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Population Status of Iodine and Its Potential Effects on Thyroid Function and Autoimmunity in Southwestern Colombia

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Abstract

Background: This study aimed to investigate the iodine status and its potential effects on thyroid function and autoimmunity in Colombia.

Methods: This was a cross-sectional study, in population of urban and rural areas, from four geographic regions in the Department of Cauca, Colombia; the participants were 412 healthy adults, a third from rural areas. The following variables were evaluated: median urinary iodine concentration (mUIC), serum thyrotropin (TSH), clinical and ultrasonographic (US) goiter assessment, and anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg) and anti-TSH receptor (TRAb) concentrations.

Results: The mUIC levels were 153.9 µg/L (interquartile range (IQR): 220.06); 30% had "excessive" mUIC and a quarter had "low" mUIC. The positivity of anti-Tg and anti-TPO was higher in subjects > 60 years ($P = 0.017$ and $P \leq 0.001$, respectively). A high prevalence of "low" mUIC was found in the "low" socioeconomic status (SES) and of "more than adequate or excessive" in the "high" SES when compared with the "medium" SES ($P \leq 0.001$). The prevalence of goiter by physical examination was 41.7% and 34% by US. The highest mUIC levels were significantly more prevalent in women, in subjects with elevated TSH and in those from rural areas.

Conclusions: The population status of iodine in Colombia is U-shaped; the high prevalence of goiter, hypothyroidism, and thyroid autoimmunity can be explained by excess or deficit of iodine and by probable environmental goitrogens.

Keywords: Autoimmunity; Goiter; Iodine; Thyroid; Thyrotropin; Salt

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Introduction

Iodine intake-associated disorders are serious public health issues around the world. Iodine deficiency disorders (IDDs) are pervasive throughout the planet and are related with an increased risk of perinatal mortality, mental retardation and impaired brain development, hypothyroidism, endemic goiter and poor socioeconomic development, *inter alia* [1, 2].

However, notwithstanding all the initiatives from various international organizations, the approximate number of people at risk of experiencing IDD is around two billion. In countries with iodine deficiency, universal salt iodization (USI) is the strategy of choice for its prevention and control. However, the universal indicators used to monitor such disorders are not always complied with, and this may account for the significantly increased prevalence of a "more than adequate" or "excessive" iodine intake in some geographical areas [3-6].

The clinical disorders associated with excessive iodine intake have been linked to thyroid autoimmunity, hypothyroidism, hyperthyroidism, goiter, thyroid nodules, among other conditions [7-9].

The primary objective of this study was to assess the iodine status and thyroid health of the adult population in the Southwest in Colombia, a geographical area classified as "free of IDD" using measures of the median urinary iodine concentration (mUIC), clinical and ultrasonographic goiter assessment, thyrotropin (TSH), free T4 (FT4), and thyroid autoantibodies: anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg) and anti-TSH receptor (TRAb) concentrations. Our secondary objectives were to explore the potential effects of iodine status on thyroid function and autoimmunity, as well as other probable associated factors.

Materials and Methods

Subjects

The study population comprised adults in the urban area of Popayan and three rural areas (Timbio, Bolivar and Piendamo) in the Department of Cauca, Colombia. Participants were recruited between June 30, 2018 and September 19, 2019. The sample size was based on the total number of inhabitants in the four geographical areas selected (n = 268,778), according

to the data from the National Administrative Statistics Department, Colombia, 2016 [10].

Considering an estimated 10% prevalence of thyroid autoimmunity [11], a 95% confidence interval (CI) and an estimated 3% error, the sample size was estimated at 384 subjects (the total number of participants was increased by 15% to account for any potential dropouts during the study, for a total of 412 study subjects). The subject distribution was as follows: urban area, n = 266; rural area, n = 146. The sampling mode for the urban area was probabilistic (simple random) and for the rural area was non-probability based on convenience.

Ethical issues

All procedures of the present study were conducted in compliance with the Helsinki Declaration for research on human beings. This study was approved by the Ethics in Research Committee of the research vice-rector office of the Universidad del Cauca-Colombia (ID: 4656, January 25, 2018).

Experiment procedure

The inclusion criterion was adults ≥ 18 years old, and the exclusion criteria were: use of levothyroxine (or any thyroid derivative), intake of anti-thyroid agents and/or selenium or iodine containing supplements (whether constantly or intermittently) during the last 6 months; partial or total thyroidectomy and radioactive iodine therapies or procedures (over the past 24 months). The sociodemographic data (origin, socioeconomic status (SES)) were collected. A brief questionnaire was administered 48 h before to identify any family history of thyroid disease (self-reported) and salt consumption habits. In order to establish the average salt consumption per person/day, the participants received one pound of iodized salt (on the same day of the appointment), and they were told to use that salt in all their food preparations (without changing the "usual" normal amounts they used in their food) requiring salt over 48 consecutive hours; then the salt container was weighed to estimate the overall household salt consumption. To calculate the average consumption per person/day, the total amount of salt used over the 2 days was divided into the number of people usually living and eating in the household (considering at least two meals per day). The result was divided by 2, in order to estimate the average salt consumption per person/day. Anthropometric and clinical measurements were taken (weight (kg), size (cm), systolic blood pressure (SBP) (mm/Hg), diastolic blood pressure (DBP), and heart rate (beats per minute (bpm))).

