Int J Endocrinol Metab. 2018 October; 16(4 (Suppl)):e84727. doi: 10.5812/ijem.84727.

Published online 2018 October 24. **Review Article**

Tehran Thyroid Study (TTS)

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Received 2018 September 01; **Revised** 2018 October 02; **Accepted** 2018 October 07.

Abstract

Context: This review summarizes key findings of the Tehran thyroid study (TTS), a large scale community-based study with approximately a two decade follow-up, about the incidence, prevalence, and natural course of thyroid disorders as well as associations between thyroid diseases and metabolic syndrome (MetS), dysglycemia, and cardiovascular disease (CVD).

Evidence Acquisition: PubMed, Scopus, and Web of Science databases, and the library of Research Institute for Endocrine Sciences were used to search for TTS articles. Articles were subdivided based on the fields of prevalence, incidence and natural course, and associations of thyroid function with the incident hypertension (HTN), MetS and CVDs.

Results: The 2.5th and 97.5th percentiles of serum thyrotropin (TSH) were 0.32 and 5.06 mU/L, respectively. Estimated reference intervals (2.5th and 97.5th percentiles) for thyroid peroxidase antibody (TPOAb) levels were 1.5 - 32.8 and 2.1 - 35 IU/mL in men and women, respectively. Euthyroid persistency was 93.24% during 6 years. There was a negative association between free thyroxine (FT4) levels and insulin resistance. Decreasing FT4 values over time would predict MetS in euthyroid and subclinical hypothyroid subjects (TSH < 10 mU/L). The incidence of thyroid disorders in patients with diabetes, pre-diabetes and healthy controls was 14, 18, and 21 per 1000 person-years, respectively, indicating significantly lower incidence in individuals with diabetes compared to healthy controls. Serum FT4 within the reference range was positively associated with all blood pressure (BP) measures in the total population and in men; however, serum TSH was positively associated with only systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure of men. No associations were found between various states of thyroid function and prevalence and incidence of CVD.

Conclusions: A well designed cohort study aimed to investigate the gap in knowledge regarding thyroid disorders can generate many hypotheses to be examined in randomized controlled trials.

Keywords: Tehran Thyroid Study, Metabolic Syndrome, Cardiovascular Disease

1. Context

Thyroid diseases have a high prevalence, ranking as the most common endocrine disorder after diabetes. The incidence and long term consequences of thyroid diseases have been evaluated in the Wickham's 20 year-survey, revealing the annual incidence of hypothyroidism to be 4.1 (3.3 - 5.0)/1000 survivors/year and 0.6 (0.3 - 1.2)/1000 survivors/year in men and women, respectively. The mean incidence of hyperthyroidism in women was 0.8 (0.5 - 1.4) /1000 survivors/year (1). Subclinical hypo- and hyperthyroidism affect 5 - 15% and 1 - 2.1% of the general population, respectively (2).

The Tehran thyroid study (TTS), a prospective population-based cohort study, is being conducted within the framework of the Tehran lipid and glucose study (TLGS) (3). Of the TLGS participants, 5786 were randomly selected between March 1997 - December 2004 to participate in the TTS to investigate of the epidemiology of thyroid diseases and their long term consequences with regards to the metabolic diseases, CVD and mortality in the iodine sufficient population of Tehran (4). This review briefly presents the key findings from studies conducted on this cohort and summarizes several contemporary TTS publications on different aspects of thyroid diseases.

2. Evidence Acquisition

PubMed, Scopus, and Web of Science databases, and the library of Research Institute for Endocrine Sciences were used to search for TTS articles. Articles were subdivided based on the fields of prevalence, incidence and natural course, and associations of thyroid function with the incident hypertension (HTN), MetS and CVDs.

