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Markers of Cardiometabolic Risk and Thyroid Dysfunction in U.s. Adolescents: Nhanes Iii

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MARKERS OF CARDIOMETABOLIC RISK AND THYROID DYSFUNCTION IN U.S. ADOLESCENTS: NHANES III

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30 Pages

The global prevalence of metabolic syndrome (MetS) and its associated components (high fasting glucose, waist circumference, blood pressure, triglycerides, and low HDL) have increased over the past few decades. In addition, abnormal thyroid hormone levels have been found to manifest in a cascade of metabolic dysfunction, which may be linked to MetS in youth. PURPOSE: The purpose of the study is to investigate the association between MetS, its components, and markers of thyroid function in a nationally-representative sample of adolescents. METHODS: The National Health and Nutrition Examination Survey III (1988-1994) collected data on the components of metabolic syndrome and thyroid function in 1,322 adolescents aged 12-18.9 years (613 males and 709 females). Participants were grouped based on MetS status, number of MetS components, and markers of thyroid function using age- and sex-specific reference values (including thyroid stimulating hormone (TSH), thyroxine (T4), antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb). Logistic models were used to predict the status of the thyroid markers (as high/low) from MetS status, controlling for age, sex, and race/ethnicity. RESULTS: In males MetS prevalence was 6.1% (16.7% had at least 2 MetS components). In females, MetS prevalence was 4.8% (22% had at least 2 MetS components). Males with ≥2 MetS components had significantly higher odds of

being TPOAb positive (OR = 7.9, 95%CI [1.7,36.8]) and were not likely to be TgAb positive (OR = 0.7 95%CI [0.1,6.4]). Females with ≥2 MetS components were 1.8 times more likely to be TPOAb positive (OR = 1.8 95%CI [0.5,6.5]) and 1.3 times more likely to be TgAb positive (OR = 1.3 95%CI [0.4-4.3]). In males, TG, WC, HDL-C, and DBP were significantly increased in the elevated TPOAb group (all P<0.05). No significant differences were observed in females. Odds ratios for MetS components were calculated according to TSH decile. Male subjects in the top decile of TSH had significantly higher odds of elevated TG; females were less likely to have increased BP (both P<0.05). Males in the bottom TSH decile were unlikely to present with elevated fasting glucose while females are unlikely to have elevated TG, WC, or fasting glucose (all P<0.05). CONCLUSION: Covert thyroid dysfunction often accompanies many components of MetS. Therefore, we encourage future researchers to investigate the clinical utility of restoring thyroid function as a component in the consolidation of treatment for MetS. The present study is unable to explain the effect of TPOAb on MetS, although we do believe there is a link. Research should be conducted on the biochemical processes in which TPOAb may influence MetS. Plausibly, the present study, and studies conducted prior to ours suggest a bidirectional relationship between MetS and thyroid dysfunction.

KEYWORDS: Cardiometabolic, Metabolic Syndrome, Thyroid, Antibodies, Adolescents

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Introduction

The global prevalence of metabolic syndrome (MetS) and its associated comorbidities have increased at an alarming rate (Ford, Giles, & Mokdad, 2004). Ford et al. (2008) found the prevalence of metabolic syndrome in U.S. adolescents, ages 12-17 years, was approximately 4.5% (~1.1 million adolescents). This condition is related to various morbidities, including Type II diabetes, cardiovascular disease, and a plethora of cancers, and impacts the renal, hepatic, skin, ocular, sleep, reproductive, and cardiovascular systems (Kaur, 2014).

The hypothalamic-pituitary-thyroid axis regulates the synthesis and secretion of TSH and thyroid hormones (Braverman et al., 2012). Initially, thyrotropin-releasing hormone is synthesized by hypothalamic neurons and secreted into the hypothalamic-pituitary portal venous system. It is then carried through this system to the pituitary where it stimulates the synthesis and secretion of thyroid stimulating hormone (TSH). TSH the primary regulator of thyroid function, is a glycoprotein synthesized and secreted from the anterior pituitary gland. TSH binds its receptors in the thyroid gland, stimulating the synthesis and secretion of thyroxine (T4) and triiodothyronine (T3). Regulation of the thyroid hormones is further controlled using a negative feedback loop.

In relation to autoimmune thyroid issues, two antibodies (antithyroglobulin antibodies and antithyroid peroxidase antibodies) are measured during the diagnostic stage of thyroid dysfunction. Thyroglobulin is a glycoprotein dimer secreted into the follicular lumen to serve as the matrix for the synthesis of T4 and T3, as well as the storage form of the hormones and

iodide. Thyroglobulin reenters the cell to be digested in lysosomes when T4 and T3 are needed, leading to the release of the hormones into the blood stream (Braverman et al., 2012). Antithyroglobulin antibodies suggest autoimmune hypothyroidism, yet their function is unclear. The primary use of antithyroglobulin antibodies (TgAb) testing is for patients with differentiated thyroid cancers as an adjunctive test to serum measurements and may be an independent detector of changes in tumor size.

Thyroid peroxidase (TPO) is a glycoprotein with a prosthetic heme I group. TPO catalyzes the oxidation of iodide which is essential for the incorporation of iodide onto tyrosine residues in thyroglobulin and coupling of the iodotyrosines to generate T4 and T3. Antithyroid peroxidase antibodies (TPOAb) show affinity for an immunodominant region of the TPO molecule. TPOAbs are detected in nearly 100% of individuals suffering from autoimmune hypothyroidism and 80% of individuals with Graves' disease.

Thyroid dysfunction is generally observed as one of two states. Hypothyroidism, a decrease in production and secretion of free thyroxine (fT4) and free triiodothyronine (fT3) accompanied by increased thyroid stimulating hormone (TSH) secretion. The opposing state thyrotoxicosis (or hyperthyroidism) presents with elevated serum concentrations of fT4, fT3, or both (Braverman & Cooper, 2012, pg 523 & 354). Canaris et al. (2000) found abnormal thyroid levels in 9.9% of adults not taking thyroid medications. During a state of dysfunction, thyroid hormones have a negative effect on cellular metabolism and processes. Delayed diagnosis of hypothyroidism in infants, children, and adolescents may impact skeletal growth and maturation, pubertal development, and adult height (Braverman et al., 2012; Srinivasan & Misra, 2015).

Waring et al. (2012), stated that thyroid dysfunction and MetS are the most common endocrine disorders with major overlap. Relatedly, abnormal thyroid hormone levels exacerbate a cascade of metabolic dysfunction leading to an aggravation of defined MetS components (Martínez-Sánchez, Alvarez, Fernø, Nogueiras, Diéguez, & López, 2014). Original studies, reviews, meta-analysis, etc. have been conducted on the associations of MetS and thyroid dysfunction in adults (Delitala et al., 2017; Iwen et al., 2013). Yet, few have looked at how these associations exist in youth. Furthermore, of the few studies conducted in the young, most have low levels of external validity (confounded by cultural differences).