Measurement

mUIC

The mUIC was measured in a casual urine sample between 7 and 9 am, using spectrophotometry (modified Sandell-Kolthoff reaction) [12]. All samples were transferred to sterile tubes, frozen for the next 24 h at -20 °C and transported for biochemical analysis. The results were classified as follows (in µg/L): < 100: low iodine intake; 100 - 199: adequate iodine intake; 200 - 299: more than adequate iodine intake; ≥ 300: excessive iodine intake [13, 14].

Thyroid function

Serum samples were obtained by venipuncture, and blood was collected in 10-mL test tubes. All samples of blood were collected and centrifuged during the routine visits. Serum samples were frozen at -80 °C and stored in a biobank in a specialized clinical laboratory (MCP, Popayan-Colombia). TSH, FT4, anti-TPO, anti-Tg and TRAb were measured using chemiluminescent immunoassay (IMMULITE® 2000 Systems Analyzers; Siemens, Munich, Germany). The coefficients of variation (CVs %) were 4.6%, 6.4%, 4.96%, 8,0% and 8.3% for TSH, FT4, anti-TPO, anti-Tg and TRAb, respectively. The results were classified as follows: TSH: 0.4 - 4.0 mIU/L (normal value); < 0.4 and > 4.0 mIU/L (abnormal value). FT4 levels were only measured in those individuals with a TSH value classified as "abnormal". The FT4 normal range was 0.89 - 1.76 ng/dL (manufacturer cutoffs). The upper limits of normal for the assays, as denoted by the manufacturers' reference ranges for diagnosis of thyroid autoimmunity, were used to denote a positive titer for anti-TPO (≥ 35 IU/mL), for anti-Tg (≥ 40 IU/mL) and for TRAb (≥ 0.10 IU/L).

Thyroid size

Clinically, the size of the thyroid was established according to the World Health Organization criteria as grade 0, grade I and grade II [14]. The thyroid volume was also determined with high-resolution thyroid ultrasonography (US) using a linear array 10- to 12-MHz probe (SONOACER3, SAMSUNG MEDISON). Longitudinal and transverse scans were performed to measure depth, width, and length of each lobe. Thyroid lobe volume was calculated as 0.479 × depth × width × length (cm). Thyroid volume was calculated as the sum of the volumes of both lobes, excluding the isthmus. Goiter was defined as a volume ≥ 12.5 mL in females and ≥ 15 mL in males [15, 16].

Statistical analysis

The qualitative variables were analyzed using frequencies and percentages. The quantitative variables were analyzed or the normality of the quantitative variables was evaluated using the Shapiro-Francia normality test to establish the use of parametrical statistics (median and standard deviation (SD)) or non-parametric statistics (median and interquartile range (IQR)). To assess the existing relationship between the independent variables (mUIC, age, gender, SES, body mass index (BMI)) and the dependent variables (goiter (yes/no) and thyroid function), a negative binomial regression and a logistical regression were used. The prevalence ratios (PRs) were estimated and a bivariate analysis using X^2 was conducted to identify

