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Evaluation of Thyroid Hormone Levels and Urinary Iodine Concentrations in Koreans Based on the Data from Korea National Health and Nutrition Examination Survey VI (2013 to 2015)

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No nationwide data have been published about thyroid hormone levels and urinary iodine concentrations (UICs) in Korea. The Korea Centers for Disease Control and Prevention and the Korean Thyroid Association established a project to evaluate the nationwide thyroid hormone profile and UICs in healthy Koreans as part of the Korea National Health and Nutrition Examination Survey (KNHANES) VI (2013 to 2015), a nationwide, cross-sectional survey of the Korean population that enrolled 7,061 individuals who were weighted to represent the entire Korean population. Based on the KNHANES VI, the geometric mean value of serum thyroid stimulating hormone was 2.16 mIU/L, and its reference interval was 0.59 to 7.03 mIU/L. The mean value of serum free thyroxine was 1.25 ng/dL, and its reference interval was 0.92 to 1.60 ng/dL. The median UIC in the Korean population was reported to be 294 μg/L, corresponding to 'above requirements' iodine intake according to the World Health Organization recommendations. A U-shaped relationship of UIC with age was found. The prevalence of overt hyperthyroidism and overt hypothyroidism in the Korean population based on the KNHANES VI was 0.54% and 0.73%, respectively.

Keywords: Korea; Thyroid hormones; Iodine

INTRODUCTION

No nationwide data have been published about the reference intervals of serum free thyroxine (T_4), thyroid stimulating hormone (TSH), and urinary iodine concentration (UIC) in Korea. A few studies dealing with the reference intervals of serum free T_4, TSH, and UIC have been performed in limited population samples in Korea. The previous studies analyzed subjects receiving a health check-up, patients with thyroid disease, and a population living in an isolated village [1-3]. Therefore, the Korea Centers for Disease Control and Prevention, in conjunction with the Korean Thyroid Association, established a project to evaluate the nationwide thyroid hormone profile and UICs in healthy Koreans as part of the Korea National Health and Nutrition Examination Survey (KNHANES) VI (2013 to 2015) in 2012. The KNHANES was originally designed to evaluate the

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health and nutritional status, health risk factors, and the prevalence of major chronic diseases in the Korean population, as well as to provide data for the development of health policies and programs in Korea starting in 1998. The KNHANES VI (2013 to 2015) was a nationwide, cross-sectional survey of the Korean population that used a stratified, multistage clustered probability sampling to select a representative sample of the civilian, noninstitutionalized Korean population. In this data set, approximately 2,400 individuals (about one-third of the total sample) were selected each year between 2013 and 2015 using stratified subsampling and underwent measurements of serum free T_4, TSH, and anti-thyroperoxidase antibody (TPOAb). The final sample consisted of 7,061 individuals aged 10 years and older, and was weighted to represent the entire Korean population. UIC was measured in a spot urine sample in 6,564 of the participants. All participants responded to questionnaires regarding their personal and family history of thyroid disease and their history of using drugs that could affect thyroid hormone levels.

REFERENCE INTERVALS OF SERUM TSH AND FREE T_4 BASED ON THE KNHANES VI

The National Health and Nutrition Examination Survey III (NHANES III) from the USA suggested that serum TSH levels might vary according to age, gender, ethnicity, and assay method. Therefore, serum TSH reference intervals should be established using specimens from TPOAb-negative, ambulatory, euthyroid subjects who have no personal or family history of thyroid dysfunction, no visible goiter, and are taking no medication [4]. Serum TSH levels measured in a euthyroid reference population showed a left-skewed distribution with a long tail towards the higher levels. The values became more normally distributed when they were log-transformed. It is standard practice to log-transform serum TSH levels to calculate the 95% confidence limit.

Park et al. [5] and Kim et al. [6] identified 5,987 reference individuals who were used to define the precise reference intervals of serum free T_4 and TSH levels based on the KNHANES VI. The reference individuals were selected from TPOAb-negative (<34.0 IU/mL), ambulatory, euthyroid subjects who had no personal or family history of thyroid dysfunction, no visible goiter, and were taking no medication. The geometric mean value (defined as the *n*th root of the product of *n* numbers) of serum TSH was 2.16 mIU/L, and it was lower in the age group of 40 to 49 years and higher in the age groups of 10 to 19 years and 70 years or older [7]. Thus, a U-shaped association was observed between age and serum TSH levels. The geometric mean value of serum TSH was significantly higher in women than men (2.24 mIU/L vs. 2.09 mIU/L, $P<0.001$). The serum TSH reference intervals established from the 95% confidence limits of the log-transformed values were 0.59 to 7.03 mIU/L (women, 0.56 to 7.43 mIU/L vs. men, 0.62 to 6.57 mIU/L), which was right-shifted [8]. Serum TSH reference intervals were not significantly correlated with age. The serum free T_4 reference intervals were 0.92 to 1.60 ng/dL. The mean serum free T_4 level in reference individuals was 1.25 ng/dL. The mean serum free T_4 level in men was significantly higher than that in women (1.29 ng/dL vs. 1.20 ng/dL, $P<0.0001$), and serum free T_4 levels significantly decreased with age after 20 years old (P for trend <0.0001). Serum TPOAb was detected in 7.30% of subjects (men 4.33%, women, 10.62%; positive results were defined as ≥34.0 IU/mL).

