Hair Iodine for Human Iodine Status Assessment

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Background: Today, human iodine deficiency is, after iron, the most common nutritional deficiency in developed European and underdeveloped third world countries. A current biological indicator of iodine status is urinary iodine, which reflects very recent iodine exposure; a long-term indicator of iodine status remains to be identified.

Methods: We analyzed hair iodine in a prospective, observational, cross-sectional, and exploratory study involving 870 apparently healthy Croatians (270 men and 600 women). Hair iodine was analyzed with inductively coupled plasma mass spectrometry.

Results: The hair iodine median was 0.499 μg/g, and was 0.482 and 0.508 μg/g for men and women respectively, suggesting no sex-related difference. We studied hair iodine uptake by analyzing the logistic sigmoid saturation curve of the median derivatives to assess iodine deficiency, adequacy, and excess. We estimated overt iodine deficiency to occur when hair iodine concentration was below 0.1–0.15 μg/g. Then there was a saturation range interval of about 0.1–2.0 μg/g where the deposition of iodine in the hair was linearly increasing ($R^2 = 0.994$). Eventually, the sigmoid curve became saturated at about 2.0 μg/g and upward, suggesting excessive iodine exposure.

Conclusion: Hair appears to be a valuable and robust biological indicator tissue for assessing long-term iodine status. We propose that an adequate iodine status corresponds with hair iodine uptake saturation of 0.565–0.739 μg/g (55–65%).

Introduction

IODINE IS THE HEAVIEST ESSENTIAL TRACE ELEMENT in humans (1). Its role is critical for normal function of the thyroid gland and production of thyroid hormones (2). Uptake of iodide into the thyrocytes is mediated by an intrinsic membrane glycoprotein, the sodium–iodide symporter (NIS), which actively co-transports two sodium cations per each iodide anion; NIS-mediated transport of iodide is driven by the electrochemical sodium gradient generated by the Na^+/K^+-ATPase (3). Since iodine is essential for thyroid hormone synthesis, it is evident that adequate iodine intake is critical for all the metabolic processes of the human body (4).

Humans get most of their iodine through food intake and iodized salt (5,6). Indeed, neither lack nor excess of iodine is good for human health, since they both affect the normal function of the thyroid gland (7). Moreover, the need for iodine is not constant but depends upon the dynamic physi-ological status of the body, including development, growth, gravidity, lactation, and physical activity (8). Indeed, iodine deficiency may be linked either directly or indirectly to many health conditions (2). The fairly common clinical entity of endemic goiter is the goiter induced by iodine deficiency (9). Recently, we demonstrated that iodine deficiency is strongly associated with clinically manifest human depression (10).

Today, a lack of iodine is one of the most common nutritional deficiencies in the world, and it is present in both underdeveloped third world countries, as well as in developed European countries such as the United Kingdom, Italy, and Germany (11). Thus far, various methods have been suggested to assess human iodine status and to detect iodine deficiency and/or excess (12). Urinary iodine (UI) excretion is conventionally considered to be a tolerable approximation of very recent dietary iodine intake. However, while UI can provide reliable data for a population, it cannot be used to assess the average iodine status of an individual, given

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significant day-to-day variation in dietary iodine intake (13). Since even mild iodine deficiency should be avoided (14), there is a need for a reliable, robust diagnostic indicator for assessing iodine status (15).

The aim of this study was to explore how much iodine may be found in the hair of an apparently healthy population having an adequate iodine dietary intake, to study the frequency distribution of the observed iodine concentrations relative to sex, and to estimate the levels that may be associated with a possible risk of iodine deficiency and overexposure (16). We have previously demonstrated the high reliability of hair for multielement profile analysis (17); hair is easily accessible, easy to store and transport, and it usually has concentrations of iodine well above the detection limits necessary for accurate chemical analysis. Currently, monitoring of iodine deficiency by the World Health Organization (WHO) has included (i) analyzing population dietary iodine intake, (ii) analyzing clusters of population spot UI data, (iii) assessing thyroid size by palpation and/or ultrasound, and (iv) measuring thyroid gland functional parameters such as thyrotropin (TSH) and/or thyroglobulin (18,19). Our study suggests hair iodine (I_H) as a possible supplement to this list of indicators for monitoring iodine deficiency.

Subjects and Methods

This prospective, observational, cross-sectional, and exploratory study was approved by the Ethical Committee of the Institute for the Research Development of the Sustainable Eco Systems, and conducted by strict adherence to the Declaration of Helsinki on Human Subject Research (20) and to the complementary Croatian national bylaws and regulations (10). Every subject gave his/her written consent to participate in the study and filled out a short questionnaire on his/her health status and medical history (21) (data not shown).