Khatiwada et al. (2016), suggested the effects of concurrent MetS and thyroid dysfunction may compound risk of CVD. In 2015, a study of obese children found TSH levels did not differ within sexes dependent on the presence or absence of MetS, however, fT3 and fT4 tended to be higher in boys with MetS than those without (Minami, Takaya, Takitani, Ishiro, Okasora, Niegawa, & Tamai, 2015). Furthermore, TSH in the normal range was positively associated with systolic blood pressure (SBP), non-HDL-C, and glucose levels in girls. Roos et al. (2007) found that in euthyroid adults, TSH was only associated with one MetS risk factor, triglycerides (TG), while there was a significant relationship between fT4 and waist circumference (WC), TG, high density lipoprotein (HDL-C), and fasting glucose.

Acknowledging the aggregation of variables interacting within thyroid dysfunction and MetS, it is crucial that researchers and clinicians systematically address the question of how these pathologies manifest and their potential relationships in adolescents. Therefore, the aim of this study is to examine the associations of thyroid dysfunction and MetS in a nationally-representative sample of U.S. adolescents.

Methods

Sampling & Subjects

This cross-sectional study utilized data collected from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994). NHANES III utilized a stratified, multistage probability design resulting in a nationally representative sample of the total U.S. noninstitutionalized civilian population. Boys and girls aged 12-18.9 were included in the study and the final sample included 1322 subjects (613 males and 709 females) (Table 1). We excluded pregnant females, those with missing key variables for metabolic syndrome and thyroid function, and those that fasted for less than six hours prior to serum blood draws.

Metabolic Components

Jolliffe & Janssen's (2007) definition of adolescent-specific MetS, designed in NHANES data, was used to categorize MetS and its components. In brief, this definition was created via LMS regression where MetS criteria were linked to adult National Cholesterol Education Program - Adult Treatment Panel III (ATP) criteria which included: high waist circumference (≥102 cm in men and 88 cm in women), elevated SBP (≥130 mmHg) or DBP (≥85 mmHg), a low HDL-C (<1.03 nmol/l in men and <1.30 nmol/l in women), high triglycerides (≥1.7 nmol/l), and elevated fasting glucose (≥ 5.6 nmol/l). Male and female SBP curves represented the 92nd and 93rd percentiles, respectively; DBP curves represented the 97th and 99th percentiles, respectively. HDL-C curves for males and females represented the 26th and 43rd percentiles, respectively. TG curves represented the 89th percentile in both sexes. MetS was stratified by sex and participants were categorized as individuals with 0 or 1 metabolic risk factors versus those with 2 or more metabolic risk factors. Due to the small sample size of usable adolescents, compounded by the small number of adolescents outside of the thyroid clinical range, we chose

to base some analyses on the presence of ≥2 MetS components instead of the conventional ≥3 MetS components.

Thyroid Variables

For TSH and T4, participants were categorized according to age- and sex-specific reference values using definitions by Zurakowski et al. (1999). The NHANES III thyroid variable antithyroid microsomal antibody is also known as anti-thyroid peroxidase antibodies (Czarnocka, Ruf, Ferrand, Carayon, & Lissitzky, 1985). For TPOAb and TgAb cutpoints we utilized Hollowell et al. (2002) values. Using the hormone cutpoints outlined by Zurakowski, four categories were created, for each sex, including high TSH, low TSH, high T4, and low T4. Antithyroid antibodies were collected and analyzed in conjunction with thyroid hormones as they affect autoimmunity resulting in dysfunctional synthesis and secretion. For TPOAb, participants were categorized as normal TPOAb (<0.5 IU/ml) or high TPOAb (>0.5 IU/ml). TgAb was categorized as normal TgAb (<1.0 IU/ml) or high TgAb (>1.0 IU/ml). Ranges for TPOAb and TgAb categories were not stratified by sex or age since this is not supported within the literature.

Measurement Protocols

SBP and DBP were recorded as the average of 3-4 seated, resting measurements. Waist circumference was measured to the nearest 0.1 cm at the location the iliac crest meets the midaxillary line of the body. All serum blood measurements were taken after at least a 6 hour fast. Radioimmunoassay was used for the measurement of T4. TSH was measured using a chemiluminescent immunometric assay. Direct radioimmunoassay system measured antithyroid peroxidase antibodies and antithyroglobulin antibody using a highly purified, stable preparation of I-labeled thyroid peroxidase enzyme and I-labeled thyroglobulin, respectively. Assays were standardized against MRC (Medical Research Council). Cholesterol, TG, and HDL-C were

analyzed using a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Glucose was measured using the glucose hexokinase method. (Department of Health and Human Services. National Center for Health Statistics. NHANES III Reference Manual and Reports. Hyatsville, MD: Center for Disease Control and Prevention, 1996).

Experimental Design

Three models were analyzed for each of the four thyroid variables. All models were grouped by metabolic health status (0-1 MetS Components or ≥2 MetS components). Model 1 consisted of boys and girls controlling for sex, age, and race-ethnicity. Model 2 included boys alone and did not control for sex, age, or race-ethnicity. Model 3 included girls alone and did not control for sex, age, or race-ethnicity. To compare metabolic health status with TSH, T4, TPOAb, and TgAb categories, between-group analyses were conducted. All models analyzed participants in the top and bottom 10% of sex- and age-specific reference ranges against those in the middle 80%. Analysis of the top and bottom 10% of sex- and age specific reference ranges were used to increase subsample size and include individuals with sub-clinically dysfunctional thyroid hormone ranges. All models also analyzed participants by the normal, high, and low groups (TSH and T4).

Statistical Analysis

SPSS Version 21 (Armonk, New York) was used for data analysis. The complex sample design was accounted for in each analysis, utilizing the NHANES weight, stratification, and clustering. Descriptive statistics were used to ensure normal frequencies within datasets. Subjects with variables consisting of nil values, or codes suggesting unusable data were removed from analysis.

Results

SBP, HDL-C, fasting glucose, thyroxine, and TPOAb were statistically different between sexes (Table 1). Age, WC, DBP, TG, TSH, and TgAb were not different between sexes (Table 1). In males MetS prevalence was 6.1% according to the ATP III definition. Furthermore, 16.7% of males had at least 2 MetS risk factors. In females, the prevalence of MetS was 4.8%, while 22% had at least 2 components of MetS. Descriptive statistics can be found in Table 1. Males with ≥2 MetS components had significantly higher odds of being TPOAb positive (OR = 7.9, 95%CI [1.7,36.8]) and were not likely to be TgAb positive (OR = 0.7 95%CI [0.1,6.4]). Females with ≥2 MetS components were 1.8 times more likely to be TPOAb positive (OR = 1.8 95%CI [0.5,6.5]) and 1.3 times more likely to be TgAb positive (OR = 1.3 95%CI [0.4-4.3]). Odds of being antibody positive in males and females with ≥2 MetS components versus those with ≤1 MetS components can be found in Table 3. The estimated marginal means were calculated to show differences between MetS components in subjects with elevated TPOAb and those within the acceptable range. In males, TG, WC, HDL-C, and DBP were significantly increased in the elevated TPOAb group (all $P<0.05$) (Table 4). No significant differences were observed in females (Table 5). Odds ratios for MetS components were calculated according to TSH decile. As shown in Figure 1, male subjects in the top decile of TSH had significantly higher odds of elevated TG; females were less likely to have increased BP (both $P<0.05$). Figure 2 shows the odds of increased cardiometabolic risk in subjects in the bottom decile of TSH. Males in the bottom TSH decile are unlikely to present with elevated fasting glucose while females are unlikely to have elevated TG, WC, or fasting glucose (all $P<0.05$). No significant results were found for T4 or TgAb.