3. Results

3.1. Reference Values of Thyroid Function Tests in the Iranian Population

The appropriate population specific, gender and age-related reference intervals for thyroid-stimulating hormone (TSH) and free thyroxine (FT4) are necessary to interpret results of thyroid function tests and determine the epidemiological prevalence of thyroid dysfunction in any population. We determined thyroid hormones normal ranges in our population, an iodine sufficient population. According to the National Academy of Clinical Biochemistry (NACB) criteria, the mean ± SD and median (interquartile range [IQR]) for TSH were 1.77 mU/L ± 1.24 and 1.46 (0.93 - 2.23) mU/L, respectively. The 2.5th and 97.5th percentiles of TSH were 0.32 mU/L and 5.06 mU/L respectively. The mean ± SD and median (IQR) for FT4 for all negative thyroid peroxidase antibody (TPOAb) subjects were 1.19 ± 0.16 and 1.18 (1.08 - 1.31) ng/dL, respectively (4). Regarding reference intervals for TPOAb, 2.5th and 97.5th percentiles were 1.5 - 32.8 and 2.1 - 35 IU/mL in men and women, respectively. No significant difference in age categories was observed. To predict clinical and subclinical hypothyroidism, optimal cutoff points for TPOAb were 18.38 and 14.77 IU/mL, respectively (5). The geometric mean and overall upper reference limit of TSH were 1.40 and 4.12 mIU/L in the National health and nutrition examination survey (NHANES III) from the United States of America (6); corresponding values for TSH in the Chinese population were 1.90 and 0.59 - 5.98 mIU/L, respectively (7).

Overall different iodine intakes, hereditary and genetic influences on the set-point of thyroid hormones such as polymorphisms in thyroid hormone pathway genes and FT4/TT4, TSH assay methods might be reasons for the variety in upper limits of TSH in different populations (8). Determination of population specific reference limits for thyroid tests helps to classify and manage thyroid diseases accordingly.

3.2. Prevalence and Incidence of Thyroid Disorders

Epidemiology of thyroid disorders depends on various ethnic and geographical factors (9). Table 1 shows prevalence and incidence of thyroid dysfunction states reported in the TTS. Over a 6-year follow-up, the annual incidence rates of subclinical and overt hypothyroidism were 7.62 (95% CI 7.39 - 7.85) and 2.0 (95% CI 1.94 - 2.06] per 1000 persons, respectively. Annual incidence rates of subclinical and overt hyperthyroidism were 0.92 (95% CI 0.90 - 0.95) and 0.68 (95% CI 0.66 - 0.70) per 1000 persons, respectively (10).

In the Amouzegar et al. study (11) within the framework of the TTS, overall, 12.8% were TPOAb positive, with higher prevalence among women than in men (16.0 vs. 8.5%, P = 0.001). The prevalence of TPOAb positivity in the total population was 11.9, 14.9 and 13.6% in the young, middle aged and elderly, respectively. The total incidence rate (95% CI) of TPOAb positivity in the total population was 7.1 (6.36 - 7.98) per 1000 person-years of follow-up; this rate was higher among young participants [8.5 (7.5 - 9.7) per 1000 person-years. Sex stratified analysis showed that TPOAb positivity was higher in women, being 9.3 (8.2 - 10.7) per 1000 person-years. Based on the Cox proportional hazard model, the hazard of developing TPOAb positivity was higher in women, and those with younger age and higher serum TSH concentrations. Moreover, development of TPOAb positivity in each phase was significantly associated with increasing TSH concentration during the seroconversion phase, compared to baseline levels (11).

Prevalence of hypothyroidism was 0.5% in men and 7.1% in women in the Vanderpump et al. (1) study (12) and these values were 0.9% and 4.8% in the HUNT study, respectively (13). Flynn et al. reported 3,486 incident cases of primary hypothyroidism with incidence rate (95% CI) of 4.98 (4.81 - 5.17)/1000 person-years in women and 0.88 (0.80 - 0.96)/1000 person-years in men.

3.3. Natural Course of Thyroid Function

Euthyroid persistency was 93.24% during 6 years. Predictive factors for conversion to thyroid dysfunction were TSH, FT4 and TPOAb levels, sex, and smoking. Criteria for early diagnosis of hypothyroidism (i.e., 94% sensitivity and 82% specificity, P < 0.0001) were obtained based on baseline and 3-year follow-ups of thyroid function tests and TPOAb. Early diagnosis of hypothyroidism was significantly associated with impaired glucose tolerance (relative risk [RR] 3.03 [CI 1.36 - 6.75]), high cholesterol (RR 2.46 [CI 1.45 - 4.18]), obesity (RR 2.92 [CI 1.64 - 5.2]), and hypertension (RR 1.68 [CI 1.53 - 1.84]) (10).

