Cohort Profile

Natural Course of Thyroid Disease Profile in A Population in Nutrition Transition: Tehran Thyroid Study

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Abstract

Background: There is a lack of data regarding the incidence rate, etiology, risk factors, and natural course of thyroid disorders and their relationship with cardiovascular disease and mortality in populations undergoing nutrition transition. Therefore, we aimed to assess the natural course of thyroid disease in Tehranians, a population in nutrition transition.

Methods and design: Between March 1997 and December 2004, 5769 individuals, aged ≥ 20 years, were selected from district No.13 of Tehran and followed up every three years. Data on risk factors for cardiovascular disease such as diabetes, hyperlipidemia, smoking, obesity, hypertension, low levels of physical activity, and dietary habits were obtained at baseline and again every three years. Cardiovascular and mortality outcomes were assessed in detail.

Conclusion: The results of this study will provide a better recognition regarding the incidence and risk factors of thyroid disorders and their relationship with cardiovascular outcomes and mortality in a community in nutrition transition.

Keywords: Hyperthyroidism, hypothyroidism, Iran, Tehran Lipid and Glucose Study, Tehran Thyroid Study, thyroid

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Background

Thyroid diseases have a high prevalence, being the most common endocrine disorder following diabetes.[1] The incidence and long- term consequences of thyroid disease have been evaluated in Wickham's survey revealing the annual incidence of hypothyroidism over 20 years to be 3.5 per 1000 and 0.6 per 1000 in men and women, respectively.[2] Subclinical hypo -and hyperthyroidism affect about 5% – 15%,[3,4] and 1% – 2.1%,[3] of the general population, respectively.

The results of the National Health and Nutrition Examination Survey (NHANES) showed higher levels of thyroid stimulating hormone (TSH) concentration and more prevalent positivity of antithyroid antibodies in women which increased with age.[3]

Another interesting topic is the progression overtime of subclinical to overt thyroid disease. Progression of subclinical hypothyroidism to hypothyroidism is 5% – 8% per year but the rate of progression of subclinical hyperthyroidism to overt disease remains undetermined;[5] some studies showed this to be at a rate of 1% – 5 % per year.[6,7] The prevalence and incidence of thyroid disorders depend on geographic areas, increasing age, ethnicity, and most importantly the amount of iodine intake of the population.[2,8,9] Iodine is a nonmetallic element found in the human body in trace amounts and is principally responsible for synthesis of thyroid hormones. A deficiency of this element produces a constellation of signs and symptoms collectively termed iodine deficiency disorders (IDD), including endemic goiter, hypothyroidism, cretinism, decreased fertility, miscarriage, increased infant mortality, hypothyroxinemia, trophoblastic or embryonic fetal disorders, and mental retardation.[10]

The relationship between subclinical hypo- and hyperthyroidism and coronary heart disease (CHD) needs to be clarified, because not all studies have shown positive associations between mild thyroid dysfunction and ischemic heart disease (IHD) and cardiovascular mortality.[11,12]

Well-designed longitudinal studies are needed for determination of the incidence rate, etiology, risk factors, and natural course of noncommunicable diseases (NCD) such as thyroid diseases. There is a paucity of information regarding NCD in countries in nutrition transition.[13] The Tehran Thyroid Study (TTS) is a population- based cohort study being conducted within the framework of the Tehran Lipid and Glucose Study (TLGS).[14] The aim of this study was to evaluate the prevalence and natural course of thyroid diseases and also the long- term consequences of thyroid dysfunction in terms of IHD and the cardiovascular and all cause mortality in the urban, iodine- sufficient population of Tehran, the capital of Iran.[15]

Research Goals

Primary

The primary research goal was the evaluation of natural changes in thyroid function and courses of thyroid diseases in a population in nutrition transition.

Secondary

Secondary goals included determining the relationship between

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thyroid diseases and cardiovascular risk factors, CHD, and all-cause mortality.

Study design

The TTS is being conducted within the framework of the TLGS, a large long- term integrated community-based study for identification and prevention of NCD initiated in 1997.[14]

Study population

Between March 1997 and December 2004, 5769 individuals aged ≥ 20 years, residents of district No.13 of Tehran, were selected using multistage cluster random sampling. Baseline measurements were documented and participants were invited for follow- up studies every three years. All individuals returned for reassessments after six and nine years, respectively.