Discussion

The most important findings in the current study are related to the links between multiple MetS components and markers of thyroid function in a nationally representative sample of U.S. adolescents. We attempted to elucidate the relationship between antithyroid autoantibodies and the components of MetS in U.S. adolescents. Our analysis found a significant relation between participants in the bottom decile of TSH and fasting glucose level in males and females.

The current study found four of the six components of MetS (TG, WC, HDL, and DBP) were significantly associated with increased TPOAb values in males. Prior studies have shown that elevated TPOAb may signal impending thyroid dysfunction, however, little is known about the direct mechanisms relating antithyroid autoantibodies to MetS components (Mehran, Amouzegar, Tohidi, Moayedi, & Azizi, 2014). Nikkilä & Kekki (1972), found that thyroid hormones influence regulation of production and removal of plasma TG. In thyrotoxicosis, mean plasma TG levels and average total TG turnover rate are elevated. The primary feature of TG metabolism in hypothyroidism is a decrease in removal efficiency leading to a moderate increase in TG concentration. Increased adiposity (associated with WC) in hypothyroidism is primarily caused by decreased energy expenditure (Bianco, Maia, Da Silva, & Christoffolete, 2005). The current study found an association between TSH and waist circumference in females-only, which may be explained by the small sample. According to Tan, Shiue, and Kung (1988), thyroid hormone significantly effects the activity of hepatic lipase (HL). The researchers found that overexpression of HL due to hyperthyroidism led to decreased HDL-C levels. HDL-C levels increased after 3-4 months of treatment on antithyroid drugs. Streetan, Anderson, Howland, Chiang, & Smulyan (1988), showed a significant rise in DBP occurs during the change from hyperthyroidism to hypothyroidism; a significant fall in DBP is noted when euthyroidism is

restored. Streetan et al., suggest hypothyroidism may lead to hypotension due to increased extracellular fluid volume and fluid retention. Furthermore, Streetan hypothesized that some individuals with hypotension may have undiagnosed hypothyroidism that can be managed with thyroxine replacement therapy.

We found the odds of having elevated fasting glucose while being categorized in the bottom decile of TSH level is unlikely (males (OR = 0.1 95%CI [0.1-0.4], females OR = 0.1 95%CI [0.1-0.7]). In agreement with our findings, prior studies have shown that upon the development of hyperthyroidism glucose turnover increases significantly (Marecek, & Feldman, 1973; Okajima, & Ui, 1979). Furthermore, Okajima et al., suggest the effects of hyperthyroidism are similar to those of catecholamines in relation to metabolic alterations. In a separate study, Okajima et al. (1979), found endogenous insulin suppression did not decrease hyperthyroid induced increases in glucose turnover rates (while in a starved state). It is unlikely insulin action mediates thyroid-dependent stimulation of glucose turnover (glucose disposal rate constant) as insulin secretion is diminished and circulating insulin undergoes rapid breakdown (decreased insulin half-life) in hyperthyroidism (Renauld et al., 1971; Cavagnini et al., 1974; Orsetti et al., 1974). Field et al. (1962), found evidence that TSH does not act by increasing glucose transport, instead it acts by increasing stimulation of glucose oxidation.

Hunter et al. (2000), found a low prevalence of hypothyroidism in the young, however, values were at least twice those of previous estimates, “possibly indicating a rising incidence of autoimmunity in young people” (Hunter, Greene, MacDonald, & Morris, 2000). Isolated occurrences of MetS and thyroid dysfunction lead to various metabolic issues that increase in magnitude and mortality with age (Meng, Liu, Zhang, Liu, Song, Tan, & Ren, 2015). Minami et

al. (2015), hypothesized that involvement of thyroid function in the development of MetS might differ between children and adults.

Strengths of the study include the nationally representative sampling and the uniqueness of researching thyroid variables and MetS components in American adolescents. The main limitation of the study is the cross-sectional methodology utilizing data from 1988-1994. Therefore, the study does not allow determination of causation. It must be acknowledged that when conducting a multivariate study including endocrine function, it is difficult to control for confounding variables. Future research should examine the influence of sex hormones on the associations of MetS and thyroid function. Research should also include long-term longitudinal studies examining the outcome of individuals in the top and bottom 10% of normal thyroid ranges.

Conclusion

Covert thyroid dysfunction often accompanies many components of MetS. Therefore, we encourage future researchers to investigate the clinical utility of restoring thyroid function as a component in the consolidation of treatment for MetS. The present study is unable to explain the effect of TPOAb on MetS, although we do believe there is a link. Research should be conducted on the biochemical processes in which TPOAb may influence MetS. Plausibly, the present study and studies conducted prior to ours suggest a bidirectional relationship between MetS and thyroid dysfunction.

References

Braverman, L. E., & Cooper, D. (2012). *Werner & Ingbar's the thyroid: a fundamental and clinical text*. Lippincott Williams & Wilkins.

Bianco, A. C., Maia, A. L., Da Silva, W. S., & Christoffolete, M. A. (2005). Adaptive activation of thyroid hormone and energy expenditure. *Bioscience reports*, *25*(3-4), 191-208.

Canaris, G. J., Manowitz, N. R., Mayor, G., & Ridgway, E. C. (2000). The Colorado thyroid disease prevalence study. *Archives of internal medicine*, *160*(4), 526-534.

Czarnocka, B., Ruf, J., Ferrand, M., Carayon, P., & Lissitzky, S. (1985). Purification of the human thyroid peroxidase and its identification as the microsomal antigen involved in autoimmune thyroid diseases. *FEBS letters*, *190*(1), 147-152.

Dayan, C. M. (2001). Interpretation of thyroid function tests. *The Lancet*, *357*(9256), 619-624.

P Delitala, A., Fanciulli, G., M Pes, G., Maioli, M., & Delitala, G. (2017). Thyroid hormones, metabolic syndrome and its components. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *17*(1), 56-62.

Nikkilä, E. A., & Kekki, M. (1972). Plasma triglyceride metabolism in thyroid disease. *The Journal of clinical investigation*, *51*(8), 2103-2114.

Field, J. B., Johnson, P., Kendig, E., & Pastan, I. (1963). Further studies on effects of thyroid-stimulating hormone on thyroid glucose oxidation. *CHEMISTRY*, *238*(4).

Ford, E. S., Giles, W. H., & Mokdad, A. H. (2004). Increasing prevalence of the metabolic syndrome among US adults. Diabetes care, 27(10), 2444-2449.

