients with high TSH (> 10 uIIU/ml) and low FT4 levels (< 0.93 ng/dl) were classified as having overt hypothyroidism. Patients with normal TSH and FT4 were considered euthyroid.

Exclusion criteria
1- Patients with hyperthyroidism
2- Patients who are taking any medication that could affect the thyroid function or lipid level
3- Pregnant females
4- Patients with renal or liver disorders and congestive cardiac failure
5- Patients with secondary hypothyroidism or surgically removed thyroid gland

Metabolic syndrome was diagnosed by the presence of three or more of the following criteria (16).
• Fasting glucose ≥ 100 mg/dL (or receiving drug therapy for hyperglycemia)
• Blood pressure $\geq 130/85$ mm Hg (or receiving drug therapy for hypertension)
• Triglycerides ≥ 150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
• HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
• Waist circumference >102 cm (40 in) in men or ≥ 88 cm (35 in) in women; if Asian American, ≥ 90 cm (35 in) in men or ≥ 80 cm (32 in) in women (The international diabetes federation [IDF] criteria allow the use of a body mass index [BMI] >30 kg/m^2 in lieu of the waist circumference criterion.)

All subjects were interviewed about their age, habits, occupation, and past history of diabetes, hypertension, dyslipidemia and hypothyroidism as well as their drug intake. Subjects underwent a physical examination consisting of the determination of waist circumference and systolic and diastolic blood pressure. Waist circumference was measured with a tape measure mid-way between the lower rib margin and the iliac crest. Blood pressure was recorded with the same mercury manometer in the sitting position after 10 - 15 minutes rest. Each subject had two measurements of blood pressure at 5 minutes intervals. Venous blood sampling was performed in the morning after an overnight fast for determination of plasma glucose, triglyceride, and High Density Lipoprotein (HDL) cholesterol. Laboratory techniques for biochemical analysis were glucose oxides for blood glucose, and the enzymatic method for triglyceride and HDL cholesterol.

Serum TSH and FT4 measurements were made using Roche Elecsys modular analytics E 170 using electrochemiluminescence immunoassay (ECLIA method). The analytical sensitivity of TSH was 0.005 υIU/ml and for FT4 was 0.023 ng/dl. Normal range for TSH was (0.27-4.2)υIU/ml and for FT4 was (0.93-1.7) ng/dl.

The research protocol was reviewed and approved by the Ethical Community of the Faculty of Medicine and Health Sciences, Sana'a University. All participants provided informed consent after explaining the study objectives and that the data will be used only for purpose of the research. Health education both verbally and using educational materials was provided to all participants and those who were found to have any medical problem were referred to the specialized clinic for proper management and follow up.

Statistical analysis was undertaken using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS, Chicago IL USA).

Differences between groups were tested statistically using the chi square test for categorical and T test for numerical variables. Data were considered statistically significant when the p-value was ≤ 0.05.

Results

Table 1: Clinical and laboratory characteristics of hypothyroid and euthyroid group

Factor	Total=450	Hypothyroid group=350	Euthyroid group=100	p-value
Female gender	341	279(79.7%)	62(62%)	0.002
WS ≥88cm in female ≥102cm in male	148	137(39.1)	11 (11%)	0.008
BP ≥130|85mmg	138	120(34.2)	18(18%)	0.0018
FBS ≥100mg|dl	89	81(23.1%)	8(8%)	0.0008
TG ≥ mg|dl	111	99(28.2%)	12(12%)	0.0008
HDL ≤40 mg|dl in men ≤50 mg|dl in women	120	107(30.5%)	13(13%)	0.0004
MS	127	110 (39.4%)	17(17%)	0.004

WS=waist circumference, BP= blood pressure, FBS = fasting blood sugar, TG = triglyceride, HDL = high density lipoprotein, MS = metabolic syndrome

The overall prevalence of the MS in the hypothyroid group was 37.4%, while the prevalence of MS in the euthyroid group was 17% (P-value > 0.005). In the hypothyroid group subclinical hypothyroidism was more prevalent than overt hypothyroidism (28.5% vs 8.8 %). Patients with hypothyroidism are more frequently female , centrally obese and have high BP than those with normal thyroid function test (79.7%, 39.1%, 34.2% vs 62%, 11%, 27% respectively) also the prevalence of high FBS ,TG, and low HDL was significantly higher in the hypothyroid group than in the euthyroid group (23.1%, 28.2%, 30.5% vs 8%, 12%, 13% respectively) (P-value > 0.005).