The Effraimidis et al. study showed that baseline higher TSH, lower FT4 serum levels and presence of TPOAb are among risk factors for progression of euthyroidism to hypothyroidism (14).

3.4. Thyroid Function and Body Mass Index

Considering the intriguing relationship between the thyroid and weight status, the association between body mass index (BMI), as the outcome, and changes of thyroid function tests within the reference range, as the predictor,

Table 1. Epidemiology of Thyroid Dysfunction States in the Tehran Thyroid Study (TTS)[a,b]

	Prevalence, %	Incidence [Per 1000 Person-Years (95% CI)]
Subclinical hypothyroidism	5.5	7.62 (7.39 - 7.85)
Overt hypothyroidism	2.0	2.0 (1.94 - 2.06)
Subclinical hyperthyroidism	3.7	0.92 (0.90 - 0.95)
Overt hyperthyroidism	2.2	0.68 (0.66 - 0.70)

[a] Adopted from reference (10).
[b] Definitions: Subclinical hypothyroidism: serum TSH > 5.06 mU/L with normal FT4 level. Overt hypothyroidism: serum TSH > 5.06 mU/L and FT4 < 0.91 ng/dL. Subclinical hyperthyroidism: serum TSH < 0.34 mU/L and normal FT4 level. Overt hyperthyroidism: serum TSH < 0.34 mU/L with serum FT4 > 1.55 ng/dL.

in 1100 normal-weight participants at baseline was investigated over a 10-year follow-up (15). Modified Poisson regression analysis for binary outcome (BMI < 25 or ≥ 25 kg/m^2), after adjustment for age, sex, smoking, and TPOAb status, showed a negative association between ΔFT4 and follow-up BMI (relative risk, 95% CI: 0.55 [0.37 - 0.80]) without any significant association between ΔTSH and follow-up BMI (relative risk, 95% CI: 0.99 [0.96 - 1.01]). Moreover, in multinomial logistic regression analysis, no associations were observed between changes of serum FT4 or TSH and different categories of follow-up BMI (normal BMI, overweight, and obese) for either overweight or obese vs. normal-weight participants.

3.5. Thyroid Function and Metabolic Syndrome

Thyroid hormones have pleiotropic effects on different components of metabolic syndrome (MetS) and abnormal thyroid function may have a role in the development of MetS (16).

3.5.1. Metabolic Syndrome in Clinical and Subclinical Hypo- and Hyperthyroid States

Associations of thyroid dysfunction with MetS are not clearly defined. Results of a study from the TTS (17) showed that overt and subclinical hypothyroidism are associated with MetS and two of its components, i.e. abdominal obesity and hypertriglyceridemia, especially in the elderly and hyperthyroidism may be associated with impaired fasting glucose. Moreover, overt hypothyroidism was predictor of MetS only in male population; a gender difference possibly due to the fact that most women in this study were premenopausal, therefore, the advantageous effects of estrogen may inhibit progression to MetS. On the other hand, BMI in women was significantly higher than in men; higher TSH values could be related to obesity rather than a true hypothyroidism. After age stratification, the risk of MetS was significantly higher only in subclinical hypothyroid subjects, aged > 50 years even after adjustment for sex, BMI and smoking.

3.5.2. Metabolic Syndrome in the Euthyroid State

There is conflicting data on associations of thyroid function tests within the reference range with MetS. Investigation of this subject in the TTS (18) indicated that lower normal FT4 concentrations were significantly associated with higher risk of insulin resistance and MetS; findings did not change after excluding individuals with positive TPOAb (18).