Ford, E. S., Li, C., Zhao, G., Pearson, W. S., & Mokdad, A. H. (2008). Prevalence of the metabolic syndrome among US adolescents using the definition from the International Diabetes Federation. *Diabetes care*, *31*(3), 587-589.

Hollowell, J. G., Staehling, N. W., Flanders, W. D., Hannon, W. H., Gunter, E. W., Spencer, C. A., & Braverman, L. E. (2002). Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *The Journal of Clinical Endocrinology & Metabolism*, *87*(2), 489-499.

Huang, P. L. (2009). A comprehensive definition for metabolic syndrome. *Disease models & mechanisms*, *2*(5-6), 231-237.

Hunter, I., Greene, S. A., MacDonald, T. M., & Morris, A. D. (2000). Prevalence and aetiology of hypothyroidism in the young. *Archives of disease in childhood*, *83*(3), 207-210.

Iwen, K. A., Schröder, E., & Brabant, G. (2013). Thyroid hormones and the metabolic syndrome. *European thyroid journal*, *2*(2), 83-92.

Jolliffe, C. J., & Janssen, I. (2007). Development of age-specific adolescent metabolic syndrome criteria that are linked to the Adult Treatment Panel III and International Diabetes Federation criteria. *Journal of the American College of Cardiology*, *49*(8), 891-898.

Khatiwada, S., Sah, S. K., Rajendra, K. C., Baral, N., & Lamsal, M. (2016). Thyroid dysfunction in metabolic syndrome patients and its relationship with components of metabolic syndrome. *Clinical diabetes and endocrinology*, *2*(1), 3.

Kaur, J. (2014). A comprehensive review on metabolic syndrome. Cardiology research and practice, 2014.

Le, T. N., Celi, F. S., & Wickham III, E. P. (2016). Thyrotropin Levels Are Associated with Cardiometabolic Risk Factors in Euthyroid Adolescents. *Thyroid*, *26*(10), 1441-1449.

Marecek, R. L., & Feldman, J. M. (1973). EflFect of Hyperthyroidism on Insulin and Glucose Dynamics in Rabbits. *Endocrinology*, *92*(6), 1604-1611.

Martínez-Sánchez, N., Alvarez, C. V., Fernø, J., Nogueiras, R., Diéguez, C., & López, M. (2014). Hypothalamic effects of thyroid hormones on metabolism. *Best Practice & Research Clinical Endocrinology & Metabolism*, *28*(5), 703-712.

Mehran, L., Amouzegar, A., Tohidi, M., Moayedi, M., & Azizi, F. (2014). Serum free thyroxine concentration is associated with metabolic syndrome in euthyroid subjects. *Thyroid*, *24*(11), 1566-1574.

Meng, Z., Liu, M., Zhang, Q., Liu, L., Song, K., Tan, J., ... & Ren, X. (2015). Gender and age impacts on the association between thyroid function and metabolic syndrome in Chinese. *Medicine*, *94*(50).

Minami, Y., Takaya, R., Takitani, K., Ishiro, M., Okasora, K., Niegawa, T., & Tamai, H. (2015). Association of thyroid hormones with obesity and metabolic syndrome in Japanese children. *Journal of clinical biochemistry and nutrition*, *57*(2), 121-128.

Okajima, F., & Ui, M. (1979). Metabolism of glucose in hyper-and hypo-thyroid rats in vivo. Glucose-turnover values and futile-cycle activities obtained with 14C-and 3H-labelled glucose. *Biochemical Journal*, *182*(2), 565.

Okajima, F., & Ui, M. (1979). Metabolism of glucose in hyper-and hypo-thyroid rats in vivo. Minor role of endogenous insulin in thyroid-dependent changes in glucose turnover. *Biochemical Journal*, *182*(2), 577.

Orsetti, A., Collard, F., & Jaffiol, C. (1974). Abnormalities of carbohydrate metabolism in experimental and clinical hyperthyroidism: studies on plasma insulin and on the A-and B-chains of insulin. Acta diabetologia latina, 11(6), 486-492.

Renauld, A., Pinto, J. E. B., Sverdlik, R. C., & Foglia, V. G. (1971). Studies on the effect of hyperthyroidism on the insulin response to hyperglycemia in the dog. *Hormone and Metabolic Research*, *3*(04), 247-251.

Roos, A., Bakker, S. J., Links, T. P., Gans, R. O., & Wolffenbuttel, B. H. (2007). Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *The Journal of Clinical Endocrinology & Metabolism*, *92*(2), 491-496.

Streeten, D. H., Anderson, G. H., Howland, T., Chiang, R., & Smulyan, H. (1988). Effects of thyroid function on blood pressure. Recognition of hypothyroid hypertension. *Hypertension*, *11*(1), 78-83.

Srinivasan, S., & Misra, M. (2015). Hyperthyroidism in children. *Pediatrics in review*, *36*(6), 239-248.

Tan, K. C. B., Shiu, S. W. M., & Kung, A. W. C. (1998). Effect of thyroid dysfunction on high-density lipoprotein subfraction metabolism: roles of hepatic lipase and cholesteryl ester transfer protein. *The Journal of Clinical Endocrinology & Metabolism*, *83*(8), 2921-2924.

U.S. Department of Health and Human Services. National Center for Health Statistics. NHANES III Reference Manual and Reports. Hyatsville, MD: Center for Disease Control and Prevention, 1996

Zurakowski, D., Di Canzio, J., & Majzoub, J. A. (1999). Pediatric reference intervals for serum thyroxine, triiodothyronine, thyrotropin, and free thyroxine. *Clinical chemistry*, *45*(7), 1087-1091.

Table 1

Characteristics of Subjects

	Male	Female	Total
N	613	709	1322
Age (yrs)	15.9 (0.1)	16.0 (0.1)	15.9 (0.1)
Race-Ethnicity (%)			
Non-Hispanic White	69.1 (3.4)	64.1 (3.4)	
Non-Hispanic Black	13.8 (1.7)	14.9 (1.8)	
Mexican American	9.1 (1.3)	8.0 (1.2)	
Other	8.0 (2.4)	13.0 (3.0)	
Metabolic Syndrome (%)			
Metabolic Syndrome Positive	6.1	4.8	
≥ 2 Metabolic Syndrome Components	16.7	22.0	
Waist Circumference (cm)	77.8 (0.7)	76.9 (0.8)	77.3 (0.5)
*Systolic Blood Pressure (mm Hg)	111.8 (0.5)	104.4 (0.6)	108.0 (0.4)
Diastolic Blood Pressure (mm Hg)	61.9 (0.9)	61.1 (0.6)	61.5 (0.6)
*High Density Lipoprotein – Cholesterol (mmol/L)	1.2 (0.1)	1.3 (0.1)	1.3 (0.1)
Triglycerides (mmol/L)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
*Fasting Glucose (mmol/L)	5.0 (0.1)	4.8 (0.1)	4.9 (0.1)
*Thyroxine (nmol/L)	110.0 (1.8)	117.1 (2.2)	113.4 (1.6)
*High Thyroxine	5.2	16.7	
* Low Thyroxine	0.6	3.1	
Thyroid Stimulating Hormone (mIU/L)	2.0 (0.2)	1.6 (0.1)	1.8 (0.1)
High TSH	3.5	2.7	
Low TSH	3.5	3.4	
*Antithyroid Peroxidase Antibodies (%) >0.5 (IU/ml)	2.8 (1.0)	6.9 (1.7)	
Antithyroglobulin Antibody (%) >1.0 (IU/ml)	3.4 (1.3)	7.1 (1.5)	