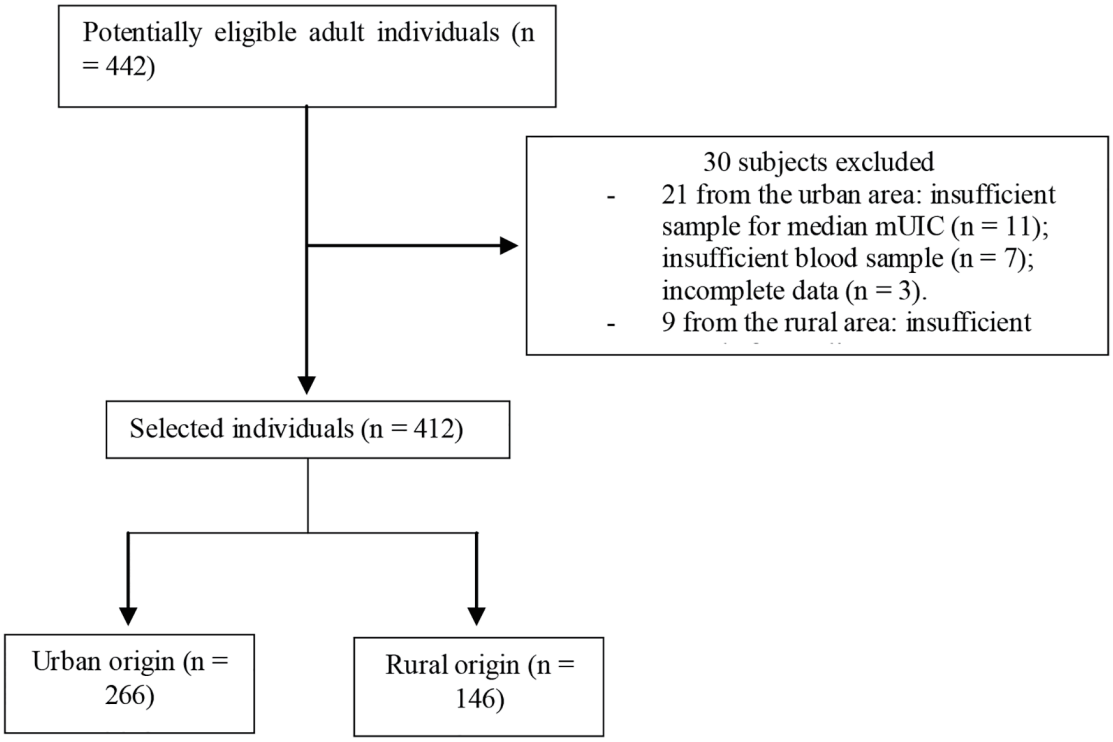

Figure 1. Flowchart of the participants included in the trial. mUIC: median urinary iodine concentration.

the variables for inclusion in the regressions; subsequently, the simple regressions were analyzed to calculate the PR with their corresponding 95% CI. Finally, a multivariate analysis was conducted to identify the adjusted PR and analysis of variance (ANOVA) and Tukey test were used to determine the significant differences between the groups of mUIC and the relevant variables. The data were captured in Excel and were then transferred to the R program version 4.0.2 using the Nortest Library and SPSS version 25.

Results

Baseline characteristics of the participants and salt consumption habits

A total of 442 individuals were assessed, of which 21 from the urban area and nine from the rural area were excluded; finally, 412 individuals were admitted to the study (Fig. 1).

Most of the subjects were females and the average age was 42.5 years (SD: 14.62); the majority came from the urban area and were from a low SES. The average size was 158 cm (SD: 8.164), with a body weight of 67.5 kg (SD: 12.90) and a BMI of 26.7 kg/m^2 (SD: 4.39). The mean SBP and DBP were 119.6 (SD: 12.20) and 72.7 (SD: 7.43) mm Hg, respectively, and the mean heart rate was 71.4 bpm (SD: 6.30). Over one-third of the participants reported a family history (first-degree relative) of thyroid dysfunction, abnormal thyroid size, or a diagnosis of thyroid cancer (Table 1).

Of the subjects, 99.2% claimed using salt for human consumption and 94% said they used iodized salt; the average consumption of salt/person/day was 13.2 g (SD: 4.21), distributed as follows: 14.3 g in the urban area and 12.1 g in the rural area; based on the SES, the distribution was as follows: low SES, 13.9 g; middle SES, 14.2 g; and high SES: 14.8 g. No differences were found in the intake of salt based on origin or SES (P = 0.26).

Differences between the presence of thyroid autoimmunity and distribution according to age and origin

The distribution of thyroid autoantibodies was as follows: 22/412 (5.3%) of the participants were TRAb-positive; 10% were anti-Tg-positive; 18.2% were anti-TPO-positive (31.3% of the participants had at least one of the three positive autoantibodies). The distribution of thyroid autoantibodies according to age (< 60 or ≥ 60 years) was as follows: for TRAb, of the 360 subjects < 60 years, 20 of them (5.5%) were TRAb-positive; in contrast, subjects ≥ 60 years, 2/52 were TRAb-positive (3.84%) (X^2: 0.263; odds ratio (OR): 0.680; 95% CI: 0.154 - 2.998 (P = 0.608)). Moreover, in terms of anti-Tg positivity, it was documented in 31/360 (8.61%) and in 10/52 (19.23%) of the subjects < 60 and ≥ 60 years, respectively (X^2: 5.718; OR: 2.527; 95% CI: 1.156 - 5.522 (P = 0.017)). Anti-TPO positivity was reported in 57/360 (15.83%) among the general population, and in 57/360 (15.83%) and in 18/52 (34.61%) in < 60 and in ≥ 60 years, respectively (X^2: 10.765; OR: 2.814; 95% CI: 1.488 - 5.324 (P ≤ 0.001)). Similarly, the positivity of thyroid antibodies based on origin (urban vs. rural) for TRAb,

Table 1. Sociodemographic and Anthropomorphic Characteristics, and Family History of Thyroid Disorders