3.5.3. Metabolic Syndrome and Long Term Thyroid Hormone Variations

There is controversial data regarding the association of the TSH and FT4 with MetS and its components, mostly from studies with a cross-sectional design, which hampers determining a cause and effect relationship. Associations of thyroid hormone variations in subclinical and euthyroid ranges with the incidence of MetS and its components were assessed over a 10 year follow-up (19) and showed decreasing FT4 values (not TSH) over time would predict MetS in euthyroid and subclinical hypothyroid subjects (TSH < 10 mU/L). Each ng/ml decrease in FT4 was associated with 40% increased risk of MetS within 10 years, after adjustment for sex, age, and smoking, an association that disappeared after BMI adjustment. FT4 values could predict the incidence of MetS especially in non-obese adults with normal or subclinical thyroid function. Cumulative effect of FT4 decline over 10 years, at 4 follow-ups, was predictive for abdominal obesity and higher triglyceride values after adjustment for age, sex, BMI and homeostasis model assessment-insulin resistance (HOMA-IR); therefore, it seems that other mechanisms, except for BMI and IR may be responsible for the association of these metabolic abnormalities and FT4. Moreover, this study showed a negative association of FT4 with IR (19).

TSH was not associated with incidence of MetS or any of its components in the crude or adjusted models, except for serum triglycerides (TGs) and waist circumference; the relationship between TSH and TGs remained even after fur-

ther adjustment for HOMA-IR and BMI indicating that the relationship of TSH and TGs may be modified by mechanisms other than IR and BMI.

3.6. Thyroid and Insulin Resistance

In a cross-sectional study, associations of thyroid hormones within the reference range and TPOAb with IR were investigated in 2758 euthyroid subjects (20). Multivariate linear regression analysis revealed a positive association between serum TSH and HOMA-IR (β = 0.05, P = 0.01) and a negative association of FT4 and HOMA-IR (β = -0.06, P < 0.01) only in men. The multiple logistic regression analysis based on the presence or absence of IR showed that higher serum FT4 was associated with lower risk of IR in men [odds ratio (OR): 0.27, 95% CI 0.12 - 0.61]. No relationship was reported in women. Moreover, there were no significant differences in HOMA-IR, fasting insulin or fasting blood glucose between the TPOAb-negative and -positive groups (20).

3.7. Thyroid Dysfunction in Patients with Impaired Glucose Metabolism

In the TTS, for the first time, the prevalence, incidence and predictive factors of thyroid disorders in individuals with dysglycemia were assessed; the incidence of thyroid diseases among 435 individuals with diabetes, 286 individuals with pre-diabetes, and 989 healthy controls at baseline was 14, 18, and 21 per 1000 person-years, respectively, being significantly lower in those with diabetes than in healthy controls; this difference was not significant after adjusting for covariates. Participants with baseline serum TSH > 1.94 mU/L or TPOAb $\geq$ 40 IU/mL had higher risk for incidence of thyroid diseases compared to those with TSH $\leq$ 1.94 mU/L or TPOAb < 40 IU/mL in all mentioned three groups. Baseline TSH > 1.94 mU/L was predictive of thyroid diseases with 70% sensitivity and specificity. We showed that baseline serum TSH (receiver operating characteristic [ROC] area, 95% CI: 0.73, 0.68 - 0.77) had better predictive value than TPOAb (ROC area, 95% CI: 0.65, 0.61 - 0.69) for development of thyroid diseases. Incidence of thyroid diseases in patients with type 2 diabetes or pre-diabetes was not higher than in healthy controls (21).

3.8. Thyroid Function and Blood Pressure

To investigate the association of different blood pressure (BP) components with serum TSH and FT4 levels in euthyroid subjects, 4,756 euthyroid individuals with mean (SD) age of 40.1 $\pm$ 14.38 years were selected (22). Three tertiles of serum TSH were defined as follows: 1st (0.32 < TSH < 1.21 mU/L), 2nd (1.21 - 2.07 mU/L) and 3rd (2.07 - 5.06 mU/L) tertiles. Negative associations between TSH and systolic BP (SBP) in the first and second TSH tertiles and between TSH and pulse pressure (PP) in the second TSH tertile were reported. No significant association was detected between TSH and diastolic BP (DBP) or mean arterial pressure (MAP) in different TSH tertiles. Serum FT4 levels of individuals in the first TSH tertile were significantly associated with MAP. There were also significant relationships between serum FT4 and DBP in the first and second TSH tertiles. After adjustment for BMI, smoking status, gender and age, the association between TSH and SBP, DBP, PP and MAP did not reach a significant level in any of TSH tertiles; increased FT4 concentrations were associated with elevated DBP in the third tertile, and SBP, MAP and PP in all tertiles. In the logistic regression analysis, different TSH tertiles were not associated with HTN (22).