*Data reported as means (standard error) or subsample (standard error); * Statistically significant between groups (P<0.05).*

Table 2

Odds of High/Low TSH and T4 Values by Metabolic Syndrome Components

		Male Odds Ratio [95%CI]	Female Odds Ratio [95%CI]	Combined Odds Ratio [95%CI]
TSH	High Reference Range	16.7[1.5-192.2]	1.4[0.3-7.0]	5.0[1.4-18.2]
	Top Decile	4.2[1.2-15.2]	0.8[0.2-2.5]	1.8[0.7-4.8]
	Low Reference Range	∞	0.1[0.03-0.5]	0.1[0.002-0.3]
	Bottom Decile	0.2[0.1-0.9]	0.2[0.1-0.6]	0.2[0.1-0.5]
T4	High Reference Range	1.3[0.3-5.4]	1.1[0.5-2.5]	1.2[0.5-2.6]
	Top Decile	1.7[0.6-4.7]	0.8[0.3-2.2]	1.2[0.5-2.8]
	Low Reference Range	1.4[0.3-6.3]	0.6[0.1-3.0]	0.6[0.2-1.8]
	Bottom Decile	0.6[0.2-2.4]	0.9[0.3-2.3]	0.8[0.4-1.9]

Odds ratios compare males and females with ≥2 metabolic syndrome components against those with ≤1 metabolic syndrome components; Male and female odds ratios are unadjusted for sex, age, and race-ethnicity, Combined odds ratios are adjusted for sex, age, and race-ethnicity.

Table 3

Odds of Positive Antithyroid Antibodies by Metabolic Syndrome Components

	Male Odds Ratio [95%CI]	Female Odds Ratio [95%CI]	Male & Female Odds Ratio [95%CI]
Antithyroid Peroxidase Antibody - Positive	7.9[1.7-36.8]	1.8[0.5-6.5]	2.6[1.1-6.7]
Antithyroglobulin Antibody - Positive	0.7[0.1-6.4]	1.3[0.4-4.3]	1.1[0.3-3.3]

Odds ratios compare males and females with ≥2 metabolic syndrome components against those with ≤1 metabolic syndrome components; Male and female odds ratios are unadjusted for sex, age, and race-ethnicity; Combined odds ratios are adjusted for sex, age, and race-ethnicity.

Table 4

Male Antithyroid Peroxidase Antibody Estimated Marginal Means

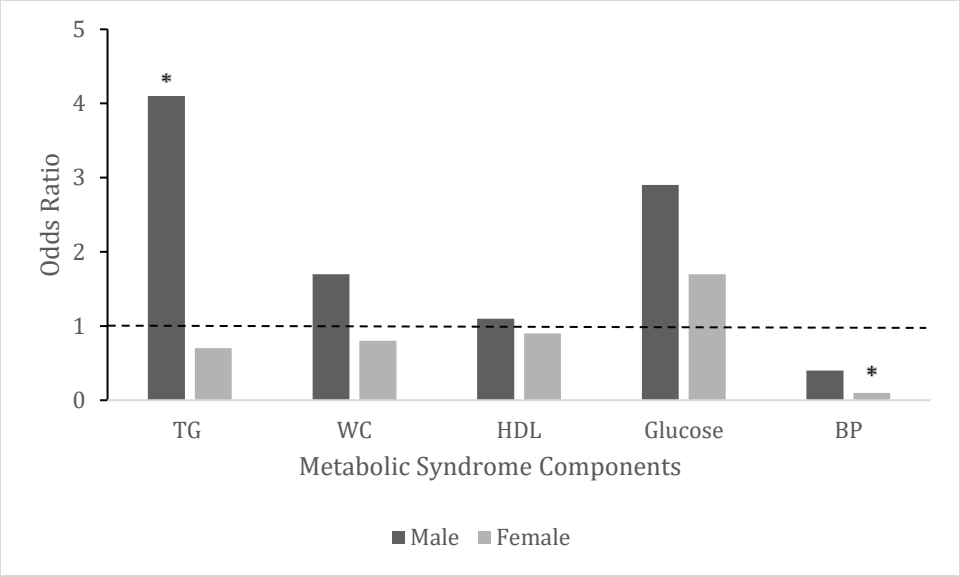
	↑ Antithyroid Peroxidase Antibodies	↔ Antithyroid Peroxidase Antibodies
* Triglycerides	1.3	0.9
† Waist Circumference	88.8	76.9
‡ HDL	1.1	1.3
Fasting Glucose	4.9	5.0
Systolic Blood Pressure	115.0	110.6
* Diastolic Blood Pressure	68.0	62.1

** P<0.05, † P<0.01, ‡ P=0.001*

Table 5

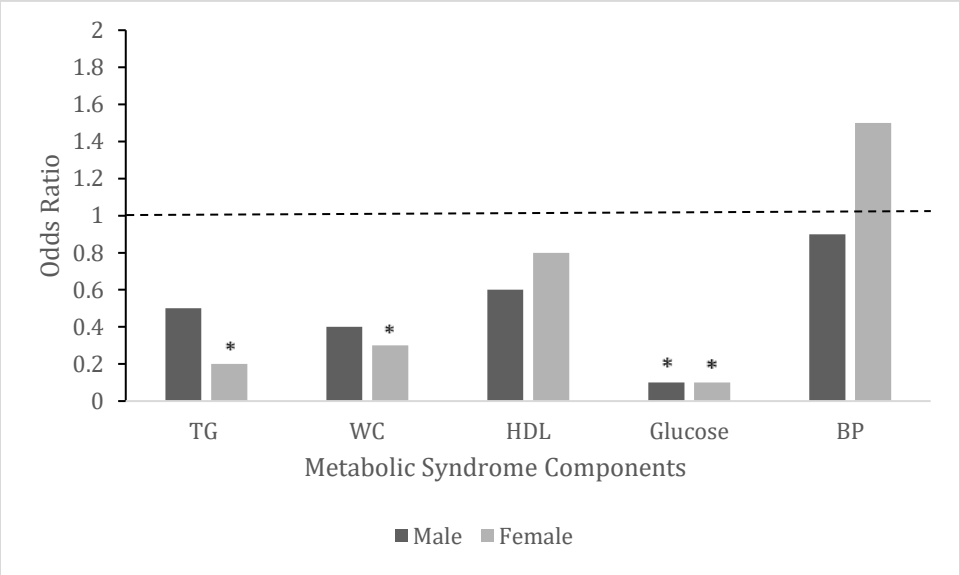
Female Antithyroid Peroxidase Antibody Estimated Marginal Means

	↑ Antithyroid Peroxidase Antibodies	↔ Antithyroid Peroxidase Antibodies
Triglycerides	1.1	0.961
Waist Circumference	79.0	77.7
HDL	1.4	1.4
Fasting Glucose	4.8	4.8
Systolic Blood Pressure	104.4	107.5
Diastolic Blood Pressure	59.0	60.3



**P<0.05*

Figure 1. TSH top decile.