Variables	Frequency	Percentage (%)
Gender		
Female	336	81.6
Male	76	18.4
Age in years		
< 40	189	45.9
40 - 59	171	41.5
≥ 60	52	12.6
Ethnicity		
Mestizo	397	96.4
Indigenous	87	1.9
Afro descendent	7	1.7
Origin		
Rural	146	35.4
Urban	266	64.6
SES		
Low	314	76.2
Medium	62	15.1
High	36	8.7
BMI (kg/m^2)		
Low weight	6	1.5
Normal	136	33
Overweight	173	42
Obesity I	75	18.2
Obesity II	17	4.1
Obesity III	5	1.2
Family history of thyroid disorders (self-reported)[a]		
Yes	154	37.4
No	258	62.6

[a]First-degree family history (self-reported) of goiter, hypothyroidism, hyperthyroidism, and thyroid cancer. BMI: body mass index; SES: socioeconomic status.

was 8/146 (5.47%) and 14/266 (5.26%) (X^2: 0.009; OR: 0.958; 95% CI: 0.392 - 2.341 (P = 0.926)); for anti-Tg, was 13/146 (8.9%) and 28/266 (10.52%) (X^2: 0.277; OR: 1.204; 95% CI: 0.603 - 2.40 (P = 0.599)). Finally, with regards to anti-TPO, positivity was present in 22/146 (15.1%) and 53/266 (19.9%) (X^2: 1.493; OR: 1.402; 95% CI: 0.814 - 2.417 (P = 0.222)).

Differences in terms of mUIC and distribution according age, SES and thyroid autoantibodies

Table 2 shows the distribution of mUIC based on gender, SES and origin. The mUIC in the population was 153.9 µg/L (IQR: 220.06); 100 subjects (24.31%) had low mUIC, 176 (42.7%) had adequate mUIC, 13 (3.2%) more than adequate mUIC and 123 (29.9%) had values ≥ 300 µg/L. mUIC in females was 149 µg/L (IQR: 216.68) and in males 182 µg/L (IQR: 268.7); among individuals who claimed not to use iodized salt, mUIC was 149 µg/L and among those using iodized salt was 153 µg/L. The distribution according to age was as follows: 18 - 39.9 years (148.7 µg/L); 40 - 59.9 years (147.8 µg/L); ≥ 60 years (289 µg/L). The mUIC among the low SES was 144 µg/L (IQR: 122.5); among the middle SES was 184.7 µg/L (IQR: 255.8); and in the high SES was 311.3 µg/L (IQR: 277). Significant differences were identified between the presence of "low" mUIC and a "low" SES and a "more than adequate or excessive" mUIC and the "high" SES in contrast with the middle SES (X^2: 38.266; P ≤ 0.001). The bivariate analysis (Log-binomial regression) also showed a significant difference in terms of origin and level of mUIC, with a higher prevalence of excessive mUIC among the rural population (PR: 3.11; 95% CI: 1.88 - 5.34; P ≤ 0.001). Moreover, the distribution of mUIC based on BMI was as follows: low BMI,

Table 2. Distribution of mUIC According to Gender, SES and Origin

Variables	mUIC				N	P-value
	Low intake	Adequate	More than adequate	Excessive		
Gender						
Female	85 (25.3%)	150 (44.6%)	10 (3%)	91 (27.1%)	336	0.065
Male	15 (19.7%)	26 (34.2%)	3 (3.9%)	32 (42.1%)	76	
Total					412	
SES						
High	5 (13.9%)	6 (16.7%)	4 (11.1%)	21 (58.3%)	36	≤ 0.001
Middle	9 (14.8%)	23 (37.7%)	2 (3.3%)	27 (44.3%)	61	
Low	86 (27.3%)	147 (46.7%)	7 (2.22%)	75 (23.8%)	315	
Total					412	
Origin						
Rural	34 (23.3%)	83 (56.8%)	3 (2.1%)	26 (17.8%)	146	≤ 0.001
Urban	66 (24.8%)	93 (35%)	10 (3.8%)	97 (36.5%)	266	
Total					412	

mUIC: median urinary iodine concentration; SES: socioeconomic status.

123.3 µg/L (IQR: 87.94); normal, 169.2 µg/L (IQR: 239.2); overweight, 154.6 µg/L (IQR: 284.1); obese, 132.7 µg/L (IQR: 105). There were no significant differences in terms of mUIC and the presence of thyroid autoantibodies (Fig. 2).

Differences between mUIC and thyroid function

The mUIC among TSH < 0.4 mIU/L individuals was 381.8 µg/L (but just 1.45% of the subjects had suppressed TSH; hence, no analyses were conducted in this particular subgroup); 144 µg/L for those with a TSH between 0.4 and 4.0 mIU/L and, 191.9 µg/L among the participants with a TSH > 4.0 mIU/L. Of the participants, 324 (78.6%) had a normal range TSH; 84 (20.4%) had high values (70/84 were FT4 normal (83.3%) and 14/84 (16.6%) had low FT4 levels); finally, four exhibited a suppressed TSH (all of normal FT4) (Table 3).