I_H was analyzed in a random sample of 870 apparently healthy adults (270 men, 600 women), with an average age of 42.6 years (SD = 15.7, median = 46), who were concerned about the state of their health. They came from the general population across the country; most of them living in Zagreb, Croatia's capital city. All the subjects ate their usual home-prepared mixed diet, and none of them reported any adverse medical conditions. Croatia is a European country with a long coastal access to the Adriatic Sea (Mediterranean), and it was reported to be a country with no apparent iodine deficiency problem. Indeed, Croatia is categorized as a country having an optimal UI excretion of 100–199 μg/L (17,22). All the dietary salt In Croatia is regularly iodized. The fortification of table salt in Croatia started in 1949 at 10 mg of KI per kg of NaCl; in 1992, the level of fortification was increased to 25 mg KI per kg NaCl. Ten years later, an overall median of 140 μg iodine per liter of urine was reported for subjects from the Croatian school population; the current WHO set point for adequate iodine nutritional status is an UI excretion of 130 μg/L (23). Hence, we think that the I_H concentration of the studied cohort represents the iodine dietary intake of the general population reasonably well.

Hair analysis was performed by following the International Atomic Energy Agency recommendations (24) and other validated analytical methods and procedures (25). Approximately 0.5–1.0 g of hair was cut from the occipital head region above the *protuberantia occipitalis externa*, stored in numbered envelopes, and kept refrigerated at 4°C before being randomly assigned for analysis. Individual hair samples were cut prior to chemical analysis so that they were less than 1 cm long, stirred for 10 min in an ethyl ether/acetone (3:1 ww), rinsed three times with redistilled H_2O, dried at 85°C for 1 h to constant weight, immersed for 1 h in 5% EDTA, rinsed again in redistilled H_2O, dried at 85°C for 12 h, wet digested in HNO_3/H_2O_2 in a plastic tube, and sonicated. The samples were analyzed for iodine content by inductively coupled plasma mass spectrometry (ICP MS; Elan-9000; Perkin-Elmer, Waltham, MA) at the ANO Center for Biotic Medicine (CBM), Moscow, Russia, an ISO-certified high-tech analytical laboratory. All chemicals were pro analysis grade (Khimmed Sintez, Moscow, Russia). We used certified GBW0910b Human Hair Reference Material (Shanghai Institute of Nuclear Research, Shanghai, China) [coefficient of variation (CV) = standard deviation (SD)/mean 0.48] (26).

Current CBM iodine reference values (μg/g) for I_H are 0.65–9.00 and 0.65–8.00 for men and women respectively. The I_H reference concentrations were derived from 13,000 apparently healthy Russian subjects of both sexes who came mostly from the Moscow region. The data were first obtained in 2003 and were checked again in 2008. The lower percentile range was 25% and the upper percentile range was 95%. Our detection limit for I_H was 0.01 μg/g, and the coefficient of variation between the assays was 0.408 (*SD/*mean) (17). Iodine belongs to the pleiad of 208 elements and their isotopes sharing the same mass number (number of isotopes/elements): 1 Ag, 7 Cd, 12 In, 21 Sn, 27 Sb, 26 Te, 24 I, 25 Xe, 17 Cs, 17 Ba, 12 La, 11 Ce, 6 Pr, and 2 Nd (27).

The results were expressed as a frequency distribution, mean, and median of I_H concentrations. The frequency occurrence of iodine in men and women above and below the median was assessed with the chi-square test and the difference was considered to be significant when $p < 0.05$ (28).

To scrutinize the I_H concentration frequency distribution further, we used the median derivative model to fit the sigmoid logistic regression analysis function for men and women separately (see Appendix) (16,29,30):

$$A_2 + (A_1 - A_2)/[1 + (x/x_0)^p]$$

where A_1 is the initial value (lower horizontal asymptote), A_2 is the final value (upper horizontal asymptote, x_0 is the center (point of inflection, in our case it is the median M_0), and p is the power (the parameter that affects the slope of the area about the inflection point). The Qtiplot Data Analysis and Scientific Visualization program was used for this analysis (www.soft.proindependent.com/qtiplot.html). The same program was used to assess the exponential functions.