District No. 13, located in the eastern part of the Tehran city, with an area of about 13 sq. kms is under coverage of the Shahid Beheshti University of Medical Sciences. Three medical health centers in this area which have the field data of > 90% of all covered families were selected. All demographic databases, including information on gender, age, family dimension, postal address, and telephone numbers of families living in these three centers were extracted. Each family was invited to participate in the TTS. The population of district No. 13 is representative of the overall population of Tehran (Iran National Census, 1996).[16] Age distribution of the study population has been shown in Table1.

Definition of risk factors

Serum total cholesterol (TC) level was considered normal, moderately high, and high when levels were < 200, 200 – 239, and ≥ 240 mg/dL, respectively. A desirable level of low- density lipoprotein – cholesterol (LDL-C) was defined as <130, moderately high as 130 – 159, and high as ≥ 160 mg/dL. Triglycerides (TGs) were defined as desirable with a level < 200, as moderate risk between 200 – 400, and as high risk ≥ 400 mg/dL. Serum high- density lipoprotein – cholesterol (HDL-C) was considered in three levels of risk; < 35, 35 – 59, and ≥ 60 mg/dL.[17] Hypertension was defined according to JNC-VI [Joint National Committee] criteria[18] as mean systolic blood pressure (SBP) ≥ 140 mmHg, mean diastolic blood pressure (DBP) ≥ 90 mmHg, and being treated with antihypertensive drugs. WHO criteria were used to classify glucose metabolism status.[19] Overweight and obesity were defined as body mass index (BMI) 25 – 29.9 kg/m^2 and BMI > 30 kg/m^2, respectively.

Medical history and clinical examination

At the first visit, the study was explained to individuals and demographic data were obtained. All clinical examinations were performed at the beginning of the study and again every three years for all subjects. All participants invited to the TTS unit, after signing informed written consent, were referred to trained physicians. The participants were interviewed to obtain past medical history, detailed personal and family history regarding possible thyroid disease such as goiter, hyperthyroidism, or hypothyroidism and current medication; radioiodine intake, smoking habits, physical activity levels, and any medication that may interfere with thyroid function test results were also obtained. A brief physical examination including anthropometric measurements with focus on the thyroid gland was performed and thyroid size was reported according to WHO classification.[20] The Rose angina questionnaire was filled out and ECG was taken for all individuals aged over 30 years.

The participants remained seated for 15 minutes, when a qualified physician measured blood pressure twice, using a regular adult cuff according to the circumference of the participant's arm with a standard mercury sphygmomanometer, calibrated by the Iranian Institute of Standards and Industrial Researches. The blood pressure was measured on the right arm, at the heart level, and the cuff was inflated 30 mmHg above the level at which the radial pulse disappeared. We measured the blood pressure twice and considered the mean as the final recording pressure. The first sound was recorded as SBP [Korotkoff phase 1], and the disappearance of the sound was considered as DBP [Korotkoff phase 5] during deflation of the cuff, at a 2 – 3 mm per second decrement rate. Anthropometric measurements were taken with shoes removed and the participants wearing light clothing. Weight and height were measured according to the standard protocol. Waist circumference was measured at the level of the umbilicus and hip circumference was measured at the widest girth of the hip. BMI was calculated by dividing the weight in kilograms by the square of height in meters.

A 12-lead rest ECG was recorded by two trained and qualified technicians according to a standard recording protocol developed by the School of Public Health, University of Minnesota[21] using a PC-ECG 1200 machine. CHD was defined based on Whitehall criteria.[22] A history of chest pain was obtained using the Persian translated Rose Questionnaire and data were interpreted according to previously published guidelines.[23]

Physical activity levels

Physical activity levels were evaluated at the beginning of the study, using the Lipid Research Clinic (LRC)[24] and the Modifiable Activity Questionnaires (MAQ).[25]