Differences between thyroid function and age, gender, BMI, SES and mUIC

The multiple regression model showed a significant relationship between the presence of hypothyroidism and age ≥ 60 years in females and a low SES. The frequency of hypothyroidism was higher among individuals with excessive iodine intake. In the

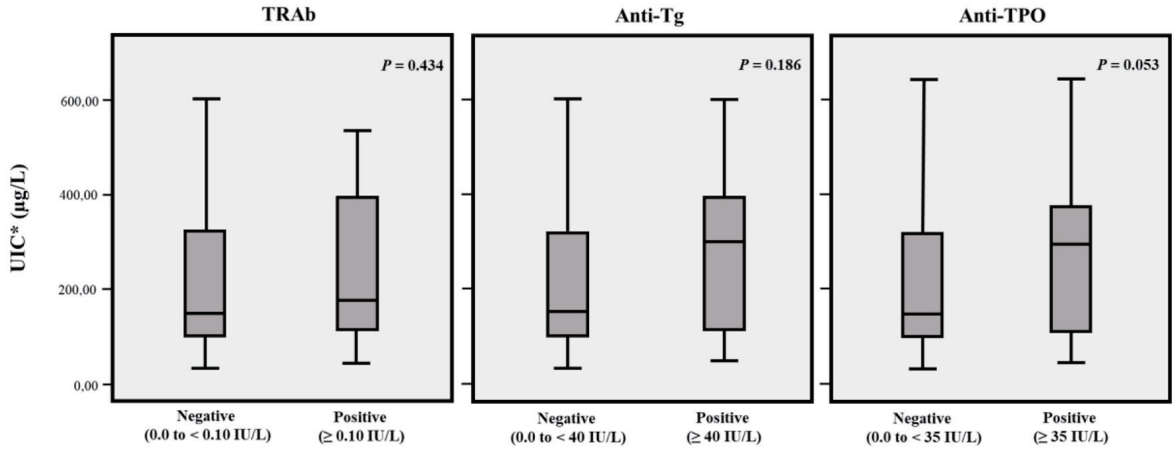

Figure 2. mUIC according to negative or positive TRAb, anti-Tg and anti-TPO. *mUIC (µg/L) in TRAb negative or positive subjects was 152.8 (IQR: 219.7) and 178.7 (IQR: 287.4), respectively. In anti-Tg negative or positive subjects mUIC (µg/L) was 150.5 (IQR: 219) and 301 (IQR: 289.2), respectively. In anti-TPO negative or positive subjects mUIC (µg/L) was 152 (IQR: 221.4) and 176 (IQR: 236.8), respectively. mUIC: median urinary iodine concentration; TRAb: anti-TSH receptor; anti-Tg: anti-thyroglobulin; anti-TPO: anti-thyroid peroxidase.

Table 3. Comparison of the Clinical Characteristics of Adults With Various mUIC

Characteristics	Deficiency (< 100 µg/L)	Adequate (100 - 199 µg/L)	More than adequate (200 - 299 µg/L)	Excessive (≥ 300 µ/L)	P-value[a]
Number of participants	100	176	13	123	-
mUIC (IQR)	70.1 (58.6 - 86.1)	143.9 (122.6 - 168)	230.5 (209.6 - 289.1)	408 (353.8 - 518)	≤ 0.001*
Age in years (median (SD))	41.3 (12.7)	40.7 (13.14)	48.2 (17.4)	45.5 (17.1)	0.013**
BMI (mean (SD))	27.2 (4.2)	26.7 (5.0)	26.3 (2.8)	26.4 (3.6)	0.58
TSH (median (IQR))	2.1 (1.48 - 3.19)	2.4 (1.63 - 3.47)	3.12 (1.18 - 5.33)	2.82 (1.13 - 4.74)	0.034***
TRAb (median (IQR))	0.10 (0.08 - 0.13)	0.10 (0.10 - 0.10)	0.10 (0.07 - 0.10)	0.10 (0.09 - 0.10)	0.791
Anti-Tg (median (IQR))	20 (19.2 - 29)	20 (20 - 24.75)	20 (20 - 33.5)	21 (20 - 34)	0.008****
Anti-TPO (median (IQR))	10 (9.8 - 20.12)	10.8 (10 - 23.25)	26 (10 - 49.5)	16 (10 - 31)	0.58

[a]ANOVA, HSD Tukey. P < 0.05: *between the group with excessive vs. deficient mUIC; **between the groups with excessive vs. adequate mUIC; ***between the groups with excessive vs. deficient mUIC; ****between the groups with excessive vs. adequate mUIC. Anti-Tg: anti-thyroglobulin; anti-TPO: anti-thyroid peroxidase; BMI: body mass index; IQR: interquartile range; mUIC: median urinary iodine concentration; SD: standard deviation; TRAb: anti-TSH receptor; TSH: thyrotropin.

simple regression results (and ANOVA) for variables such as age, gender, SES and mUIC, significant differences were identified in at least one of category. No differences were found between the presence of hypothyroidism and BMI (X^2 = 2.5428; P = 0.2804), neither between participants with "low" mUIC and variables such as age, origin and SES (Tables 3 and 4).