Results

Iodine was detected in all 870 hair samples, and its concentration varied widely from 0.01 to 114 μg/g, with a common median of 0.499 μg/g (men: $n = 270$, 0.482 μg/g; women: $n = 600$, 0.508 μg/g; Fig. 1a, abscissa scale A). Evidently, hair has an impressive iodine binding capacity that covers a scale of several orders of magnitude. The common median value of iodine (0.499 μg/g) was used as basic unit of concentration on our x-axis in Figure 1a (abscissa scale B). The I_H concentrations covering the range of 10 medians
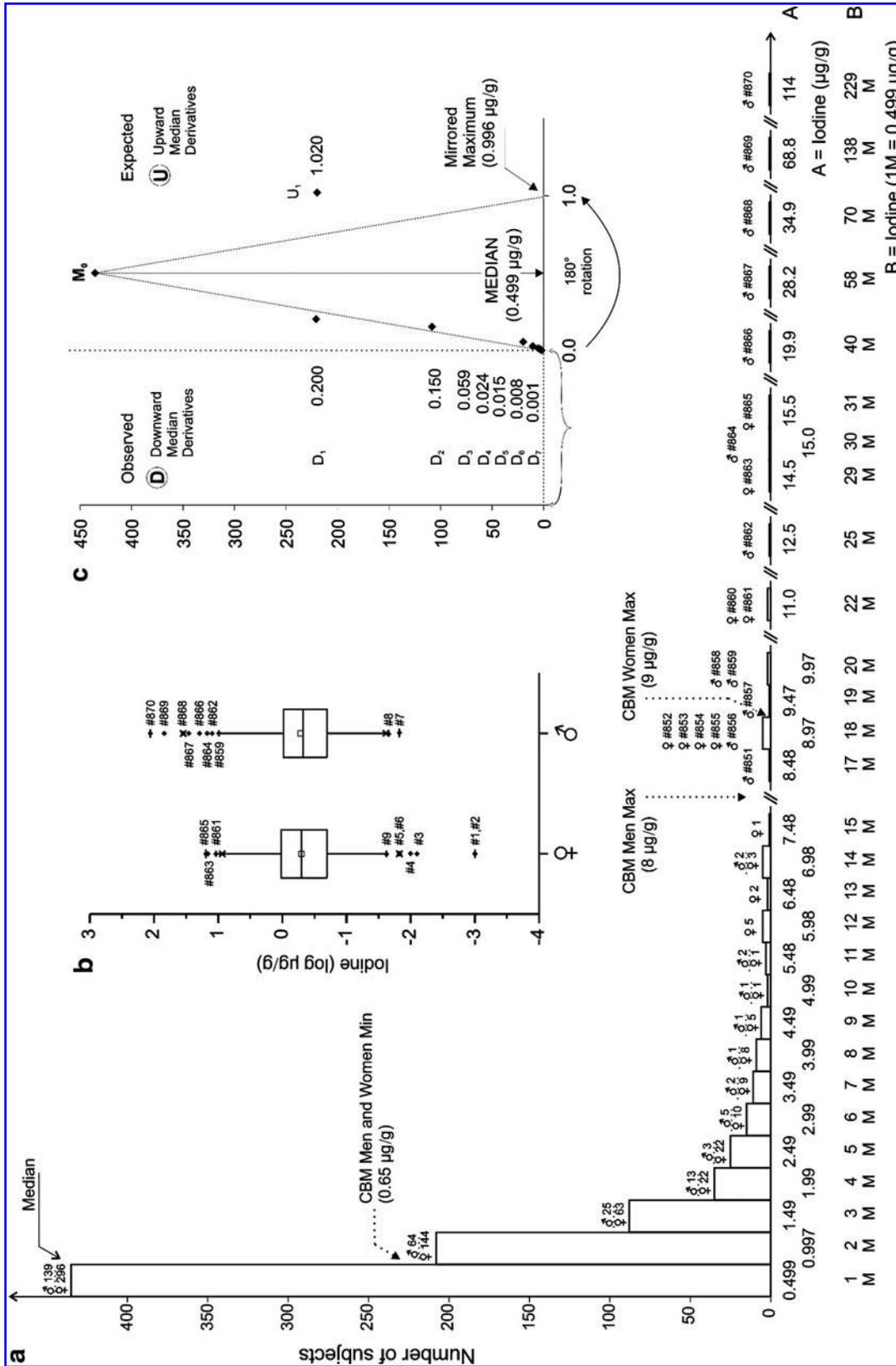
FIG. 1. **(a)** Hair iodine frequency distribution. Common median for both ♂ (*n*=270) and ♀ (*n*=600); M_0=0.499 μg/g. #, Individual subject number (subjects 1–870 are numbered sequentially depending upon the increasing iodine concentration). Abscissa A scale, iodine (μg/g). Exponential equation (Abscissa B scale, M_0–M_{10}) *y*=492.8 $e^{-0.537x}$, R^2=0.963. ANO Center for Biotic Medicine hair iodine reference values (μg/g): ♀ 0.65–8.00, ♂ 0.65–9.00. **(b)** Box and whisker plot of the hair iodine log concentrations. –, min/max; ×, 1%/99% percentile; □, mean; ♦, outliers; top whiskers=maximum, greatest value excluding outliers; bottom whiskers=minimum, least value excluding outliers. Box: bottom line=lower quartile, 25% of data less than this value; top line=upper quartile, 25% of data greater than this value; middle line=median. **(c)** Mirror-image model of the hair iodine median derivatives for assessing the tentative level of what would be environmental "background" iodine concentration today. See Appendix for model and Table 1 for model input values. ♂, men; ♀, women; M_0, median; D_1–D_7, ♂+♀ common downward (descending) median derivatives; U_1, ♂+♀ common upward (ascending) median derivative.

