Iodine status and its correlations with age, blood pressure, and thyroid volume in South Indian women above 35 years of age (Amrita Thyroid Survey)

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ABSTRACT

Background: Thyroid disorders are more commonly seen among females and the prevalence increases with age. There is no population data from India focusing on iodine levels and their correlations with thyroid volume and other factors in adult women.

Aim: This study was designed to establish the iodine status and its relation with various factors including thyroid volume measured by ultrasound among the females of Kerala.

Materials and Methods: This was a cross sectional house to house survey among the females above 35 years of age in a randomly selected urban area in Cochin Corporation, Kerala State, India. Selected subjects were interviewed, examined and blood and urine tests were done. Thyroid volume was calculated using ultrasound.

Results: Among the 508 subjects who participated in the checkup, 471 subjects were included for analysis. Mean age was 50.3 + 10.7 years and 53.2% were postmenopausal. A total of 98% of the subjects were using iodized salt and median urinary iodine excretion (UIE) was 162.6 mcg/l. UIE had negative correlation with age and systolic blood pressure (BP), but had no correlation with thyroid volume (TV), thyroid nodularity, free thyroxine 4 (FT4), thyroid stimulating hormone (TSH) or anti thyroid peroxidase (TPO) levels. Iodine deficiency was more commonly seen in subjects with hypertension and also among postmenopausal females.

Conclusions: This study showed that females > 35 years were iodine sufficient, though one third of the subjects had UIE levels less than the recommended level. Iodine levels had significant negative correlation with age and systolic BP and no correlation with thyroid volume or biochemical parameters. Iodine deficiency was significantly higher in subjects with new and known hypertension and this relation merits further evaluation.

Key words: India, iodine, thyroid

INTRODUCTION

Iodine is an important micronutrient needed for the synthesis of thyroid hormones which is essential for the normal functioning of human body. Diet is the major source of iodine and lack of adequate iodine content in the food would result in iodine deficiency. This can be very detrimental especially to the developing fetus and young children. In adults, iodine deficiency can cause a variety of disorders such as goiter, hypothyroidism, and mental impairment.[1] Since iodine deficiency could be easily corrected by food fortification with iodine, World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF) has recommended universal salt iodization as an easy and cheap method of iodine supplementation in 1993.[2] But despite all these efforts, iodine deficiency remains a public-health problem in 47 countries. However, as a result of supplementation, iodine intake is more than adequate, or even excessive, in 34

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countries, an increase from 27 in 2003.\textsuperscript{[3]} Excessive iodine intake could also contribute to thyroid disorders such as development of goiter, subclinical or overt hypothyroidism, and increased auto immune thyroiditis etc.\textsuperscript{[4,5]} Hence, a constant surveillance of iodine status is essential to maintain the right level of iodization among the population.

Though India has been classified as an iodine sufficient country by WHO\textsuperscript{[6]} pockets of iodine deficiency still exists. Previous studies of school children from south Indian state of Kerala had shown a goiter prevalence of 16.6\% and the consumption of iodized salt as 48.9\%. The urine iodine content less than 100 mcg/l was around 50\%.\textsuperscript{[8]} But there are not many studies among adults in this population other than our previous study which showed that the prevalence of goiter was 12\% despite adequate iodine status. It has also demonstrated a high prevalence of undetected thyroid disorders especially among middle age and above females.\textsuperscript{[7]} It is well known that the prevalence of hypothyroidism increases with age and that it is more common in women. Therefore, the aim of present study is to assess the iodine status and its relation to thyroid volume and other factors in this population of females > 35 years.