Differences between the prevalence of goiter established with a physical examination vs. US

The physical examination identified 172 subjects with goiter (41.7%), of which 39% were grade I and 2.7% were grade II. With US, 140 (34%) of the individuals were identified with goiter. Among the individuals with a normal thyroid volume according to US (n = 272), 46 (26.7%) had clinical goiter; among those with goiter according to the US examination, clinical goiter was identified in 126/172 (73.3%) (kappa index = 0.191; standard error (SE): 0.013).

Differences between the presence of goiter, thyroid autoimmunity and SES and between excessive mUIC, gender, TSH, origin and SES

With regards to goiter distribution (per clinic) according to mUIC, of the total number of subjects with goiter (n = 172), 45 (26.2%) individuals with mUIC < 100 µg/L had goiter and for levels of mUIC of 100 - 199 µg/L, 200 - 299 µg/L and > 300 µg/L, the proportion of goiter was 46.5%, 3.5%, and 23.8%, respectively. Of the total number of participants with goiter, 38/172 (22.1%) were anti-TPO-positive, as compared to those without goiter: 37/240 (15.4%) (X^2: 2.999; OR: 1.556; 95% CI: 0.941 - 2.572 (P = 0.083)). No differences were found between anti-Tg and TRAb positivity and the presence or absence of goiter (X^2: 0.002; OR: 1.013; 95% CI: 0.526 - 1.950 (P = 0.969) and X^2: 1.565; OR: 0.580; 95% CI: 0.245 - 1.374 (P = 0.211)), respectively. With regards to the middle SES participants, the prevalence of goiter was 40% less than in the high SES (X^2 = 9.2717; PR: 0.60; 95% CI: 0.39 - 0.91 (P = 0.02)) (Table 5). There were no differences between the presence of goiter and the levels of mUIC (X^2 = 5.1117; P = 0.08), age (X^2 = 5.4139; P = 0.07), and gender (X^2 = 0.69137; P = 0.41). However, for a level of mUIC ≥ 300 µg/L, some differences were identified with regards to variables such as: gender ((higher proportion of females with excess mUIC as compared to males) (PR: 1.916; 95% CI: 1.089 - 3.370, P = 0.011)); and elevated TSH (PR: 1.726; 95% CI: 1.015 - 2.935, P = 0.010). No differences were identified between a level of mUIC < 300 µg/L and gender (X^2: 7.239; P = 0.065).

Discussion

This study evidences a "U-shaped" iodine intake distribution in the southwestern region of Colombia, which is classified

Table 4. Adjusted PR for Hypothyroidism[a]

Variables	Category	Adjusted PR	95% CI	P-value
Age (years)	≥ 60 vs. < 40	2.45	1.59 - 3.78	≤ 0.001
Gender	Female vs. male	1.52	1.10 - 2.09	0.01
SES	Low vs. high	0.53	0.36 - 0.78	≤ 0.001
mUIC	Excessive vs. adequate	2.73	1.47 - 5.08	≤ 0.001

[a]Hypothyroidism was tentatively defined as TSH > 4.0 mIU/L. Confounding variables for adjustment included: age, gender, SES and levels of mUIC. CI: confidence interval; mUIC: median urinary iodine concentration; PR: prevalence ratio; SES: socioeconomic status; TSH: thyrotropin.

Table 5. Adjusted PR for Goiter and Excessive mUIC[a]

Parameter	Variables	PR	95% CI	P-value
mUIC ≥ 300 µg/L	Gender (female vs. male)	1.916	1.089 - 3.370	0.011
	Elevated TSH (vs. normal)	1.726	1.015 - 2.935	0.010
	Origin (rural vs. urban)	3.11	1.88 - 5.34	0.01
Goiter	SES (middle vs. high)	0.60	0.39 - 0.91	0.02

[a]Confounding variables for adjustment included: gender, elevated TSH, origin, and SES. CI: confidence interval; mUIC: median urinary iodine concentration; PR: prevalence ratio; SES: socioeconomic status; TSH: thyrotropin.