$(M_0–M_{10})$ is best described by the exponential equation $y = 492.8\,\mathrm{e}^{-0.537\,X}$ $(R^2 = 0.96)$. Extending the abscissa scale B beyond the M_{10} would progressively decrease the value of the correlation coefficient. Moreover, about 90% of all the I_H concentrations fall within the range of the first four medians $(M_0–M_4)$, suggesting that the upper normal limit of I_H is less than $2.0\,\mu g/g$. The box-plot data (Fig. 1b) were log transformed to correct for skewedness of the data, and there was no difference between the number of men and women above and below the common median ($p < 0.5$) when a chi-square test was used. We checked the health data from the interview records and contacted the 10 subjects with the highest I_H concentration. For six of them, diagnostic X-ray contrast medium was used within the 6-month period preceding sampling; for the other four subjects, no data could be found to help identify the source of high iodine.

We also estimated what would be an expected normal range of I_H concentrations if the I_H follows the simple first order kinetics of deposition (Fig. 1c). Indeed, if we rotate the observed triangle ($D_7 \cdot$ median $\cdot M_0$) by 180° around the median $\cdot M_0$ axis, we get the mirror image that would satisfy the theoretical premise of first-order kinetics (16). We would suggest, according to this ''mirror''-based approximation, a I_H level of $1.0\,\mu g/g$ as the limit for adequate iodine metabolic status. Our suggestion will need further confirmation and validation in future studies.

Based upon the comparative logistic sigmoid curve of I_H median derivatives, we suggest that an iodine concentration below $0.09\,\mu g/g$ for both men and women indicates overt iodine deficiency (Fig. 2a). This sigmoid curve was fitted with the data shown in Table 1. Evidently, because of such low I_H concentrations, the thyroid is in great need of iodine, so that little may be left for deposition in the hair follicle and hair growth, which may be a possible explanation for the poor hair quality of iodine-deficient persons. Moreover, thyroxine advances the onset of anagen in resting hair follicles (31). I_H concentrations above the lower asymptote of d_3 and D_3 (Fig. 2a) showed a progressive upward linear trend of iodine accumulation that is characteristic of a physiological saturation mechanism (27). This distinct saturation curve begins to plateau somewhat below $2.0\,\mu g/g$, such that the state of I_H oversaturation/overexposure has been reached (here overexposure should not be confused with toxicity). Thus, the linear part of physiological iodine saturation dose–response curve covers the range $0.1–2.0\,\mu g/g$ of iodine. The I_H linear saturation range is shown for both men and women combined (Fig. 2b), and separately for both sexes (Fig. 2c). There is no discernible sex-dependent difference in I_H between men and women.

The observed linear range segment allows us to estimate the capacity of hair to become saturated with iodine and to assess what is adequate (Fig. 3). Essentially, the I_H increments (Δ) resemble a three-component kinetics model of enzyme kinetics (32,33). The first component is composed of the I_H increments $\Delta_1–\Delta_6$, which rises proportionally in a constant linear fashion, the second and steeper or ''faster'' component was linear for $\Delta_7–\Delta_9$ increments, and the third component segment of increments $\Delta_{10}–\Delta_{12}$ rapidly approaches the I_H saturation level. Thus, I_H concentrations of $0.209–0.497\,\mu g/g$ (saturation capacity 20–50%) may be regarded as iodine sparse (not deficient but inadequate), those from $0.565–0.739\,\mu g/g$ (saturation 55–65%) as ''genuine'' iodine adequate, and those of $0.857–1.222\,\mu g/g$ (saturation

capacity 70–80%) as iodine plentiful (more than adequate but not excessive).

Discussion

The value of trace element hair analysis has been a matter of debate for years (34–37). The discussion has primarily focused on problems due to external environmental contamination, shampoo and pre-analytical hair-washing procedures, appropriate methods of the hair biological matrix destruction, and analytical reproducibility. Today, after a lot of refinement, the prevailing consensus is that trace element hair analysis is a valuable method for assessing the nutritional metabolic status and assessing toxicity in a noninvasive way (38,39). To our surprise, the observed I_H median was $0.499\,\mu g/g$ (0.482 and $0.508\,\mu g/g$ for men and women respectively), and is below the current ANO CBM concentration standard of 0.65–9.00 and $0.65–8.00\,\mu g/g$ for men and women respectively. That may suggest either an inadequately high standard, or an inadequate nutritional iodine intake, or both. We think that the observed discrepancy between our current (lower) estimates of adequate iodine nutritional status and those (higher) of ANO CBM standards stems, in part, from the mechanical implementation of a preconceived percentile grid upon the untransformed (log) iodine analytical data. Contrary to recently published data on how well supplied the Croatian population is with iodine (12), apparently more than half of the population has an unsatisfactory inadequate iodine status. This, however, requires further validation. Based on our data, we assume that a desired iodine status would require a I_H saturation of $0.565–0.739\,\mu g/g$ and that more than adequate iodine would not exceed $2.0\,\mu g/g$. The I_H concentrations reflecting toxic levels remain to be elucidated. The current indicator of iodine nutritional adequacy in Croatia (UI) provided results that were too ''optimistic'' with regard to the population iodine status, and a large low-level iodine population segment may be masked by determining an indicator such as UI. Furthermore, there may be a problem in supplying and/or using iodized salt to/by the public. We have been under constant pressure to reduce our daily salt intake for decades, which can be associated with decreased available dietary iodine. This, on the other hand, can easily be corrected by adjusting the salt iodination. Our method of analyzing trace element median derivatives (16,29,30) offers a new way to analyze samples accurately with a large inherent variability and skewed population frequency distribution. Indeed, the logistic model of median derivatives presentation allows for direct visualization of individual trace element dose–rate phenomena—an Ostwald-type of sigmoid (S) curve that can be used to describe the velocity of transformation at any instant, which is proportional to the amount of material that is undergoing the change, that is, the growth of hair and I_H incorporation (40).