A few differences are evident between the KNHANES results and those of previous Western reports. First, the serum TSH levels in the KNHANES were markedly higher than those presented in previous Western reports. For example, the mean value and upper reference limit of serum TSH in the NHANES III were 1.40 and 4.12 mIU/L, whereas the corresponding results from the KNHANES were 2.16 and 7.03 mIU/L, respectively [9]. All values from the KNHANES were right-shifted. Excessive iodine intake in the Korean population may explain these differences. Genetic differences regarding the set-point of thyroid hormone have been proposed, and such differences might be another reason for the higher TSH level in Korea. Second, a U-shaped curve between age and serum TSH levels, with lower levels in middle-aged participants and higher levels in younger and older participants, was only found in the KNHANES. In most studies, serum TSH levels gradually increased with age. A U-shaped curve was also found between age and UIC. Therefore, the change in the serum TSH level with age was influenced by the change in the UIC [10]. Increased TSH and decreased thyroid hormone levels have been reported to be associated with a prolonged life span [11]. Therefore, the determination of age-specific reference ranges of serum TSH in a given country is very important for providing adequate treatment.

REFERENCE INTERVALS OF UIC BASED ON THE KNHANES VI

Previous studies have found most Koreans to have sufficient iodine intake [12,13]. However, no nationwide survey has investigated iodine intake in the entire Korean population. More than

90% of dietary iodine is excreted in the urine, and UIC is considered to be an index of recent iodine intake. In non-pregnant, non-lactating women, a UIC of 100 μg/L corresponds roughly to a daily iodine intake of approximately 150 μg under steady-state conditions [14,15]. Kim et al. [16] published results on the UIC in Koreans based on the KNHANES VI, which was the first nationwide report. UIC was measured in 8,318 non-pregnant subjects over 6 years old. They reported that the median UIC in the Korean population was 294 μg/L, corresponding to 'above requirements' iodine intake according to the World Health Organization (WHO) recommendations. The unique diet of Koreans, including basic ingredients made from sea tangle or kelp and seaweed soup, is considered to be a major cause of these trends [17,18]. According to the WHO recommendations for iodine nutritional status, only 23% of respondents were in the adequate range (UIC 100 to 199 μg/L), and 65% were classified as having an intake that was 'above requirements' (UIC 200 to 299 μg/L) or 'excessive iodine intake' (UIC ≥300 μg/L). However, 12% showed 'insufficient' iodine intake (UIC <100 μg/L). The median UIC was higher among school-aged children (6 to 12 years, 511 μg/L) and lower among participants in their 70s (251 μg/L) than in other age groups. After adjusting for age, gender, body mass index, and smoking status, serum TSH levels were significantly correlated with the UIC (r=0.154, P< 0.0001). The changes in UICs with age showed a U-shape. The median UIC increased with household income level (P for trend <0.001). Individuals living in seaside or urban areas had higher UICs than those in inland or rural areas. This trend is consistent with the findings of previous studies [19,20].

PREVALENCE OF OVERT HYPERTHYROIDISM AND OVERT HYPOTHYROIDISM IN KOREANS

Kim et al. [6] published a study presenting the prevalence of thyroid dysfunction in the Korean population based on the KNHANES VI. They reported that the prevalence of overt and subclinical hyperthyroidism was 0.54% (men 0.30%, women 0.81%) and 2.98% (men 2.43%, women 3.59%), respectively. They also reported that the prevalence of overt and subclinical hypothyroidism was 0.73% (men 0.40%, women 1.10%) and 3.10% (men 2.26%, women 4.04%), respectively, and its prevalence increased with age until the 50 to 59 age group. Seo et al. [21,22] published findings on the prevalence of overt hyperthyroidism and overt hypothyroidism using medicare claims data provided by the Health Insurance Review and Assessment Service (HIRA) in 2013 and 2015, respectively. They reported that the prevalence of overt hyperthyroidism and overt hypothyroidism was 0.34% (men 0.20%, women 0.47%) and 1.43% (men 0.44%, women 2.40%), respectively. The prevalence derived from the KNHANES VI data included individuals with those conditions who were not receiving treatment, but excluded well-controlled euthyroid patients, while the prevalence derived from the HIRA data may have included subclinical patients receiving overtreatment, while excluding individuals with those conditions who were not receiving treatment. Therefore, these two sets of results should not be compared without adjustment. To summarize, the prevalence of overt hyperthyroidism and overt hypothyroidism in Koreans may be 0.34% to 0.54% (men, 0.20% to 0.30%; women, 0.47% to 0.81%) and 0.73% to 1.43% (men, 0.40% to 0.44%; women, 1.10% to 2.40%), respectively.

CONCLUSIONS

The Korea Centers for Disease Control and Prevention and the Korean Thyroid Association established a project to evaluate the nationwide thyroid hormone profile and UICs in healthy Koreans as part of the KNHANES VI (2013 to 2015), a nationwide, cross-sectional survey of the Korean population. Based on the KNHANES VI, the geometric mean value of serum TSH was 2.16 mIU/L, and its reference interval was 0.59 to 7.03 mIU/L. The mean value of serum free T_4 was 1.25 ng/dL, and its reference interval was 0.92 to 1.60 ng/dL. The median UIC in the Korean population was reported to be 294 μg/L, corresponding to 'above requirements' iodine intake according to the WHO recommendations. A U-shaped relationship of UIC with age was found. The prevalence of overt hyperthyroidism and overt hypothyroidism in the Korean population based on the KNHANES VI was 0.54% and 0.73%, respectively.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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