as an IDD-free area. One-third of the individuals have a high iodine intake (or at least more than adequate), while one-fourth of the population exhibits a low intake, with a higher prevalence of iodine deficiency in the lower SES and a higher prevalence of excessive iodine intake in the high SES; this is also the case for the rural population. These results are consistent with other national studies. For instance, prior to the introduction of the USI program in 1947 in Colombia, the iodine status in the population was established based on the rate of goiter, which for that time was 53% (in some regions the rate was > 80%). Following the implementation of the USI program, the rate of goiter in Colombia dropped to < 2% in 1965 [8]. However, more recently, the national survey on Nutritional Status (Colombia, 2015) found that 75% of school-age children (5 - 12 years) and 70% of women in child-bearing age (13 - 49 years) had excessive iodine levels and 4.4% and 4.9% presented iodine deficiency, respectively. Iodine deficiency was more prevalent in the rural area and iodine excess was more prevalent in the urban area [9].

Additionally, the fact that there were no differences in terms of origin and SES with regards to the average consumption of salt per day, indicates that probably the findings associated with iodine excess or deficiency may be due to factors such as the high intake of food products with high iodine content or some cooking habits, such as the use of concentrated chicken, meat, or fish stock (high in iodized salt) or the non-reported or unknown use of iodine-containing vitamin supplements (for the high SES and for individuals in the rural areas), or maybe wider access to low iodine-content salt (because of cultural beliefs or preferences) or simply because people in certain populations think that the salt they use is iodized when in fact it is not (the low SES groups). Regardless of the situation, evidently the public health programs to monitor and control iodine levels in the population are not being implemented [17, 18].

Similarly, the average salt consumption in this population (13.23 g/day) is far above the international daily recommended level (< 5 g/day). We had previously shown that in school-age children (< 12 years) the average salt consumption was 18.13 g/day [19, 20]. This indicates - at least in part - the lack of educational and awareness programs about the consequences of excessive salt intake early in life, not just because of the risk of thyroid dysfunction, but also because of cardiovascular outcomes such as the risk of hypertension, *inter alia*.

This study found a significant relationship between anti-TPO and anti-Tg positivity in individuals > 60 years old. This finding has also been documented in other trials showing the relationship between age and a higher frequency of positive thyroid antibodies [21-23]. However, the association between a higher frequency of positive thyroid antibodies and older individuals has not been reproducible in other studies; hence, longitudinal studies should be conducted to elucidate this matter. The higher frequency of thyroid autoimmunity in our population could be influenced by environmental factors, nutritional habits, or vitamin-D, selenium, and iron deficiency and smoking, among other factors [24, 25].

Furthermore, over one-third of the population studied reported a first-degree relative with some sort of thyroid disorder, which is consistent with other previous studies that reported a "cluster" distribution of the autoimmune thyroid disease, with 40-50% of the affected individuals reporting a close relative with a thyroid condition [26].

Moreover, the high frequency of hypothyroidism in our population is highly noticeable (> 20%), since it has been established that the prevalence of primary hypothyroidism among the general population ranges between 0-3% and 3-7% in the US, and between 0-2% and 5.3% in Europe (depending on the definition used) [27].

A meta-analysis of seven trials assessing the prevalence of "undiagnosed" hypothyroidism in nine European countries (including primary and subclinical hypothyroidism) reported a 5% prevalence, with an estimated incidence of 226.2 (222.26 - 230.17) per 100,000 per year [28].

These data are in contrast with the frequency of hypothyroidism in the Japanese population, where the frequency of both primary and subclinical hypothyroidism is around 8%, or in India, where the prevalence of subclinical hypothyroidism has been estimated at 19.3% [29, 30].

Other studies also show an increased frequency of hypothyroidism with ageing; for instance, in Brazil and in Australia, the prevalence of hypothyroidism among the elderly population was 5.7% and 0.7%, respectively [31, 32].

However, hypothyroidism is more frequent in females than in males (with an incidence peak between 30 and 50 years). For instance, in the United States of America, hypothyroidism affects around 4% of the women between 18 and 24 years old and 21% of women over 74 years old [33, 34].

The lifetime risk of developing primary hypothyroidism has been found at 4.1% for females and 1.3% for males. The differences found in regards to the frequency of hypothyroidism in our population with regards to other populations may be due to various reasons; for instance, the "U-shape" population distribution for iodine intake (one end deficiency and one end excess) is certainly associated with an increased risk of hypo-

thyroidism; and the high frequency of thyroid autoimmunity, both could account for the increased prevalence of hypothyroidism in our population. However, it should be kept in mind that the comparison of epidemiological studies assessing the frequency of thyroid dysfunction could be complex, since the result may be influenced by factors such as the definition or the determination of a universal cut point for the TSH value (that adequately classifies the patient with thyroid dysfunction) or the selection criterion of the population assessed, or by age, gender, and environmental or genetic factors including race, *inter alia* [35].