Laboratory analysis

Fasting blood samples were drawn from all participants between 7:00 and 9:00 AM into vacutainer tubes at each reassessment. An oral glucose tolerance test after the administration of 82.5 g glucose monohydrate (equivalent to 75 g glucose anhydrate) solution was performed for all non- pharmacologically treated diabetic participants, aged > 20 years. Fasting and two-hour glucose concentrations were assayed, using the enzymatic colorimetric method with glucose oxidase technique. Serum TC and TGs were measured; using enzymatic calorimetric tests with cholesterol esterase, cholesterol oxidase, and glycerol phosphate oxidase, respectively. HDL-C was measured after precipitation of the apolipoprotein B containing lipoproteins with phosphotungistic acid. LDL-C was calculated from the serum TC, TGs, and HDL-C concentrations expressed in mg/dL using the Friedwald formula,[26] if TGs concentration was lower than 400 mg/dL. Assay performance was monitored at every 20 tests interval using the lipid control serum, Precinorm (normal range), and Precipath (pathologic range) wherever applicable (Boehringer Mannheim, Germany) and TruLab N and TruLab P (Pars Azmon Inc., Iran). All these biochemical tests were performed on the day of sampling, using commercial kits (Pars Azmon Inc., Iran) by the Selectra 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands). All samples were analyzed when quality control met the acceptable criteria. Inter- and intra-assay coefficients of variations were less than 2.3% for glucose, less than 2.1 % for TG, less than 2 %

Table 1. Comparison of frequencies of age distributions in the study population of the Tehran Thyroid Study, as the urban Tehranians and urban population of Iran

Age group (years)	Study population (%)	Urban population of Tehran (%)	Urban population of Iran (%)
29–20	27	19	17
39–30	26	16	14
49–40	18	11	9
59–50	14	6	5
69–60	10	5	6

for TC, and less than 3% for HDL- C.

Free thyroxine (FT4) and TSH were determined on -70ºC stored serum samples by the electrochemiluminescence immunoasaay (ECLIA) method, using Roche Diagnostics kits and Roche/Hitachi Cobas e- 411 analyzer (GmbH, Mannheim, Germany). Lyophilized quality control material (Lyphochek Immunoassay plus Control, Bio-Rad Laboratories) was used to monitor the accuracy of assay; the intra- and inter-assay CVs were 1.3 % and 3.7 % for FT4 and 1.5 % and 4.5 % for TSH determinations, respectively.

Thyroid peroxidase antibody (TPO Ab) was assayed by immunoenzymometric assay (IEMA) using related kit (Monobind, Costa Mesa, CA, USA) and the Sunrise ELISA reader (Tecan Co., Salzburg, Austria); intra- and inter-assay CVs were 3.9 % and 4.7%, respectively.

Dietary assessment and lifestyle interventions

Dietary assessment was performed using qualitative food frequency questionnaires (FFQ) validated in the nationwide household food consumption survey project which has been reported in Persian.[27] The interviewers used photographs of household portions in order to assess exact food intakes as household measures. Data were entered into the nutritionist III package and Mosby Nutritrac Software to obtain daily energy, nutrient intakes, and servings of foods consumed.

Lifestyle modification was implemented by improving nutrition and dietary patterns and by increasing physical activity levels and smoking cessation. Dietary intervention was planned according to results of the Knowledge, Attitude, and Practice (KAP) study, conducted in a representative sample of adults.

Outcome measurements

Each participant was followed up for any medical event by a trained nurse and the complementary data related to each relevant event was compiled by a trained physician who also collected mortality data from the hospital or the death certificate.

Approval

This study has been approved by the National Research Council of the Islamic Republic of Iran (No. 121) and has been performed with the approval of the Human Research Review Committee of the Endocrine Research Center, Shahid Beheshti University.

Concomitant conditions

All participants with any risk factors were encouraged to obtain medical advice. Yearly telephone calls were used to obtain information on all concomitant medical conditions and outcomes were recorded in detail. Use of medications, applications of procedures, and occurrence of any diseases were registered during face-to-face visits every three years.

Retention

We monitored the study population carefully to control any loss to follow- up and maintain the statistical power and validity of our findings.

Biostatistician considerations

Merging data obtained from the TTS to those of the TLGS will facilitate sizable and rich database. Data are stored on the mainframe computer at the Endocrine Research Center, Shahid Beheshti University of Medical Sciences and verification procedures were carried out to ensure that there had been accurate transcription. The data from the original study were stored in a SPSS (Statistical Package for Social Sciences) system file which was compatible with the program written for the current study. Data are refined and organized according to the requirement of each sub-project or paper. Normality of the data distribution, when required, will be evaluated by visual inspection (Histogram, P-P plot, Q-Q plot), summary measures like skewness and kurtosis and testing such as Kolomogorov-Smirnov and Shapiro-Wilk methods. For non-normal data, transformations such as logarithmic, square root, inverse, or Box-Cox transformation will be employed as appropriate. Outliers will be diagnosed and treated accordingly. In case of missing data, depending on the portion and type of the missed data, single or multiple imputation methods will be used.