\textbf{Materials and Methods}

This study was conducted as a cross sectional community survey of females > 35 years living in a randomly selected urban area. The total number of inhabitants was 7001, (females 3578) living in 1612 households. Number of subjects required for the study was calculated based on the data from a previous study\textsuperscript{[7]} which showed the prevalence of thyroid disorders as 25.4\% in this community. Considering 20\% drop in the response rate, sample size was estimated as 550 subjects. One female of above 35 years was randomly selected from the households situated in the study area using WHO cluster sampling method. Trained field workers visited the selected households and details of socio-demographic, dietary, lifestyle and medical history were collected using a validated questionnaire. Consumption of goitrogenic food was assessed using a food frequency questionnaire and 24 hour recall of two separate days where specific questions were asked regarding the consumption of known goitrogenic food items such as cabbage, cauliflower, cassava on daily basis. Goitrogen chemicals thioglucosides or glucosinolates have not been measured or quantified in the food, serum or urine in this study.

Menopause was defined as the absence of periods for more than a year in a non-pregnant female. Amenorhoea less than one year duration was classified as irregular periods only. All surveyed subjects were directed to undergo 10 h of fasting before attending the health checkup conducted in their locality. During the checkup, a clinician examined the subjects and the medical history was verified. Anthropometric measurements such as weight, height, and waist circumference were all measured. Height and waist circumference were recorded to the nearest millimeter and the weight was recorded to nearest 100 gm.

Body mass index (BMI) was calculated as per the formula weight in kg/height (ht) in m\textsuperscript{2}. Body surface area was calculated as per the DuBois and DuBois formula i.e., weight (kg\textsuperscript{0.425} \times height (cm\textsuperscript{0.725}) \times 0.007184. Lean body mass was calculated using Humes’s formula for women over the age of 30: lean body mass in Kg = \((0.29569^* (body weight in Kg)) + (0.41813^* (height in cm)) - 43.2933.\textsuperscript{[8]}

The triceps and subscapular skin fold thickness was measured to the nearest millimeter with the Lange skin fold caliper (Cambridge Scientific Industries Inc, Cambridge, MD). The subscapular skin fold thickness was measured immediately below the inferior angle of the scapula and triceps was measured as the vertical fold along the midline of the upper arm halfway between the tip of the shoulder and the tip of the elbow.

Blood pressure was determined using a sphygmomanometer and stethoscope with subject sitting and resting the arm after 5 minutes rest. Goiter evaluation was done clinically by WHO method and was classified as none, grade 1 or grade 2.

Venipuncture was done and the collected blood was transferred in ice packs to the lab and the separated serum was stored at -70°C freezers till analysis. The urine collected in iodine free-capped plastic containers was stored under refrigeration till analyzed for urine iodine level. Serum thyroid stimulating hormone (TSH) (normal range 0.27- 4.2 uIU/ml), free thyroxine (FT4) (normal range 0.93 - 1.71 ng/dl), and anti thyroid peroxisome antibody (anti TPO) were measured by Electro Chemiluminescence Immuno-Assay (ECLIA) using Elecsys 2010 Roche. Anti TPO levels more than 50 IU/ml was considered positive for thyroid autoimmunity. Fasting blood sugar was analyzed in the serum by glucose oxidase method and total cholesterol was estimated by Cholesterol Oxidase Paraaminophenazone (CHOD-PAP) method in Elecsys Autoanalyzer.

Urine iodine was estimated by simple micro plate method using ammonium persulphite digestion and Sandell Kolthoff’s reaction\textsuperscript{[9]} at All India Institute of Medical Sciences (AIIMS), Delhi, and was expressed as mcg of iodine per liter of urine (mcg/l). Urine iodine level < 100
mcg/l is considered as iodine deficiency and > 300 mcg/l is considered as having possible excess of iodine intake.\cite{10}

Ultrasound scan of the neck was done for all the participants in the field using a portable US scan machine (Larson and Turbo model) with a 7.5 M hz probe. Thyroid scan was done in the supine position the neck was extended by a pillow under the shoulder and the craniocaudal (length) mediolateral (breadth) and antero posterior (depth) were measured by the author under the guidance of an experienced radiologist. The volume of each lobe was calculated separately using WHO accepted formula -(length × width × breadth) 0.479 and added together to get the total volume of thyroid. Goiter was defined as thyroid volume > 97th centile of healthy subjects from the study population. Texture of the gland was classified as normal, nodular or diffuse.