The high prevalence of thyroid autoimmunity in this population (> 30%) is also striking, and this may be due - at least in part - to the fact that in geographical regions where USI programs are introduced, the frequency of anti-Tg is increased, probably as a result of an excessive iodine intake (or due to the introduction of USI programs in deficient areas) which could potentially lead to a higher antigenicity of Tg, and hence increased stimulus for the secretion of anti-Tg antibodies and a higher frequency of thyroid autoimmunity [36, 37].

The prevalence of goiter was also associated with excessive or insufficient iodine levels; there was for instance a significant association between elevated mUIC (≥ 300 µg/L) and the prevalence of goiter (specifically in women, in individuals with elevated TSH and in individuals from the rural areas); in contrast, there was an inverse relationship between individuals from a middle SES and the presence of goiter. The explanation for this situation could be that the higher the iodine intake, the higher the frequency of goiter (and higher TSH levels). Another argument is that overall, women take larger amounts of iodine from food (as compared to men). However, the prevalence of goiter in the population could be associated to excessive or insufficient consumption of iodine, to genetic and/or hereditary factors, to anthropometric and/or environmental factors, or to the presence of goitrogens, *inter alia*. A significant relationship was found between excessive mUIC and the prevalence of goiter, but not for all ranges of mUIC; therefore, the high prevalence of documented goiter in our population shall also take into consideration factors other than iodine intake (for instance, the presence of goitrogens and/or endocrine disruptors) [38].

This study failed to identify a good concordance between the physical examination and thyroid US; the prevalence of goiter determined through inspection and palpation was higher than using ultrasound. Nonetheless, the prevalence of goiter using US was high (34%), and suggests that the identification of goiter through inspection and palpation may be overestimating the actual prevalence of goiter. One should then keep in mind that the WHO classification is more qualitative than quantitative and could in part account for the higher prevalence of goiter identified through physical examination (such classification may overestimate the true prevalence of goiter in the population). Moreover, in Colombia there is a lack of population-based studies establishing the thyroid volume ranges based on variables such as age, gender, body weight, size, etc.; therefore, the results of this study may only be extrapolated to the established definition of goiter (12.5 mL in women and 15 mL in men). The higher performance and diagnostic procedure of US indicates that this should be the method of choice to determine and classify goiter in population studies [39, 40].

This study has some limitations; for instance, we assessed the self-reported family history of thyroid disease and habits associated with salt consumption via a questionnaire, which may have a recall bias. Additionally, the coverage of households with access to properly iodized salt in the diet may only provide limited information about the total salt intake in the diet and hence other significant sources of salt in the diet would not be represented in this study. Neither did we assess other factors that potentially and independently impact the thyroid function and the presence of autoimmunity; i.e., the presence of smoking, deficiency of other micronutrients, the presence of goitrogens and/or endocrine disruptors. The probable daily variations in individual iodine intake and mUIC should also be taken into account [14]. It should also be noted that mUIC can be influenced by kidney function and other conditions such as dehydration; for example, on an "individual" basis, a 24-h urine sample is considered necessary to assess iodine intake (since the level is more constant in iodine-deficient populations than in those with adequate intake); whereas, on a "population" basis, mUIC (in a randomly selected random sample of a random urine sample) has been shown to provide useful information on average iodine intake or iodine status community. This study, having a "population" base, complies with said recommendation [2, 14].

Conclusions

A considerable number of individuals in our population fail to achieve normal iodine levels, which could explain the high prevalence of goiter, hypothyroidism, and thyroid autoimmunity. It is imperative to ensure that monitoring and follow-up programs for iodine status of the population are developed and implemented. This study may encourage research on monitoring and follow-up of the impact of iodine on other health outcomes. Further studies are needed to validate our findings and to assess the deficiency or excess of iodine in other regions and in specific Colombian populations.

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Conflict of Interest

The authors have nothing to disclose.

Informed Consent

Consent was obtained from each subject after full explanation of the purpose and nature of all the procedures used.

Author Contributions

HVU, BBS, MPF, JMP and LRB designed the study. HVU, AMM and BBS performed the statistical analyses and created the figures. HVU, AMM and BBS drafted the manuscript. HVU, AMM and BBS interpreted the data and edited the manuscript. All authors have given final approval of the version to be published.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

Anti-Tg: anti-thyroglobulin; anti-TPO: anti-thyroid peroxidase; BMI: body mass index; bpm: beats per minute; CI: confidence interval; CVs: coefficients of variation; DBP: diastolic blood pressure; FT4: free T4; IDDs: iodine deficiency disorders; IQR: interquartile range; mUIC: median urinary iodine concentration; PR: prevalence ratio; SBP: systolic blood pressure; SD: standard deviation; SES: socioeconomic status; TRAb: anti-TSH receptor; TSH: thyrotropin; USI: universal salt iodization

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