It is anticipated that noticeable numbers of papers were prepared within the framework of the TTS, each requiring its own method of analysis and interpretation. Some general methods are as follows: Descriptive analysis will be performed using means, standard deviation and error, and median and interquartile range for numerical variables. Qualitative variables were expressed as percentages. When assumptions of the parametric statistical methods are not met, nonparametric methods of their counterparts will be used. These methods also will be used for analysis of ordinal variables. Incidence rates of hyperthyroidism, hypothyroidism, subclinical hypo- and hyperthyroidism, and autoimmune thyroid disease will be estimated per 1000 person-years and adjusted mainly for age and sex.

Pearson correlation or Spearman correlation coefficients (as appropriate) will be calculated to test the relationships among different variables. Multiple regression analyses will be used to find out the relationship between thyroid functions and variables regarded as independent. Stepwise, backward, or forward variable selection methods will be used when appropriate. The validity of regression equations will be evaluated by the coefficient of determination (multiple R square) and analysis of residuals. To determine the relationship between risk factors with the categorical outcomes, binary, multinomial, or ordinal logistic regression will be carried out adjusting for confounding variables. We will use t-

test to compare the means of two independent groups. Analysis of variance (ANOVA) will be used to compare the variables among three or more subgroups followed by appropriate post hoc test such as Tukey and Scheffe. To adjust the comparison for potential confounding variables, two- or three-way ANOVA will be used. In addition, analysis of covariance will be employed when adjusting for a covariate correlated with the dependent variable. For non-normal data, Mann-Whitney U and the Kruskal-Wallis tests will be used instead.

To compare the data among different phases of the TTS, paired t-test and repeated measures analysis of variance will be done, if their assumptions are met. When the covariance structure of the data differs from exchangeable form or when modeling trend of binary variables, Generalized Estimating Equations (GEE) methods will be used. Nonparametric methods such as McNemar, Sign, Wilcoxon, and Friedman tests will be used, as appropriate.

To compare the proportions between two or more groups, Chi-square test of independence and Fisher exact test will be employed. Mantel-Haenszel test will be used when adjustment is required.

Survival analysis methods will be employed for the assessing of secondary outcomes (e.g., cardiovascular morbidity, all cause mortality, thyroid disease incidence, etc.). To evaluate the association of different factors on survival time and potential covariability that may modify the primary and secondary outcomes, Cox proportional hazard model and other parametric models will be performed according to the data characteristics.

The adequacy of the models will be evaluated, using the Hosmer-Lemeshow statistic, Likelihood Ratio test, and Akaike information Criteria (AIC) as appropriate. In addition, ROC curve and its area under curve (AUC) will be used to compare the predictability of different fitted models.

For the analysis of data, SPSS, STATA, R, and SAS statistical software will be used, depending on the analysis required.

Management

Organization

Tehran Thyroid Unit is located in the eastern part of Tehran city. The building consists of many units such as a laboratory, the admission, information, examination rooms, nutrition, and social worker units. Following of study protocol is ensured by an administrator and additional staffs such as physicians, recruitment coordinators, electrocardiogram technicians, laboratory personnel, social workers, nurses, data collectors, and others.

Steering committee

This consists of a principal investigator, program coordinators, additional researchers, manager and head of sections in the TTS units, all of whom meet regularly. This committee is responsible for approval of the study design, policies and decisions, and oversees the administrative aspects of the TLGS Research Group.

Discussion

Thyroid dysfunction has many adverse effects on health not only does the extent of the disease need to be verified in each population but the effects of thyroid disease on other health problems have to be clarified. Most studies have been performed in developed countries and no prospective study for thyroid dysfunction has been documented from countries in nutrition transition.