**P<0.05*

Figure 2. TSH bottom decile.

CHAPTER II: EXTENDED REVIEW OF THE LITERATURE.

Specific Research

This literature review aims to elucidate the controversial nature of research on MetS and thyroid function. To synthesize a balanced view of the current depth of investigation, the author presents research on the lack of consensus, development of current referent information, and etiology. Additionally, the known associations of MetS and thyroid function will be considered. It is well understood that obesity and lifestyle have strong influences on MetS, however, the pathogenesis remains unclear (Alberti, Eckel, Grundy, Zimmet, Cleeman, Donato, & Smith, 2009). Slight disparities in establishment of diagnostic criteria may be explained by factors such as differences in analytical assays, ethnicity, and population or geographic covariates (Kapelari et al., 2008).

In 1998, WHO proposed the first formalized MetS definition emphasizing insulin resistance as a required component for diagnosis. In 2001, the NCEP ATP III developed conflicting criteria; no single factor was integral, however, the presence of 3 of 5 factors was required. In 2005, the IDF dropped the requirement for insulin resistance and attempted to unify the clinical definitions of MetS with the AHA/NHLBI. The organizations came to a consensus on 4 of the 5 risk factors excluding assessment of abdominal obesity in the form of WC thresholds (related to insulin resistance).

According to Alberti et al. (2009), establishing abdominal obesity values is difficult due to differences in relation to other MetS risk factors, predictive value of various levels of obesity on morbidity, and the difficulty of generating cut-points for continuous variables. The authors

went on to suggest that not only do ethnicities differ, but health systems require values unique to their circumstances rather than universal cut-points.

Compared with Europids, thresholds in the Asian population (e.g. China, Japan, India) should consist of lower values. The difference in MetS prevalence using high vs. low cut-points is minimal in the U.S. due to the significant correlation of abdominal obesity with MetS components and the high rates of obesity.

The IDF, AHA/NHLBI, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity proposed a unified definition of criteria for the clinical diagnosis of MetS. The authors claim the definition recognizes the influence of demographics and encourages local groups to use their own discretion.

Currently, metabolic syndrome definitions are based on limited data. Large-scale longitudinal studies focusing on various race-ethnicities, ages, gender, and locals are required for the development of externally valid MetS definitions. Clinicians must use their experience, judgement, and knowledge of individual demographics when diagnosing MetS.

In 2007, Jolliffe & Janssen conducted a study with the purpose of developing age-specific adolescent MetS criteria linked to the NCEP ATP III and IDF adult criteria. The authors noted prior research for adolescent MetS definitions used arbitrary cut-points and determined the development of health-based criteria was necessary for use in clinical and research settings.

Jolliffe's study used the MetS component cut-points developed with data from NHANES III, and continuous NHANES 1999-2002. Analysis consisted of 12-20 year old's who had fasting measurements (≥6 hours as per NHANES protocol) of HDL-C, TG, and glucose. WC and BP were measured in all participants but analysis was limited to those who fasted, which resulted in 2921 male and 3146 female participants.

To develop MetS cut-points, age- and sex-specific growth curves were developed using the Lambda Mu Sigma method (Cole & Green, 1992). MetS component growth curves were linked to the adult ATP and IDF cut-points (defined by the percentile that corresponded with the adult cut-point and regressed backward into adolescence).

Jolliffe et al. found fasting glucose stayed constant (5.6 mmol/l) from ages 12-20 years. The study resulted in the development of MetS component cut-points at 1-year increments with each cut-point reflecting the midpoint of a given year. Alberti et al. reviewed the controversy between the IDF and ATP over WC values. Jolliffe and Janssen considered this controversy and developed growth curves for each organizations cut-points. The IDF MetS criteria assumes high WC for individuals with a BMI≥30 kg/m^2, therefore, age- and sex-specific BMI cut-points were also created. The SBP and DBP curves were developed so they pass through 130 and 85 mmHg at 20.0 years of age. Male and female SBP curves represented the 92nd and 93rd percentiles, respectively; DBP curves represented the 97th and 99th percentiles, respectively. HDL-C cut-points for males declined until age 16, while female cut-points increased after age 15. In males and females, HDL-C curves represented the 26th and 43rd percentiles, respectively. TG curves for males and females followed different trajectories, however, TG curves represented the 89th percentile in both genders.

According to the ATP and IDF criteria, the study found a MetS prevalence of 7.6% and 9.6% in adolescents, respectively. Prevalence did not differ by gender or age ($p>0.2$), however, IDF-MetS was lower in non-Hispanic blacks than non-Hispanic whites and Hispanics ($p<0.05$). The prevalence of MetS increased from NHANES III to continuous NHANES based on the adolescent criteria (ATP 4.7% to 7.6% and IDF 5.3% to 9.6%; $p<0.01$), which may be representative of increased obesity.

Overall, studies must be conducted to validate the adolescent MetS criteria developed in this study. The authors suggest using intermediate CVD and metabolic outcomes such as atherosclerotic lesions and endothelial function. The new adolescent criteria is based on health-risk and reflects the changes in WC, BP, and lipoproteins that occur due to age.

Thyroid dysfunction is a controversial topic. Over the past 15 years, major debates on narrowing the accepted clinical values have persisted. The September 2005 issue of the Journal of Clinical Endocrinology & Metabolism published two contradictory articles. Wartofsky & Dickey (2005), claimed the accepted ranges for normal TSH levels were no longer valid and establishment of a true normal range for TSH was important. Alternatively, Surks, et al. (2005), conducted a study of 14,333 individuals using NHANES III data. Surks et al. stance was that levothyroxine treatment was not recommended for individuals in a subclinical hypothyroid state and that critical analysis of individuals in the upper reference range for TSH was lacking. The investigators concluded that the accepted reference ranges should remain unchanged.

Subclinical hypothyroidism is defined as elevated serum TSH with normal fT4 and fT3 levels. In 2002 the AACE, ATA, and TES cosponsored a Consensus Development Conference consisting of a panel of 13 experts meant to develop an evidence-based medicine approach to the unresolved clinical issues related to subclinical thyroid disease. Following the recommendations of the conference the leadership of the organizations determined there was not unanimous agreement by the three organizations on all conference recommendations.

Subsequently, the organizations met again to review areas of disagreement. There was significant disagreement on routine treatment of patients with serum TSH level of 4.5-10 mU/l. Post review, each organization made additional recommendations and eventually endorsed a

final draft. The authors suggest hypothyroidism is on a continuum from subclinical, to overt, to life-threatening myxedema coma (Gharib et al., 2005).