Based upon the results of this study, we suggest I_H can be used as a valuable and robust indicator of long-term dietary iodine exposure. Growing at a rate of about 0.3–0.4 mm/day, hair is a memory tissue where elements are irretrievably accrued; hair is a memory log of the intermediary metabolic events in homeostatic control of all the essential elements. At the same time, blood iodine and/or urinary concentrations are indicative of the short-term internal balancing of this element between the various tissue compartments before it is rapidly

FIG. 2. **(a)** Hair iodine logistic sigmoid function curve. The difference between the hair iodine median derivatives of men ($n=270$; □) and women ($n=600$; ○) combined. ——, logistic function: $A_2+(A_1-A_2)/[1+(x/x_0)^P]$; ---, 0.95 confidence interval; ⋯, 0.95 prediction limit. ♂: $y=0.978+(-0.015-0.978)/[1+(x/0.456)^{1.624}]$; ♀: $y=0.995+(-0.011-0.995)/[1+(x/0.499)^{1.532}]$. **(b)** Iodine linear saturation range for ($♂+♀$) (log conc). **(c)** Iodine linear saturation range separate for ♂ and ♀ (log conc). See Appendix for model and Table 1 for input values. D (♂) and d (♀), downward median derivatives; U (♂) and u (♀), upward median derivatives.
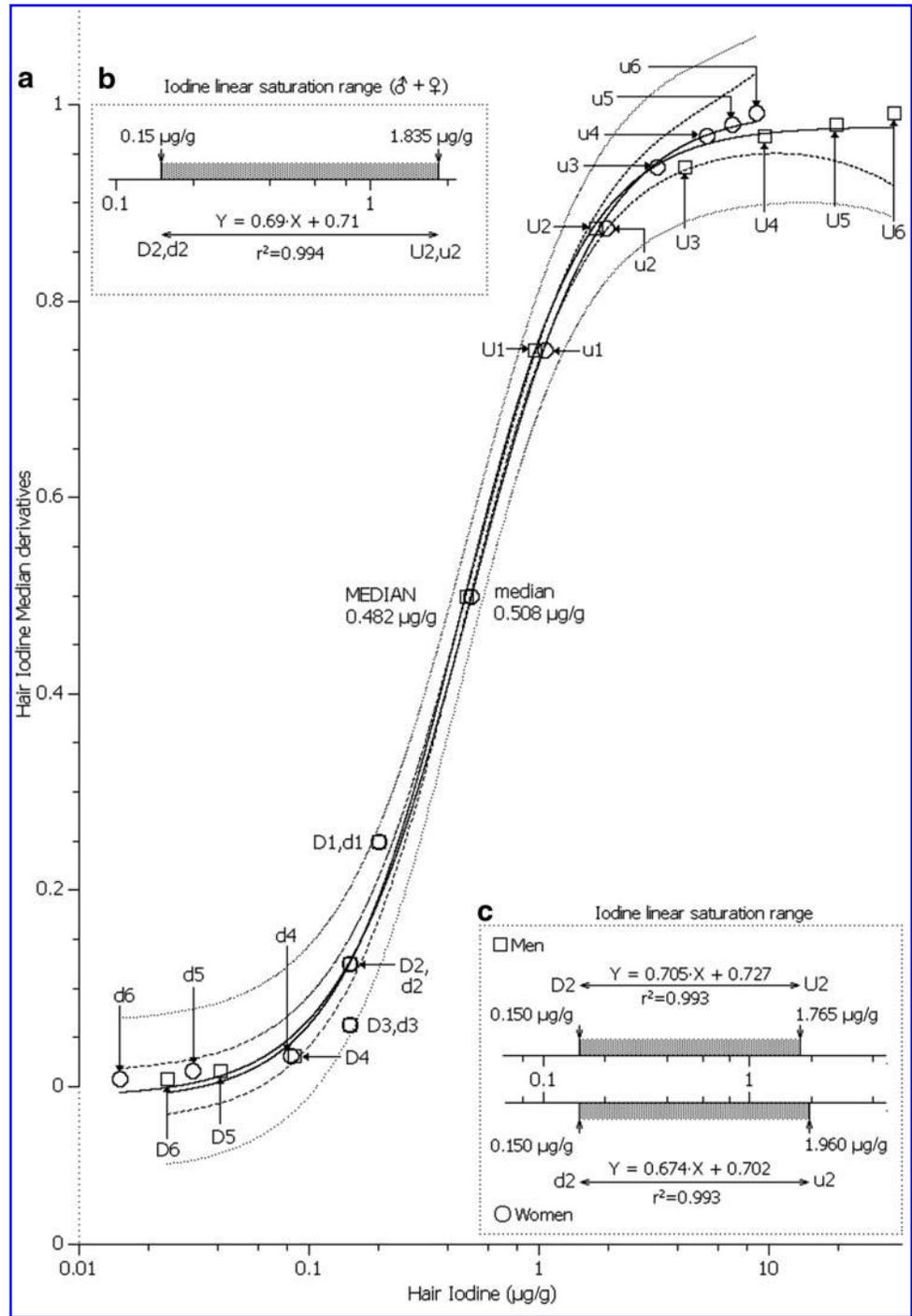
TABLE 1. HAIR IODINE MEDIAN DERIVATIVE CONCENTRATIONS FOR MEN AND WOMEN