The physical and metabolic characteristics of the hypothyroid patients with and without MS are shown in Table 2.

Table 2. The physical and metabolic characteristics of the study population by Metabolic Syndrome

Factors	Total =350	With MS=131 -subcli.100 -clinical=31	Without MS =219 -subcli.114 -clinical=113	P-value
Male gender	64(18.2%)	15 (11.4%)	49 (22.3%)	0.0103
Central obesity	137 (39.1%)	89 (67.9%)	48 (21.9%)	0.005
BP|mmHg	120 (34.2%)	88 (67.1%)	32 (14.6%)	0.005
FBS≥ 100md|dl	81 (23.1%)	60 (45.8%)	21 (9.5%)	0.005
SerumTG≥150mg|dl	99 (28.2%)	75 (57.2%)	24 (10.9%)	0.005
Serum HDL ≤40mg in males , ≤50mg in females	107 (30.5%)	81 (61.8%)	26 (11.8%)	0.005

The prevalence of MS was statistically significantly higher in female patients with hypothyroidism and MS than in those without MS. Also central obesity was higher in patients with hypothyroidism and MS than in those without MS (P-value =0.005). BP was higher in patients with hypothyroidism and MS than in those without MS.

Regarding laboratory parameters patients with hypothyroidism and MS had higher prevalence of FBS, serum TG and serum HDL than those without MS (P- value ≤ 0.05). The highest prevalent comorbidity in hypothyroid patients with MS was central obesity (67.9%) followed by high BP (67.1%), low serum HDL (61.8%), high TG (57.2%) and raised fasting blood glucose (45.8%).

Discussion

This study analyzed the prevalence of the MS in hypothyroid patients who attended the medical clinics in Al-Kuwait University Hospital (Sanaa City, Yemen) using the NCEP - ATP III criteria for definition of the metabolic syndrome. There are a few international comparable studies of the MS among adult hypothyroid patients but we could not find similar studies from nearby Arabic countries among such high risk groups. The several definitions of the syndrome that are in use (i.e. the International Diabetes Federation criteria, the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III definition, the WHO criteria), makes it difficult to compare prevalence and impact. Furthermore, since our study is a hospital-based study, the findings could not be generalized to the whole population. Nevertheless, as this is the first study about the MS from Yemen among hypothyroid patients, its results provide invaluable information on the MS in such a high risk group and should encourage researchers to investigate more on such an emerging health problem.

Metabolic syndrome (MS) and hypothyroidism are well-established forerunners of atherogenic cardiovascular disease. MS includes a cluster of risk factors characterized by hypertension, dyslipidemia, hyperglycemia, and prothrombotic and proinflammatory conditions which accelerate the atherogenic process in the body. (51,52). Hypothyroidism is well known to cause hyperlipidemia, diastolic hypertension, endothelial dysfunction, and cardiovascular disease.(53,54). Considerable overlap occurs in the pathogenic mechanisms of atherosclerotic cardiovascular disease by MS and hypothyroidism. Insulin resistance has been studied as the basic pathogenic mechanism in MS (55,56). Role of insulin resistance in development of dyslipidemia in hypothyroidism has been suggested in recent studies(57). This relationship with insulin resistance can lead to a considerable overlap between the population subsets of MS and hypothyroidism as well.

The prevalence of MS in the hypothyroid group was 37.4% which is significantly higher than in the euthyroid group 17% (P-value =0.005), also the prevalence of different MS comorbidities was higher in the hypothyroid than in the euthyroid group (Table 1) (58, 59,62).