Mirroring other expert opinions, the review panel state that the provider's clinical judgement is more critical than guidelines for routine screening. Furthermore, the review panel suggest the use of antithyroid antibodies is useful at predicting risk of developing overt hypothyroidism. In contrast, the consensus conference determined the evidence was insufficient to impose this recommendation. In agreement with the AACE, Royal College of Physicians, and ATA, the review panel endorsed the use of TPOAb for the management of thyroid dysfunction. The consensus panel recommendations were against treatment of subclinical hypothyroidism at TSH levels of 4.5-10 mU/l, however, the review panel claimed that separating the mildest disease for analysis (TSH of 5-10 mU/l) would increase difficulty of advocating for intervention because morbidity and mortality would be years away. According to the review panel, those in the controversial range of 4.5-10 mU/l should be considered for treatment (dependent on the clinician's judgement). Current evidence suggests patients with TSH>10 mU/l should receive treatment (Gharib et al., 2005).

In relation to subclinical hyperthyroidism, both the consensus conference and review panel believe patients with TSH suppression (0.1-0.4 mU/l) should be monitored while patients with complete TSH suppression (<0.1 mU/l) should be treated.

In conclusion, endocrinologist advocating for narrowing the thyroid reference ranges suggest the side effects of early diagnosis and treatment are minor in respect to the possibility of undiagnosed thyroid dysfunction (Gharib, 2005). Furthermore, large, longitudinal studies in multiple demographics are required to provide sufficient data for the development of evidence-

based guidelines. Gharib et al., suggest that experience and judgement, as well as flexibility within the current recommendations will facilitate clinicians and researchers in decision-making.

Kapaleri et al. (2008) conducted a study with the aim of establishing age-specific reference intervals for serum TSH, fT3, and fT4 in healthy children, assess sex differences in thyroid function, and compare their results with previously published reference data.

The investigators routinely collected results of serum TSH, fT3, and fT4 from a hospital based population of children aged 1 day - 18 years. 2,194 serum samples were collected and subjects were sub-grouped according to age (1 day-1 month, 1-12 months, 1-5, 6-10, 11-14, and 15-18 years, respectively). Patients with eating disorders, pituitary disease, or chromosomal anomalies were excluded from analysis. Children with conditions or medications likely to affect thyroid function were excluded from the reference group. Patients were classified using the International Classification of Diseases code and each diagnostic group was statistically evaluated in comparison to Z00.0. Serum samples from patients having diagnostic codes suggesting thyroid dysfunction were excluded a-priori.

Thyroid hormones were analyzed on an automated immunoassay using a direct chemiluminescence detection system. TSH, fT3, and fT4 values of each diagnostic group were compared to the sub-group of primarily healthy children; groups that were not statistically different were pooled with the healthy reference group. Comparison between age groups was conducted using unifactorial ANOVA with Tukey's test post-hoc. Mean values between age groups and sexes were assessed using the student's t-test. Medians and Percentiles (2.5th to 97.5th) for each variable became the reference interval.

The TSH sample size was 1,209; no difference was found between serum TSH concentrations at any age in male and female children ($p = 0.689$). Both sexes were combined for

calculation of percentiles. TSH values decreased and variance narrowed with increasing age. The fT3 sample was 1,395; values showed continuous decline after age 1 month (except in boys 1-5 years and girls 6-10 years). Mean fT3 values for males were elevated in comparison to females ($p < 0.001$). The sample size for fT4 was 1229; no sex differences were found at any age group. fT4 levels were found to decline and narrow in variance with age.

Despite the development of new techniques for determining free thyroid hormone values, the researchers assert it is still useful to use immunoassay procedures. The variable sensitivity of different measurement techniques and methodology must be taken into account when researchers and clinicians decide which reference values to use. Although it is common practice, the researchers acknowledged the use of a hospital-based population might confound reference values.

In the end, the values developed in this study slightly differed when compared to previous studies. The authors concluded that further studies need to be conducted in children and adolescents to determine the significance sex has on thyroid hormone levels. Furthermore, the presence of TPOAb should be taken into account when determining thyroid function and reference intervals (Ladenson, Singer, Ain, Bagchi, Bigos, Levy, & Daniels, 2000; Cooper, 2001).

Roos et al. (2007), conducted a study with the aim of investigating the relationship between thyroid function, insulin resistance, and components of MetS in a large euthyroid sample. 1581 individuals ages 28-75 years, from the PREVEND study in Groningen, Netherlands were included. Subjects with thyroid dysfunction, diabetes, and those using thyroid medication, insulin, or oral blood glucose-lowering medications were excluded from the study. MetS was defined according to the ATP III and IDF criteria. Euthyroidism was defined as TSH

and fT4 within the normal reference range (0.35-4.94 mIU/l and 9.14-23.81 pmol/l, respectively).

Laboratory methods included the assessment of serum TSH, fT4, fT3, and insulin concentrations using a microparticle enzyme immunoassay. Serum TGs were measured enzymatically. Serum total cholesterol and plasma glucose were assessed using Kodak Ektachem dry chemistry. HDL-C was measured with a homogenous method while LDL-C was calculated using the Friedewald-formula. Serum Apo B and Apo A-I were determined using nephelometry. Multiple linear regression models were performed for associations of thyroid function with MetS components.

The investigators found the metabolic parameters of individuals with HOMA-IR and fT4 in the lowest tertile were significantly different from those in the highest HOMA-IR tertile. fT4 and fT3 were significantly higher in men than women (both $P < 0.001$). TSH was significantly lower in men than women ($P = 0.006$). TSH was positively associated with HDL-C, TG, and Apo-I. fT4 was negatively associated with total cholesterol, LDL-C, and TG. fT3 was negatively associated with total cholesterol, LDL-C, TG, and Apo B. When controlling for insulin resistance the relation between fT4 and BP became significant whereas, the relation with fasting glucose was no longer significant.

Overall, the authors concluded that individuals in the low normal thyroid range were already at an increased cardiovascular risk. Findings from the current study suggest fT4 and fT3 in the normal range are related to cardiovascular risk rather than TSH. This may be explained by the difference in the effects thyroid hormones have on peripheral tissues versus central feedback inhibition of TSH release. Age and gender were shown to have significant correlations with components of MetS and thyroid hormones. Adjustments for insulin resistance weakened some

associations; however, all associations remained significant. Surprisingly, adjustment for obesity did not significantly change any associations.

Minami et al. (2015) conducted a study on 283 obese Japanese children aged 6-15 years. The study took place from 2009-2012 at the clinic for obese children at the Department of Pediatrics of Osaka Medical College Hospital. Blood samples and anthropometric measurements (including height weight, and WC) were taken the morning after an overnight fast; strenuous exercise was forbidden the day prior. Subjects were free of endocrine, metabolic, and renal diseases as well as conditions other than obesity. Obesity was defined as body weight>120% of standard body weight based on height and age norms for Japanese schoolchildren in 2000.

WC was measured to the nearest millimeter at umbilicus level. BP was measured three times consecutively using an automated sphygmomanometer (the third measurement was used for analysis). Comparison of obesity was evaluated using BMI-SDS. BMI- and height-SDS were calculated by dividing BMI or height by the 50th percentile for age and sex, respectively. Body composition was estimated by determining body fat percentage using BIA.