♂ ($n=270$): median (M_0)$=0.482$ μg/g iodine						♀ ($n=600$): median (M_0)$=0.508$ μg/g iodine					
MDC	n	Iodine	MDC	n	Iodine	MDC	n	Iodine	MDC	n	Iodine
D_1	135	0.200	U_1	135	0.960	d_1	300	0.200	u_1	300	1.055
D_2	68	0.150	U_2	68	1.765	d_2	150	0.150	u_2	150	1.960
D_3	34	0.150	U_3	34	4.320	d_3	75	0.150	u_3	75	3.250
D_4	17	0.086	U_4	17	9.600	d_4	38	0.083	u_4	38	5.380
D_5	9	0.041	U_5	9	19.450	d_5	19	0.031	u_5	19	6.890
D_6	5	0.024	U_6	5	34.890	d_6	10	0.015	u_6	10	8.780

Common median (M_0)$=0.499$ μg/g iodine.

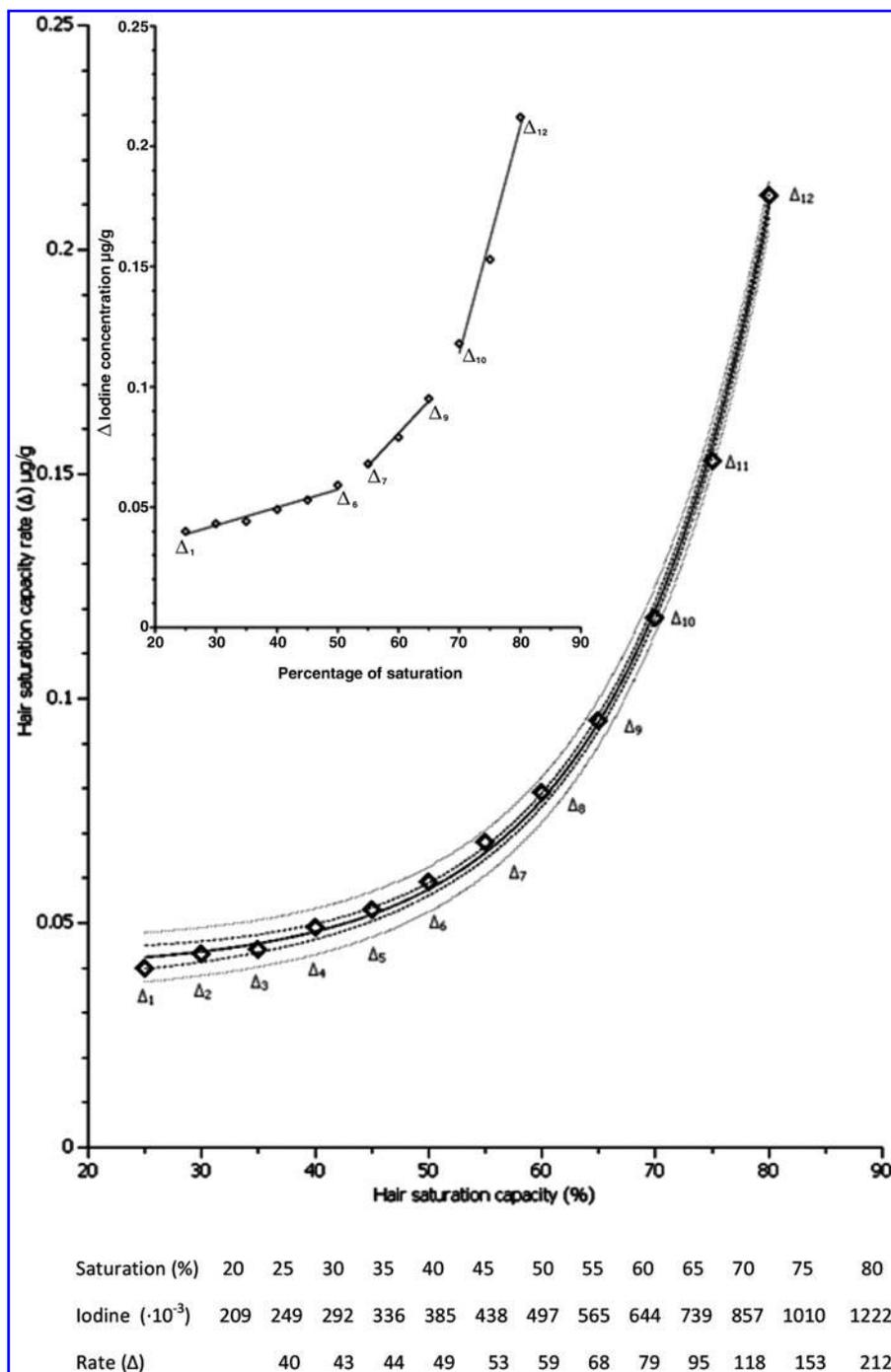♂, men; ♀, women; MDC, median derivative concentration; D (♂) and d (♀), downward MDCs; U ♂ and u (♀), upward MDCs.