The overall prevalence of the MS among hypothyroid patients in the present study was found to be 37.4% while the prevalence of MS in patients with subclinical hypothyroidism was 28.5% which is comparable to that found among hypothyroid patients in Nigeria (40%) in all hypothyroid and 35% in patients with subclinical hypothyroidism (59) and Bulgaria (34.9%) (60), and in Turkey (44%) in hypothyroid group and 35% in subclinical hypothyroid group (61), but still lower than what was found in Dhaka hypothyroid patients (82.5%) (62).

The prevalence of different MS comorbid conditions (central obesity, Hypertension , FBS, high serum TG and low HDL) was statistically significantly higher in hypothyroid patients with MS than in hypothyroid patients without MS. These findings are in concurrence with other studies which reported that both overt and subclinical hypothyroidism well effect each component of MS including blood pressure and metabolism of carbohydrate and lipids (54, 55,62).

Of the components of MS, central obesity was the prevalent MS defining criteria followed by high BP, low serum HDL, high serum TG and high FBS (56,57). Thyroid hormones play essential roles in regulating energy balance, metabolism of glucose and lipids and thus effects metabolic syndrome parameters including HDL-C, triglycerides, blood pressure and plasma glucose (63). Hypothyroidism is associated with obesity, dyslipidemia and increased risk of atherogenic cardiovascular diseases (64).

Obesity, a key component of metabolic syndrome, occurs due to increased energy intake, decreased energy expenditure, or a combination of both, thus leading to a positive energy balance. Thyroid hormones up-regulate metabolic pathways relevant to resting energy expenditure, hence, obesity and thyroid functions are often correlated. On one hand, obesity per se causes alterations in thyroid hormones, i.e., increased thyroid hormone levels,(65), increased thyroid stimulating hormone (TSH) with no effect on T 3 and T 4 ,(66) or increased TSH and T 3 with no effect on T 4, (67) while on the other hand, subclinical hypothyroidism as a result of slow metabolism can also lead to obesity,(68, 69). The mechanism of normal levels of T 3, T 4 with increased TSH in metabolic syndrome is not defined, but it has been hypothesized that metabolic syndrome is associated with insulin resistance due to the defect in post-receptor signal transduction in target tissue; a similar mechanism of thyroid receptor resistance might be operating in these obese persons.

In a study done by Kumar et al., T 3 showed positive correlation with triglycerides, low density lipoprotein cholesterol (LDL-C), total cholesterol, insulin, HOMA-IR (insulin resistance) and negative correlation with body fat. TSH correlated positively with BMI, insulin, HOMA-IR, LDL-C and negatively with high density lipoprotein cholesterol (HDL-C) (P < 0.05). Free triiodothyronine (FT 3) correlated positively with waist circumference and T 4 did not show correlation with metabolic syndrome parameters(69). In a large Chinese case control study, all components of the metabolic syndrome were associated with systematically higher TSH levels (Lai et al.)(70). In a study done by Chugh et al.,(2012) evaluating the thyroid function tests in individuals with metabolic syndrome to explore the possibility of thyroid receptor resistance, a significant increase was found in TSH levels in patients as compared to controls, while T 3 and T 4 levels were comparable in patients and controls concluding that raised TSH in patients with metabolic syndrome independent of lowered T 3 and T 4 suggests it to be a part and parcel of this syndrome(71). Another study done by Meher et al., (2013) found that body mass index, waist circumference, mean systolic pressure, diastolic pressure, fasting blood sugar, total cholesterol, LDL-C, triglycerides, and TSH were significantly higher, and FT3, free thyroxine (FT4)

and HDL-C were significantly lower in the metabolic syndrome patients compared to the control group concluding that there is a significant association between subclinical hypothyroidism and metabolic syndrome, and it highlights the importance of thyroid function tests in patients with metabolic syndrome.(64,72). It is still not clear whether alterations in thyroid hormones are a cause or an effect of obesity (metabolic syndrome) suggesting need for further evaluation on a large scale with inclusion of various hormones elaborated by adipose tissue (like leptin, resistin, adiponectin, etc.).