Statistical methods
Data was analyzed using statistical package for the social sciences (SPSS) version-11.0. Correlations of continuous variables were calculated using Pearson’s correlation coefficient and statistical test of significance of the associations with categorical variables was done by Chi-square test. Analysis of variance (ANOVA) was used for comparing mean values of the variables among more than two groups and student’s t-test was used for comparing the two groups.

RESULTS

Among the 530 females surveyed, 508 participated in the health checkup. After excluding the subjects with missing values, there were 473 subjects. Among them, two had large goiters with retrosternal extension and they were excluded from the analysis. The final sample for analysis included 471 subjects. Mean age was 50.3 ± 10.7 years and 53.2% were postmenopausal. Among these, 168 subjects (35.7%) had up to primary education, 231 (49.0%) had studied up to secondary education, whereas 72 subjects (15.3%) had higher education. Regarding the economic status, 121 (25.7%) belonged to the poor income category, 282 (59.9%) were in the middle income category, and 68 (14.4%) belonged to the high-income group. Regarding dietary habits, 96% were non-vegetarians and 98% of the subjects were using iodized salt alone or in combination with rock salt.

Urine iodine levels
Median UIE was 162.6 mcg/l. UIE < 50 mcg/l was present in 5.9% and > 400 was present in 1.5%. The distribution of urine iodine levels among the study population is given in Figure 1. Distribution of UIE among different categories of age is shown in Figure 2. Distribution of UIE levels was similar in all categories of economic status, education level, and occupation.

There was no significant difference of iodine status among the subjects with a family history or past history of thyroid disorders when compared to those without. Neither diabetes nor obesity had any relation with the iodine status. But, mean UIE was significantly \( P < 0.001 \) lower in subjects with a history of hypertension \( n=101 \) than in subjects without a history of hypertension \( n=370 \). Similar significant difference \( P < 0.001 \) was present between subjects with hypertension (HTN) defined by adult treatment panel (ATP) 3 criteria \( n=285 \) which included newly detected hypertensive subjects as well [Table 1]. There was no difference of iodine status seen between the subjects with or without diabetes. Postmenopausal females had more iodine deficiency than the pre menopausal females and it was clinically and statistically significant.
(P = 0.003). But, after correcting for age, this difference was not significant. Vegetarians had higher urine iodine levels than non-vegetarians, but the number of vegetarians (n=18) was very small to make any valid comparison.

Among the subjects, 396 (84.1%) were using iodized salt alone, whereas 67 (14.2%) were using both rock salt and iodized salt. Five subjects were using only rock salt, whereas only three subjects were using non-iodized salt. No statistical comparison was possible due to the small numbers in this category.

Among the continuous variables, UIE had negative correlation with age (r -0.122 P = 0.008) and systolic BP (-0.149 P = 0.001), but not with diastolic BP. This negative relation with systolic BP persisted even after adjusting for age. But UIE levels had no correlations with BMI, lean body mass, body fat percent, fasting blood sugar (FBS), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, FT4, TSH or anti TPO levels. UIE levels did not have any significant linear correlation with ultrasound measured thyroid volume (r 0.046 P = 0.318), but it showed a very minimal increasing trend at high UIE levels as shown in Figure 3.

Goiter and iodine status
Mean urine iodine was not different among goitrous subjects when compared to those without goiter. But among subjects with goiter, mean urine iodine was lower in those with grade 1 goiter, whereas it was higher in those with grade 2 goiter and it was clinically significant (P = 0.012) [Table 2]. Grade 1 goiter had more iodine deficiency, but less iodine excess compared to grade 2 goiters. Nearly half of both grade 1 and grade 2 goiters were associated with normal iodine status.

Ultrasound evaluation showed that 88 (18.7%) subjects had nodular changes in thyroid gland. Mean UIE levels were not significantly different between subjects with various sonological abnormalities of thyroid gland. Table 3. When the mean UIE levels of subjects with nodular changes (> 10 mm) (177.17 + 96.22 mcg/l) were compared with those without it (174.59 + 101.04 mcg/l n =383), there was no significant difference (P = 0.86) between these two groups.