Blood samples of serum total cholesterol, TG, alanine aminotransferase (ALT), glucose, and uric acid were obtained using the AU5800 automated analyzer after an overnight fast. HDL-C and LDL-C were quantified using an enzymatic method. Insulin, TSH, fT4, and fT3 were quantified using an electrochemiluminescence immunoassay. TSH, fT4, and fT3 reference ranges were 0.5–5.0 μIU/ml, 0.9–1.7 ng/dl, and 2.3–4.3 pg/ml, respectively. Insulin resistance was quantified using HOMA-R and QUICKI was calculated. The researchers used a MetS definition of WC≥75 cm (<13 years old) or WC≥80 cm (≥13 years old) or waist-to-height ratio≥0.5; TG≥120 mg/dl, and/or HDL≤40 mg/dl; SBP ≥125 mmHg and/or DBP≥70 mmHg;

and/or fasting plasma glucose≥100 mg/dl. Categorization as MetS positive required a high WC and two to three positive risk factors (dyslipidemia, hyperglycemia, and hypertension).

Subject evaluation found height-SDS, WC, body fat percentage, ALT, and fT4 were higher in boys than girls, whereas TG levels were higher in girls than boys. Elevated serum TSH was found in 19.2% of boys and 19.6% of girls. In relation to QUICKI, obese boys with TSH≥4 μU/ml differed from those with TSH<4 μU/ml. Obese girls with TSH≥4 μU/ml had higher non-HDL-C and LDL-C at a younger age compared to those with TSH<4 μU/ml. fT3/fT4 was negatively correlated with QUICKI while TSH, fT3, and fT4 were not correlated with any variables. In contrast, for obese girls all hormone levels and fT3/fT4 were negatively correlated with age, while TSH was positively correlated with levels of glucose, DBP, and non-HDL-C in accordance with prior studies (Gierach, Gierach, & Junik, 2014; Chen, Xi, Zhang, Song,Liu, Mao, & Wang, 2012). Minami et al. found that age and values of height-SDS, WC, SBP, DBP, glucose, insulin, QUICKI, fT3/fT4 and uric acid were higher in obese boys with MetS than those without MetS. In obese girls, BMI-SDS, WC, SBP, DBP, insulin, QUICKI, non-HDL-C, and uric acid were higher when MetS was present.

It is well established that insulin resistance is associated with obesity and metabolic syndrome (DeFronzo & Ferrannini, 1991). Furthermore, insulin resistance is positively associated with thyroid hormones within the normal range (Lambadiari, Mitrou, Maratou, Raptis, Tountas, Raptis, & Dimitriadis, 2011). Therefore, the interactions between these variables may culminate in hypothyroidism associated with insulin resistance progressing into metabolic syndrome (Guo, 2014; Kadiyala, Peter, & Okosieme, 2010).

Summary

In summation, there is a major debate between endocrinologists and researchers in relation to the diagnosis and treatment of MetS and thyroid dysfunction. Organizations such as the IDF, AHA/NHLBI, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity have attempted to make a unified definition of MetS that accounts for variables such as geography, race, age, etc. Organizations such as the AACE, ATA, and TES believe treatment of subclinical thyroid dysfunction is unnecessary and may be harmful in certain cases. Alternatively, research has shown that treatment of undiagnosed hypothyroidism can improve individual components of MetS (Streetan et al., 1988). Investigation into the associations and mechanisms of thyroid dysfunction and MetS in the developing adolescent should continue.

References

Alberti, K. G. M. M., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., ... & Smith, S. C. (2009). Harmonizing the metabolic syndrome. *Circulation*, *120*(16), 1640-1645.

Chen, H., Xi, Q., Zhang, H., Song, B., Liu, X., Mao, X., ... & Wang, Z. (2012). Investigation of thyroid function and blood pressure in school-aged subjects without overt thyroid disease. *Endocrine*, *41*(1), 122-129.

Cole, T. J., & Green, P. J. (1992). Smoothing reference centile curves: the LMS method and penalized likelihood. *Statistics in medicine*, *11*(10), 1305-1319.

Cooper, D. S. (2001). Subclinical hypothyroidism. *New England Journal of Medicine*, *345*(4), 260-265.

DeFronzo, R. A., & Ferrannini, E. (1991). Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes care*, *14*(3), 173-194.

Gharib, H., Tuttle, R. M., Baskin, H. J., Fish, L. H., Singer, P. A., & McDermott, M. T. (2005). Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *The Journal of Clinical Endocrinology & Metabolism*, *90*(1), 581-585.

Gierach, M., Gierach, J., & Junik, R. (2014). Insulin resistance and thyroid disorders. *Endokrynologia Polska*, *65*(1), 70-76.

Guo, S. (2014). Insulin signaling, resistance, and metabolic syndrome: insights from mouse models into disease mechanisms. *Journal of Endocrinology*, *220*(2), T1-T23.

Kadiyala, R., Peter, R., & Okosieme, O. E. (2010). Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. *International journal of clinical practice*, *64*(8), 1130-1139.

Joliffe, C. J., & Janssen, I. (2007). Development of age-specific metabolic syndrome criteria that are linked to the Adult Treatment Panel III and International Diabetes Federation Criteria. *J Am Coll Cardiol*, *49*(8), 891-898.

Kapelari, K., Kirchlechner, C., Högler, W., Schweitzer, K., Virgolini, I., & Moncayo, R. (2008). Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. *BMC endocrine disorders*, *8*(1), 15.

Ladenson, P. W., Singer, P. A., Ain, K. B., Bagchi, N., Bigos, S. T., Levy, E. G., ... & Daniels, G. H. (2000). American Thyroid Association guidelines for detection of thyroid dysfunction. *Archives of internal medicine*, *160*(11), 1573-1575.

Lambadiari, V., Mitrou, P., Maratou, E., Raptis, A. E., Tountas, N., Raptis, S. A., & Dimitriadis, G. (2011). Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes. *Endocrine*, *39*(1), 28-32.

Minami, Y., Takaya, R., Takitani, K., Ishiro, M., Okasora, K., Niegawa, T., & Tamai, H. (2015). Association of thyroid hormones with obesity and metabolic syndrome in Japanese children. *Journal of clinical biochemistry and nutrition*, *57*(2), 121-128.

Roos, A., Bakker, S. J., Links, T. P., Gans, R. O., & Wolffenbuttel, B. H. (2007). Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *The Journal of Clinical Endocrinology & Metabolism*, *92*(2), 491-496.

Surks, M. I., Goswami, G., & Daniels, G. H. (2005). The thyrotropin reference range should remain unchanged. *The Journal of Clinical Endocrinology & Metabolism*, *90*(9), 5489-5496.

Wartofsky, L., & Dickey, R. A. (2005). The evidence for a narrower thyrotropin reference range is compelling. *The Journal of Clinical Endocrinology & Metabolism*, *90*(9), 5483-5488.