Conclusion

We conclude that metabolic syndrome was common in hypothyroid patients which could be explained by the metabolic syndrome per se or be due to different metabolic co-morbidities that are associated with it.

References

1- Desroches S. Lamarche B; "The evolving definitions and increasing prevalence of the metabolic syndrome," Applied Physiology, Nutrition and Metabolism, vol. 32, no. 1, pp. 23-32, 2007.

2- "The prevalence of metabolic syndrome in various populations," The American Journal of the Medical Sciences, vol. 333, no. 6, pp. 362-371, 2007.

3- International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome

4- Cameron A. J.,. Shaw J. E, and Zimmet P. Z., "The metabolic syndrome prevalence in worldwide populations," Endocrinology and Metabolism Clinics of North America, vol. 33, no. 2, pp. 351-375, 2004.

5- Park Y.-W, Zhu S, Palaniappan L, Heshka S, Carnethon M.R, and S. B. Heymsfield, "The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994," Archives of Internal Medicine, vol. 163, no. 4, pp. 427-436, 2003.

6- Ford E.S, Giles W.H, and Dietz W.H, "Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey," Journal of the American Medical Association, vol. 287, no. 3, pp. 356-359, 2002

7- Ponholzer A, Temml C, Rauchenwald M, Marszalek M, and Madersbacher S, "Is the metabolic syndrome a risk factor for female sexual dysfunction in sexually active women?" International Journal of Impotence Research, vol. 20, no. 1, pp. 100-104, 2008

8- Wilson P.W.F, Kannel W.B, Silbershatz H, and D'Agostino R.B, "Clustering of metabolic factors and coronary heart disease," Archives of Internal Medicine, vol. 159, no. 10, pp. 1104-1109, 1999

9- Palaniappan L, Carnethon M.R, Wang Y et al., "Predictors of the incident metabolic syndrome in adults: The Insulin Resistance Atherosclerosis Study," Diabetes Care, vol. 27, no. 3, pp. 788-793, 2004.

10- Reilly M. P. and Rader D. J., "The metabolic syndrome: more than the sum of its parts?" Circulation, vol. 108, no. 13, pp. 1546-1551, 2003

11- Grundy S. M., Cleeman J. I., Daniels S. R. et al., "Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement," Circulation, vol. 112, no. 17, pp. 2735-2752, 2005

12- Wilson P. W. F., D'Agostino R. B., Parise H., Sullivan. S, and Meigs J. B., "Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus," Circulation, vol. 112, no. 20, pp. 3066-3072, 2005

13- Alberti K. G. and Zimmet P. Z., "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation," Diabetic Medicine, vol. 15, no. 7, pp. 539-553, 1998.

14- Balkau B and Charles M.A, "Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR)," Diabetic Medicine, vol. 16, no. 5, pp. 442-443, 1999

15- Cleeman J.I, "Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III)," Journal of the American Medical Association, vol. 285, no. 19, pp. 2486-2497, 2001.

16- Einhorn D, Reaven. G.M, Cobin R.H et al., "American College of Endocrinology position statement on the insulin resistance syndrome," Endocrine Practice, vol. 9, no. 3, pp. 237-252, 2003

17- Hanley AJ, Karter AJ, Williams K, et al. Prediction of type 2 diabetes mellitus with alternative definitions of the metabolic syndrome: the Insulin Resistance Atherosclerosis Study. Circulation. Dec 13 2005;112(24):3713-21.

18- Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. Jan 30 2007;49(4):403-14.

19- Giovannucci E. Metabolic syndrome, hyper insulinemia, and colon cancer: a review. Am J Clin Nutr. Sep 2007;86(3): s836-42.

20- Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 1977; 7:481.

21- Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995; 43:55.