**DISCUSSION**
Iodine is the most important micronutrient affecting the thyroid gland. Iodine levels have major role in the etiology of thyromegaly or goiter, thyroid functional disorders as well as thyroid autoimmunity. Iodine deficiency is the commonest cause of goiter worldwide, though its prevalence is decreasing due to the salt iodization program.

Though India is classified as an iodine sufficient country by WHO, areas of iodine deficiency still exists in some parts of the country. Most of these data are from school going children and iodine status of adult population in India is not widely studied. There are many studies from reproductive age group females as the iodine status of these expectant mothers has long lasting impact on the progeny. As per the data from the previous nation-wide survey, National
Table 3: Mean and SD of urine iodine levels in different types of ultrasonological texture of thyroid. (P=0.456 NS)

| US Texture of the Thyroid | Number | Mean  | Std. Deviation |
|---------------------------|--------|-------|----------------|
| Normal                    | 326    | 123.01| 100.14         |
| Single nodular            | 41     | 196.50| 100.80         |
| Multinodular              | 47     | 160.30| 89.74          |
| Diffuse                   | 30     | 174.15| 109.08         |
| <10 mm nodule             | 27     | 194.08| 104.68         |

Family Health Survey 3 (NFHS 3), conducted among adult women aged 15-49 years and men aged 15-54 years, and other studies most of the thyroid disease burden is seen among females than males and it was shown to increase steadily with age. As such, there are not many studies from India looking at the thyroid problems in adult females, though there are data on the iodine status of reproductive age females. Hence, the results of this study focused on females > 35 years form important data regarding their iodine status and its relation to thyroid volume and other factors.

Present study showed that almost 98% of households are using iodized salt despite the free availability of non-iodized salt, as Government Kerala has not banned the sale of non-iodized salt. This is similar to the previous study conducted in Ernakulam area but higher than the state average of 74% and national average of 51% as per the nation wide survey conducted in India (NFHS 3).

Median urine iodine levels of the study subjects were within normal range suggesting sufficient iodine intake in this age group females, though one third of population had UIE < 100 mcg/l. But severe iodine deficiency < 50 mcg/l was seen only in small number of subjects. These values are slightly different from the results of previous population study among 18-80 year old males and females conducted in different areas of Kochi which showed that 16.8% females had UIE < 100 mcg/l, where as 25.9% females had UIE > 300 mcg/l. This difference may be due to the older age group studied in the present study. In the present study, iodine excess was seen in fewer subjects, but severe iodine deficiency (< 50 mcg/l) was also much lower than the suggested limit of < 20% for an iodine sufficient area.

Regarding the iodine status of adults, studies of females in the reproductive age groups from India, the prevalence of IDD in the pregnant women, as apparent from UIE < 100 mcg/l had been found to be 22.9 and 9.5% in the states of Delhi and Himachal Pradesh, respectively, whereas it was seen in 21.2% of pregnant women attending a an antenatal clinic in West Bengal. Though data on subjects similar to the present study age group females are scarce, data from the adults in various parts of the world showed that UIE levels of < 100 mcg/l was seen in 11% of adults in America, 21% in South Pacific, 41.5% in Africa, 52% in Europe, and 47.2% in Eastern Mediterranean countries.

Regarding the factors associated with iodine status, though many variables were studied, only few had statistically significant correlations. Age had a negative correlation with urine iodine levels though it was not very strong. This lower iodine status of old age may be due to the poor dietary intake or lower salt intake widely seen among elderly. This kind of relation with age is not demonstrated in other large population studies.

In the present study, systolic blood pressure was found to have an inverse relation with urine iodine which persisted even after adjusting for age. Iodine deficiency was also significantly more common in subjects with a history of hypertension than the subjects without a history of hypertension. This may be due to the therapeutic salt restriction resulting in insufficient iodine intake, though the history of salt restriction was not assessed in this study. This is similar to the findings of a recently published study among Caucasian subjects with hypertension in the age group of 20-60 years where iodine deficiency has been shown to be more frequent than general population, high proportions of men (24.96%) and women (40.42%) were iodine deficient. In that study, current hypertension per se or having a history of hypertension did not associate significantly with iodine nutritional status in both men and women, however, dietary salt restriction among women was significantly associated with iodine deficiency.