FIG. 3. Hair iodine linear range saturation (I = 0.150–1.835 $\mu g/g$, $n = 870$). ——, exponential fit $y = 0.0397 + 0.0004\ e^{0.0751x}$ ($R^2 = 0.998$); ---, 0.95 confidence interval; $\cdots$, 0.95 prediction limit. Increment Δ (delta) = Following (%) – Preceding (%); Δ_1–$\Delta_6 = 0.0007x + 0.2014$ ($R^2 = 0.958$); Δ_7–$\Delta_9 = 0.0027x - 0.0813$ ($R^2 = 0.987$); Δ_{10}–$\Delta_{12} = 0.0094x - 0.554$ ($R^2 = 0.979$).

Saturation (%)	20	25	30	35	40	45	50	55	60	65	70	75	80
Iodine ($\cdot 10^{-3}$)	209	249	292	336	385	438	497	565	644	739	857	1010	1222
Rate (Δ)		40	43	44	49	53	59	68	79	95	118	153	212

excreted from the body (41). Hair is itself a dynamic tissue structure—around 90% of hair follicles are active (anagen phase), 10% are dormant (telogen phase), and others degenerate only to rise anew at another time (31). I_H is the end point of the intermediary iodine metabolism that amalgamates all the preceding dynamic differences of intermediary metabolism and their equilibration—starting with iodine dietary intake and its mixing with gastrointestinal juices, iodine bioavailability, individual differences in iodine absorption, interaction of iodine with other elements, the presence of available vitamins, difference in hormone status, the level of physical activity, metabolic turnover, age, and sex, to name

the most prominent. Indeed, initial diet is only part of the gastrointestinal input into the "black box" of intermediary metabolism before its output end point is expressed in some relevant bio-indicator tissue (42,43).

The primary goal of this study is to draw the attention of clinicians and other public health personnel to the fact that iodine status should ideally be determined by measuring iodine directly in a suitable biological matrix tissue such as hair (10). Because UI data frequency distribution showed excessive kurtosis and skewedness when presented on a linear scale (18), we have concerns about using clustered (pooled) spot UI data for assessing human iodine status. Indeed, when

iodine intake is abnormally low, adequate secretion of thyroid hormones may still be achieved by marked modification of thyroid activity. This adaptation to iodine deficiency is triggered and maintained by increased TSH stimulation (2). It is pertinent to note here that low concentrations of iodide (I^-) stimulate thyroid hormone synthesis independently of TSH (44). Indeed, iodine status assessment with I_H may provide a reliable guide for proper iodine prophylaxis in preventing endemic goiter and would help personalized health protection in people under increased metabolic energy demands (8).

Summary and Conclusion

We analyzed I_H in 870 apparently healthy subjects (270 men and 600 women) using ICP MS. Hair appears to be a valuable and robust biological indicator tissue for assessing long-term iodine status. We propose that an adequate iodine status corresponds with I_H concentrations ranging from 0.565 to 0.739 μg/g (55–65% of I_H uptake saturation capacity). The evidence presented here suggests that I_H is a long-term personal bio-indicator of human iodine status. Therefore, we believe I_H analysis may help the efforts of the WHO and UNICEF to control iodine deficiency (18,19). This is one of the first iodine assessments to use a novel source (hair) in a relatively large cohort as a potentially more widely applicable use of population iodine nutrition. The data need to be complemented in the future with data that allow us to establish reference ranges indicating adequate iodine intake through the assessment of other parameters such as thyroid volume, thyroglobulin levels, thyroid function tests, and UI.

Acknowledgments

Author Disclosure Statement

All authors claim no conflicts of interest.