22- Vanderpump MP, Tunbridge WM. The epidemiology of thyroid diseases. In: The thyroid: A fundamental and clinical text, 8th, Braverman LE, Utiger RD (Eds), Lippincott Williams and Wilkins, Philadelphia 2000. p.467.

23- Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160:526.

24- Aoki Y, Belin RM, Clickner R, et al. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). Thyroid 2007; 17:1211

25- Hollowell JG, Staehling NW, Flanders WD, et al. 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.

26- Walsh JP, Bremner AP, Feddema P, et al. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 2010; 95:1095.

27- Kajantie E, Phillips DI, Osmond C, et al. Spontaneous hypothyroidism in adult women is predicted by small body size at birth and during childhood. J Clin Endocrinol Metab 2006; 91:4953.

28- DeRuiter J.(2002). "Thyroid pathology" (PDF). Endocrine Module (PYPP 5260). Auburn University School of Pharmacy. p. 30.

29- Vanderpump MP; Tunbridge WM; French JM; Appleton D; Bates D; Clark F; Grimley Evans, J; Hasan DM et al. (1995). "The incidence of thyroid disorders in the community: a twenty-year follow-up of Whickham Survey". Clinicalendocrinology 43 (1): 55-68.

30- Fatourechi V. (2009). "Subclinical Hypothyroidism: An Update for Primary Care Physicians". Mayo Clinic Proceedings 84 (1): 65-71.

31- Hak AF, Pols HF, Visser T. Subclinical hypothyroidism is an independent risk factor of atherosclerosis and myocardial infarction in elderly women .The Rotterdam study. Study Ann.Intern.Med,200,132 ; 270-278

32- Fernandez Real JM. Lopez-Bermejo A. Castro A, Casametjana R. thyroid function is intrinsically linked to insulin sensitivity and endothelial dependent vasodilation in healthy euthyroid subject .J.Clin.Endocrinol Meteb.2006;91;3337-43

33- Reaven GM . Banting lecture , 1`988, rule of insulin resistance in human diseases , Diabetes 1988,37,1595-607

34- Defronzo RA , Ferrannini F. Insulin resistance a multi faceted syndrome responsible for NIDDM, hypertension , dyslipidemia , and atherosclerotic cardiovascular diseases , Diabetes care , 1991, 14; 173-94

35- Singh BM, Goswami B, Maliko V. Association between insulin resistance and hypothyroidism in females attending a tertiary care hospital .Indian J.Clin.Biochem.2010,25;141-5

36- Serter R, Demirbas B, Culha C, Cakal E. The effect of L-thyroxine replacement therapy on lipid based cardiovascular risk in sub clinical hypothyroidism. Invest J Endocrinol 2004; 27:897-903.

37- American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002; 8:457-69.

38- Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab 2002; 87: 1996-2000.

39- Maratou E, Hadjidakis D, Kollias A, Tsegka K, Peppa M, Alevizaki M, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 2009 (In press)

40- Duntas LH. Thyroid disease and lipids. Thyroid 2002; 12:287-93.

41- Biondi B, Klein I. Hypothyroidism as a risk factor for cardiovascular disease. Endocrine 2004; 24: 1-13.

42- Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526-34.

43- Reaven GM. Banting lecture. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-607.

44- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.

45- Alberti KG, Zimmet P, Shaw J. The metabolic syndrome- a new worldwide definition. Lancet 2005; 366: 1059-62.

46- Bakker SJL, Ter Maaten JC, Popp-Snijders C, Slaets JPJ, Heine RJ, Gans ROB. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab 2001; 86: 1206-11.

47- Chubb SAP, Davis WA, Inman Z, Davis TME. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the Fremantle Diabetes Study. Clin Endocrinol (Oxf) 2005

48- Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415

49- Grundy SM. Metabolic syndrome: Connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol 2006;47:1093-100.3.

50- Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam Study. Ann Intern Med 2000;132:270-8.4.