But dietary salt restriction may not be the only factor involved in this low iodine status as in our study even the subjects without history of hypertension, but now having high BP as per ATP 3 criteria also had similar negative correlation with iodine levels. This finding could not be explained by lower salt intake as these subjects were not aware of the hypertension and are possibly not following salt restriction. Such a direct negative relation between blood pressure and iodine levels has not been demonstrated in earlier studies, though iodine deficiency has been attributed as a risk factor for hypertension and other cardiovascular disease by some authors. About five decades ago, iodine had a therapeutic role in hypertension treatment until the intervention of newer drugs. Though the diagnosis of new hypertension is not possible from a cross sectional study as it necessitates repeated BP measurement, the negative correlation of iodine level and BP was rather intriguing. However, these findings highlight the need for recommending alternative sources of iodine for subgroups of subjects on salt restriction as...
well as evaluating iodine deficiency in a new perspective as a probable modifiable risk factor for hypertension.

But unlike iodine levels, presence of goiter was not different between those with hypertension and those without hypertension. This observation could be possibly explained by the fact that subjects in older age groups, thyroid is undergoing atrophic changes and may not show thyromegaly as efficiently as in younger people with iodine deficiency. Neither diabetes nor lipid parameters had any correlation with iodine levels in this population. None of the biochemical thyroid function parameters such as FT4, TSH, and anti TPO levels had significant relation with UIE levels in these subjects irrespective of the age groups.

Regarding the relation of thyroid volume with UIE levels, there was no statistically significant linear correlation between these two factors. This may be due to the fact that these are older perimenopausal females whose thyroid may be undergoing many structural changes and iodine levels are not the major factor determining thyroid volume though there was a slight upward trend of TV in excess levels of UIE it was not very significant. Studies have shown increased TV associated with excess levels of UIE (> 500 mcg/l), especially in children. Such an association was not demonstrated in present study probably because there were not many subjects with such high levels of UIE.

Postmenopausal females had more iodine deficiency than pre menopausal females, but after adjusting for age, this association was not significant. This observed difference is probably due to the age factor.

Regarding goiter and iodine status, there was no significant difference in iodine status among subjects with goiter compared to those with out goiter. But mean UIE levels were significantly different between subjects with grade 1 and grade 2 goiter. Similarly, iodine deficiency was almost twice more frequent in grade 1 goiter than in grade 2, while excess iodine levels were twice more common in grade 2 goiter than in grade 1 goiter. Nearly half of the goiter had normal iodine status suggesting the presence of other possible etiological factors.

Iodine levels had no significant relation with thyroid structural abnormalities in these age group females. Thyroid nodularity and nodular goiter are considered as a long term effect of iodine deficiency and is more commonly seen in areas of moderate iodine deficiency than in areas with sufficient iodine levels. Though our study shows iodine deficiency now, we do not have similar data on adults prior to the iodization of salt in this area to compare. But in a similar study among French adults, no relationship was found between prevalence of nodular thyroid structure and the state of borderline iodine status.

Though this study is first of its kind in Indian adult population, as the sample is a small selected age group of females, these findings may not be true for the adult population as a whole. However, these study findings highlight the need for further large studies to evaluate the iodine status and relation with other factors in our population.

**Conclusion**

This study showed that females > 35 years were iodine sufficient, though one third of the subjects had UIE levels less than the recommended level. Iodine levels had significant negative correlation with age and systolic BP, but had no correlation with TV, thyroid nodularity, and FT4, TSH or anti TPO levels. Iodine deficiency was more commonly seen in subjects with hypertension and also among postmenopausal females. In these subjects, 15.7% had clinical goiter and it was more common among younger females. Nearly half of the subjects with goiter had normal UIE levels, but mean UIE was higher in grade 2 goiter than in grade1 goiter.

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