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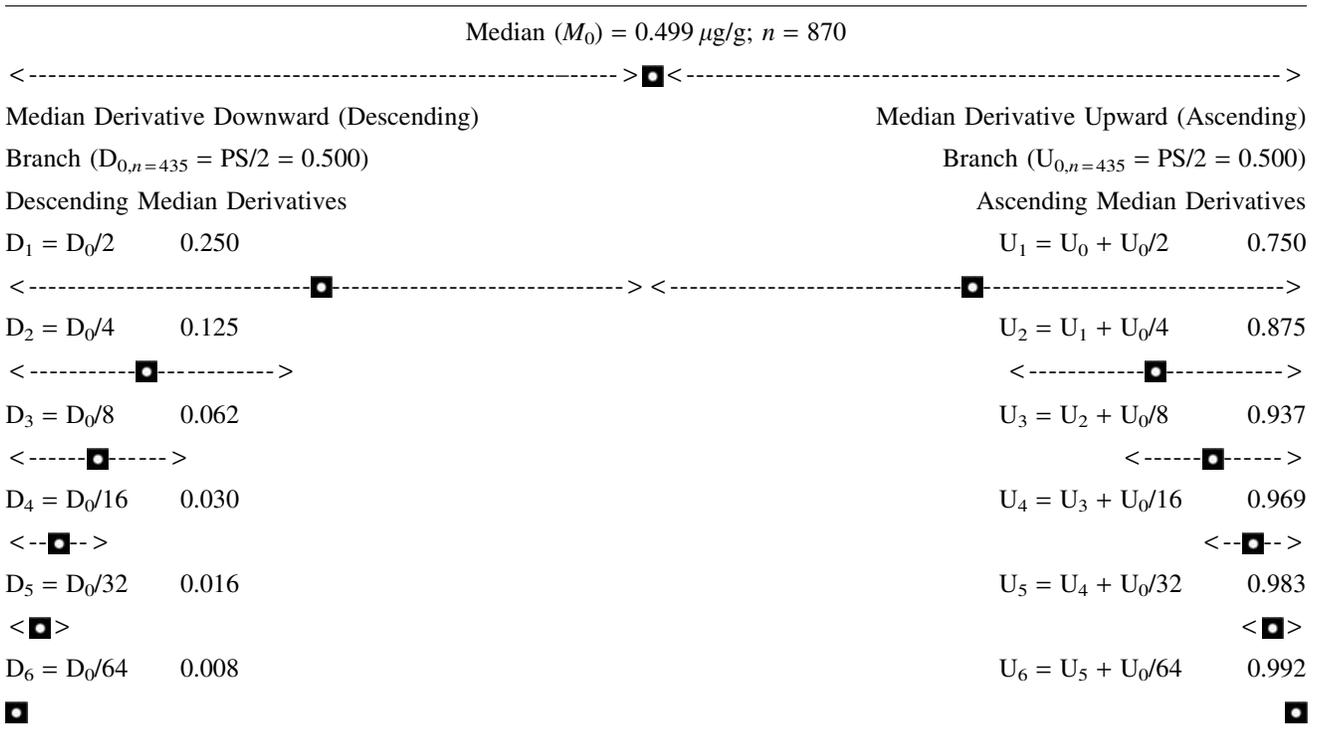*10 000 Zagreb*
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Appendix

We studied the frequency distribution of hair iodine (I_H) median and its derivatives to assess iodine deficiency, adequacy, and excess. First, we assessed the median (M_0) hair iodine concentration of our subject population. By definition, half of the studied population was above the median (upward median branch, U_0), and the other half was below the median (downward median branch, D_0). Hence, the population size (PS) for M_0 is the sum of the respective upward and down- ward median branches around the central inflection "hinge" M_0, that is, $PS = U_0 + D_0 = 0.5 + 0.5 = 1.0$. Both the respective upward and downward median branches can be further divided in the same "median of median" way into a series of sequential median derivatives ($U_{0,1,2,3...n-1,n}$ and $D_{0,1,2,3,...n-1,n}$). For every median derivative of the population, the actual hair iodine concentration can be identified. Thus, instead of mechanically throwing the preconceived percentile grid upon the observed data, we inferred the median derivative grid out from the data set itself (30).

The Median Derivatives Model (Population Size, PS = 1.000)

Median (M_0) = 0.499 μg/g; $n = 870$

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Median Derivative Downward (Descending)	Median Derivative Upward (Ascending)
Branch ($D_{0,n=435}$ = PS/2 = 0.500)	Branch ($U_{0,n=435}$ = PS/2 = 0.500)
Descending Median Derivatives	Ascending Median Derivatives
$D_1 = D_0/2$ 0.250	$U_1 = U_0 + U_0/2$ 0.750

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$D_2 = D_0/4$ 0.125	$U_2 = U_1 + U_0/4$ 0.875

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$D_3 = D_0/8$ 0.062	$U_3 = U_2 + U_0/8$ 0.937

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$D_4 = D_0/16$ 0.030	$U_4 = U_3 + U_0/16$ 0.969

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$D_5 = D_0/32$ 0.016	$U_5 = U_4 + U_0/32$ 0.983

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$D_6 = D_0/64$ 0.008	$U_6 = U_5 + U_0/64$ 0.992

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