51- Fernández-Real JM, López-Bermejo A, Castro A, Casamitjana R, Ricart W. Thyroidfunctionis intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. J Clin Endocrinol Metab 2006;91:3337-43.5.

52- Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.6.

53- DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-94.7.

54- Singh BM, Goswami B, Maliko V. Association between insulin resistance and hypothyroidism in females attending a tertiary care hospital. Indian J Clin Biochem 2010;25:141-5

55- Pangaluri R,William E,A; The prevalence of metabolic syndrome and its components in women with subclinical hypothyroidism; Asian journal of pharmaceutical and clinical research ; 6;4; 2013

56- Duntas LH. Thyroid diseases and lipids. Thyroid 2002 , 12; 287-293

57- Jee-Young Oh, Yeon-Ah Sung, Hye Jin Lee Elevated thyroid stimulating hormone levels are associated with metabolic syndrome in euthyroid young women J Endocrinol Metab. 2012 May-Jun; 16(3): 417-422.

58- Anthonia O. Ogbera, Sonny Kuku, and Olusola Dada. The metabolic syndrome in thyroid disease: A report from

Nigeria; Indian J. Intern. Med 2013; 28(2): 180-18

59- Shinkov A, Borissova M,A. Kovatcheva R. The prevalence of the metabolic syndrome increases through the quartiles of thyroid stimulating hormone in a population-based sample of euthyroid subjects; Arq Bras Endocrinol Metab vol.58 no.9 São Paulo Dec. 2011

60- Erdogan M, Canataroglu A, Ganidagli S, Kulaks?zoglu M. Metabolic syndrome prevalence in subclinic and overt hypothyroid patients and the relation among metabolic syndrome parameters; J Endocrinol Invest. 2011 Jul-Aug;34(7):488-92. doi: 10.3275/7202. Epub 2010 Jul 22

61- Haque R, Ferdousi,S. RahmanW, Uddin MN; metabolic syndrome in hypothyroid patients Bangladesh J Med. Biochem.2014, 7(2) 57-6

62- Kumar HK, Yaday RK, PrajapatiJ, Reddy CV, Association between thyroid hormone , insulin resistance and metabolic syndrome .Saudi Med. J. 2009, 30 ,907-11

63- Cappola AR, Landenson PW. Hypothyroidism and atherosclerosis .J.Clin. Endocrinol.Met. 2004;88.2438-44

64- Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, et al. Thyroid function in humans with morbid obesity. Thyroid 2006;16:73-8.

65- Bastemir M, Akin F, Alkis E, Kaptanoglu B. Obesity is associated with increased serum TSH level, independent of thyroid function. Swiss Med Wkly 2007;137:431-4.

66- Reinehr T, de Sousa G, Andler W. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. J Clin Endocrinol Metab 2006;91:3088-91.

67- Bhowmick SK, Dasari G, Levens KL, Rettig KR. The prevalence of elevated serum thyroid-stimulating hormone in childhood/adolescent obesity and of autoimmune thyroid diseases in a subgroup. J Natl Med Assoc 2007;99:773-6

68- Jayakumar RV, Nisha B, Unnikrishnan AG, Nair V, Kumar H. Thyroid status in metabolic syndrome - a clinical study. Thyroid Res Pract 2010;366-70

69- Kumar HK, Yadav RK, Prajapati J, Reddy CV, Raghunath M, Modi KD. Association between thyroid hormones, insulin resistance and metabolic syndrome. Saudi Med J 2009;30:907-11.

70- Lai Y, Wang J, Jiang F, Wang B, Chen Y, Li M, et al. The relationship between serum thyrotropin and components of metabolic syndrome. Endocr J 2011;58:23-30.

71- Chugh K, Goyal S, Shankar V, Chugh SN. Thyroid function tests in metabolic syndrome. Indian J Endocr Metab 2012;16:958-61.

72- Meher LK, Raveendranathan SK, Kota SK, Sarangi J, Jali SN. Prevalence of hypothyroidism in patients with metabolic syndrome. Thyroid Res Pract 2013;10:60-4