Moreover, to investigate the associations of serum TSH and FT4 within the reference range with different BP measured also incident prehyperetension (preHTN) and HTN, a longitudinal survey on 2282 individuals was performed during a 9-year follow-up. Multivariate-adjusted generalized estimating equation (GEE) analysis revealed a decreasing trend for all BP parameters throughout the study period, either adjusted for serum TSH or FT4 levels. Serum FT4 within the reference range was positively associated with all BP measures in total population and in men; however, serum TSH was positively associated with only SBP, DBP and MAP of men. No associations between serum TSH within the reference range and BP status were detected in multivariate transitional model; however, a 1 ng/dL higher FT4 was associated with 40% increased risk of preHTN [OR (95 % CI), 1.40 (1.02 - 1.90)], but not with HTN [OR (95 % CI), 0.93 (0.80 - 1.09)] (23).

3.9. Thyroid Function and Obesity Phenotypes

The relationship between thyroid function and different obesity phenotypes during 9 years was examined in 1938 euthyroid individuals from the TTS (24). Multivariate GEE analysis showed that each 1 ng/dL increment in FT4 levels within the reference range was accompanied with a 1.65-fold (95% CI: 1.09 - 2.5) increase of developing the metabolically healthy normal weight phenotype. Moreover, each 1.0 ng/dL increment in FT4 within the reference range was associated with a 50% decreased risk of developing the metabolically healthy obese phenotype [OR (95% CI): 0.50 (0.32 - 0.76)]. Regarding serum TSH, a significant positive association was found between serum TSH and development of the metabolically unhealthy normal weight

phenotype [OR (95% CI): 1.22 (1.01 - 1.48)].

3.10. Thyroid Dysfunction and Incident Cardiovascular Events

To investigate the relationship between different thyroid function states and the incidence of (CVD)/coronary heart disease (CHD) in the TTS, 3975 participants were selected. During a median follow-up of 11.2 years, 400 CVD events occurred. No association was observed between different thyroid dysfunction states and incidence of CVD/CHD even after the age and sex adjustment. The multivariable hazard ratios (95% CI) of subclinical hypothyroidism, hypothyroidism, subclinical hyperthyroidism, and hyperthyroidism for CVD events were 1.21 (0.77 - 1.88), 0.76 (0.33 - 1.69), 0.81 (0.46 - 1.41) and 1.48 (0.70 - 3.16), respectively (25). These findings indicate that different thyroid dysfunction states have no associations with CVD or CHD during 11 years of follow-up in a cohort with high prevalence and incidence of CVD.

4. Conclusions

This paper has summarized many of the key findings related to thyroid disorders including sex and age specific population based reference ranges of thyroid function tests, prevalence, incidence, risk factors, risk prediction for thyroid diseases and the natural course of thyroid function. Routine screening for thyroid function in healthy individuals residing in areas of iodine sufficiency is controversial. The need for such screening should fulfill all criteria for mass screening (26), indicating that its benefit outweighs the physical and psychological harm caused by efforts involved in screening. Investigators of TTS are currently in the process of collecting and analyzing data after 18 years of follow-up of thyroid function tests and serum TPOAb in this population and the results obtained may add more clues for mass screening for thyroid function. This is because although the prevalence of overt dysfunction is low, but a substantial proportion of adults have subclinical hypo- and hyperthyroidism. It is hoped that a prospective population based study such as TTS, would shed more light on the occurrence of outcomes such as death, CVD, glucose intolerance, insulin resistance, MetS, quality of life, etc. It is noteworthy to know that all of these outcomes are available in the data of TLGS, the mother project of TTS. This information may also disclose any potential evidence-based therapy for subclinical thyroid disorders. Results of the TTS add to global data knowledge and could be especially applicable to Caucasian populations. Further fundamental studies are needed to confirm the cause and effect relations in the field of thyroid hypo- and hyper function and cardiovascular outcomes and in cancer development.

Acknowledgments

The authors would like to acknowledge Ms. Niloofar Shiva for critical editing of English grammar and syntax of the manuscript.

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