The population of Iran and particularly those living in Tehran are undergoing nutrition transition during the last few decades.[14] In addition, this population after a long period of iodine deficiency, has achieved a state of iodine nutrition sufficiency in the last two decades.[15]

The present study may therefore be unique in disclosing many aspects related to evolution of thyroid disorders in a population with sufficient iodine intake.[16] Two decades ago the I.R. Iran was among countries most severely affected by iodine deficiency. Since 1989, IDD has been categorized as a priority health problem in Iran, and production, distribution, and consumption of iodized salt were begun in 1990. The first law requiring mandatory iodination of all salts for households use was passed in 1994. The results of the 1996 survey revealed that overall median urinary iodine was above that recommended by WHO/UNICEF/ICCIDD.[20] Therefore, the IDD elimination program using USI in Iran has proven to be very effective and Iran was declared IDD free by WHO-EMRO in the year 2004.[28]

The last national survey performed 17 years after the introduction of iodized salt showed that household consumption of iodized salt was 98% for all provinces. The median urinary iodine of subjects was 145µg/L. Today over 95% of Iranian households are using adequately iodized salt.[15]

The prevalence of hypothyroidism differs in various populations due to diversity of subjects in these studies; it was 9.5% in Colorado study,[1] the same as reported previously; however, this was 4.6% in a US population, as reported in the NHANES III study.[3] There is a controversy regarding the increasing level of TSH in the presence of antithyroid antibodies in both genders. The Wickham study showed that serum TSH levels rise markedly after the age of 45 years in females, whose antithyroid antibodies were positive, though this was not the case in male subjects.[2] Increasing TSH levels at higher ages were found in the NHANES III study and in other studies indicating that the levels of autoimmune antibody increase with age.[3] The prevalence of hyperthyroidism was found to be 2.2% in Colorado[1] and 3% in people, aged less than 80 years, in the NHANES III study.[3] The prevalence differs in various populations according to sex, age, and cut points considered for definition of hyperthyroidism.

Progression from euthyroidism to overt or subclinical hypo- and hyperthyroidism has been reported in many studies that depended on baseline TSH levels, the presence or absence of antithyroid antibodies, and the age and sex of the population under study.[7] An increased prevalence of thyroid dysfunction from 1.4% at baseline to 10.5% after 6.7 years of follow-up was reported previously in Tehranian population.[29] The TTS gives us the opportunity to obtain data regarding prevalence, incidence, and the natural course of thyroid diseases in an Iranian population.

The effects of overt hypo- and hyperthyroidism on cardiovascular risks factors such as serum lipid levels have been documented in large cohorts.[30,31] Overt hypothyroidism, considerably alters lipid profiles and promotes cardiovascular disease.[32] Considering the high prevalence of cardiovascular diseases worldwide and in Iran,[33] confronting this thyroid dysfunction and treating it effectively is vital to overall health status. There is inconsistent data regarding the relationship between subclinical hypothyroidism and serum TGs, lipid subparticle size, and the effect of treatment on serum lipid levels. Most existing data show a decline in level of LDL-C, HDL-C, and TGs with changes in their quality in favor of higher levels of oxidized LDL that promote atherosclerosis in pa-

tients suffering from hyperthyroidism. It is not clear if treatment could ameliorate these abnormalities. Some but not all studies showed that antithyroid therapy is associated with elevated total and LDL, cholesterol levels.[34,35]

Besides changes in cardiovascular risk factors, thyroid diseases are accompanied with cardiovascular diseases through dramatic hemodynamic alterations such as increased DBP, increased peripheral vascular resistance besides changes in cardiovascular risk factors in hypothyroidism and increased cardiac output due to enhanced heart rate and systolic contractility in hyperthyroidism.[36–38]

There are inconsistent data regarding the increased prevalence of cardiovascular disease in subclinical hypo- and hyperthyroidism, and the association between these is debatable.[11,12,39]

Existing data regarding the effects of subclinical hypo - and hyperthyroidism on cardiovascular and all cause mortality is also a matter of debate.[40–42] The association between mortality and thyroid disorders, shown in a recent meta-analysis, found an increased mortality in patients with overt hyperthyroidism.[11] Considering the lack of important data essential to ascertaining the associations between thyroid dysfunctions and cardiovascular risk factors, cardiovascular disease, and mortality in Iranian populations, we designed the TTS.

This study will provide data for prevalence, incidence, and natural course of thyroid dysfunction according to sex, age, and the thyroid autoimmune antibodies, which will facilitate the determination of the association between overt and subclinical hypo- and hyperthyroidism with cardiovascular risk factors, and CHD and total mortality. The results will also help us to address practical guidelines for thyroid disorders for our population.

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