CLINICAL STUDY

The role of thiocyanate in the etiology of goiter in an industrial metropolitan area

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Abstract

Objective: Thiocyanate (SCN^-) has concentration dependent antithyroid properties and a role in the etiology of goiter has been suggested in several studies. In 1991 an epidemiological survey conducted in the region of Halle/Leipzig (Saxony), an area with significant air pollution, suggested an inverse relationship between urinary iodine (I^-) / SCN^- excretion and goiter prevalence. 10 years later, we reinvestigated the same industrial area to clarify if the situation has changed after the elimination of most industrial waste products and moreover, if SCN^- excretion levels alone or in combination with air pollution or smoking as a SCN^- source are critical for thyroid function.

Design and methods: We investigated a cohort of 708 probands for I^- , SCN^- and creatinine excretion in spot urine samples and determined the prevalence of goiter and thyroid nodules by high resolution ultrasonography.

Results: Probands with goiter ($n = 79$, 11%) had significantly higher urinary SCN^- excretions than probands without (3.9 ± 2.8 vs 3.1 ± 3.4 mg SCN^- /g creatinine) and significantly lower urinary I^-/SCN^- ratios than patients without thyroid disorders (41 ± 38 vs 61 ± 71 $\mu\text{g I}^-/\text{mg SCN}^-/\text{l}$). Mean urinary I^- excretions were not different between probands with or without goiter. Smokers showed significantly elevated urinary $\text{SCN}^-/\text{creatinine}$ ratios in comparison to non-smokers (4.3 ± 4.3 vs 2.4 ± 2.1 mg $\text{SCN}^-/\text{g creatinine}$). ANOVA revealed a prediction of thyroid volume through age ($P < 0.001$), gender ($P < 0.001$), body weight ($P < 0.05$) and smoking ($P < 0.05$).

Conclusions: In our investigation, age, gender and smoking (raising SCN^- levels by CN^- inhalation) were predictive for thyroid volume and the urinary I^-/SCN^- ratios were able to detect probands with an increased risk of developing goiter in contrast to urinary I^- excretion levels alone. These data suggest, that in an era and area of decreased cyanide pollution, SCN^- may remain a co-factor in the multifactorial aetiology of goiter.

European Journal of Endocrinology 154 229–235

Introduction

Besides genetic determinants different environmental and individual factors are involved in the etiology of goiter, which can differ between geographic regions (1–5). Iodine (I^-) deficiency is the most important epidemiologic factor for endemic goiter. However naturally occurring goitrogenes may also contribute (3, 5, 6). Thiocyanate (SCN^-) occurs ubiquitously and has numerous biological and medically relevant effects. SCN^- promotes cell growth, has protective properties in case of toxic and mutagenic cell exposure and stimulates the immune response and the phagocytosis (7). In addition SCN^- affects thyroid function depending on the SCN^- concentration. At low concentrations, stimulation of thyroid function was found (8) whereas at pathologically elevated concentrations SCN^- acts as a competitive inhibitor of the

I^- transport into the thyrocyte (9). Raw cabbage contains high doses of SCN^- as well as other goitrogenes e.g. oxazolidone which have been supposed to harbour an even higher goitrogenous potential than SCN^- itself. Therefore, unbalanced nutrition with cabbage has been associated with increased thyroid volume and goiter (1). This may be relevant especially in regions with low I^-/SCN^- ratios caused by I^- deficiency and additional excessive consumption of cabbage (north eastern Sicily) and may thus contribute to the development of endemic goiter. In fact, goiter were present in up to 50% of school children in north eastern Sicily (1). Beside SCN^- absorption through nutrients, SCN^- is generated in the organism as a product of the cyanide-thiosulfate-mercaptopyruvate-sulfurtransferase-(Rhodanese)-system. It detoxicates cyanide (CN^-) with thiosulphate to SCN^- . If CN^- is released in considerable quantities directly by

industrial combustion or indirectly through industrial degradation processes this may result in pathological SCN^- concentrations influencing the thyroid function (7, 10, 11). In industrial areas increased SCN^- plasma and urinary SCN^- excretion levels are indicative of exposure to industrial waste products. Another independent risk factor raising SCN^- levels by CN^- inhalation is smoking (7). The generation of SCN^- through CN^- differs according to the SCN^- intake. An oral application of 32 mg NaSCN/kg over 21 days to guinea pigs (100-fold above the normal alimentary intake) did not result in a histologic change of thyrocytes (10, 11). However, the oral application of bitter almonds in a concentration of 9.4 mg CN/kg was followed by a significant increase of thyroid volume and inhibition of T_4 synthesis (11). Moreover pulmonary infections, occurring more often in industrial than in non-industrial areas, can contribute to elevated SCN^- levels since inflammatory processes themselves may increase SCN^- -levels (7, 10).

An epidemiologic survey, conducted in the region of Halle/Leipzig (Saxony) in 1991 revealed a relationship between urinary I^- and SCN^- excretions and goiter prevalence. Elevated urinary SCN^- excretion levels were observed in healthy probands and patients with goiter in comparison to probands from Greifswald/Neubrandenburg (Pomerania) (10). In addition, the I^-/SCN^- ratios were lowest in the region of Halle/Leipzig with values of $<4 \mu\text{g/mg}$ (10). Since a drastic reduction of CN^- pollution through industrial waste products has been achieved in the region of Halle/Leipzig over the last 10 years according to the World Health Organization recommendations for air quality (12, 13), whereas mild I^- deficiency is still present (14) we decided to re-evaluate the relevance of SCN^- levels with respect to goiter prevalence. For this reason we conducted a prospective study to investigate: 1) if the prevalence of goiter is correlated with urinary SCN^- excretion, 2) if patients with goiter have a decreased urinary I^-/SCN^- ratio and 3) if the I^-/SCN^- ratio is a better risk predictor for prevalence of goiter than urinary I^- or SCN^- excretion alone?

Patients and methods

We conducted a prospective trial in 2002. All probands lived in the area of Halle/ Leipzig (Saxony), a former industrial region. The probands were contacted by posters, university press and the university intranet website. The study was approved by the local Ethics Committee. All probands gave written informed consent. Probands were asked to give a spot urine sample and to fill in a questionnaire, asking for frequencies of intake of food with high I^- content, such as milk and milk products, fish, cereals, meat products, iodized table salt as well as intake of I^- containing tablets, pregnancy or lactation period and a history of smoking.

We are aware that investigating 'healthy' volunteers can cause a selection bias. However, randomly selecting volunteers by outward manifestation of a 'disease' is a valid model for a clinical prospective trial and can be used in cohort and cross-sectional studies aiming at decreasing selection bias.

The I^- -, creatinine- and SCN^- concentrations in spot urine samples were determined in 708 probands. Iodine concentration was measured according to the protocol described by Sandell and Kolthoff, which is based on the catalytic role of I^- in the reduction of ceric ammonium sulphate in the presence of arsenious acid (15, 16). Creatinine was measured as described by Jaffe (17) and SCN^- concentration was measured according to the method described by Below and Weuffen (straight line calibration method in accordance with German Standards Organization, DIN 32 645) (18). After denaturation with trichloroacetic acid, SCN^- will be converted by Chloramine-T into Chlorcyan, which is determined in a photospectrometric reaction (585 nm) (Spekol 211, Carl Zeiss Jena, Jena, Germany) in the presence of a barbitural acid-pyridine reagent. Analytical characteristics for the determination of SCN^- in urine were as follows:

- detection limit: 0.043 mg SCN^-/l
- determination limit: 0.105 mg SCN^-/l
- recording limit: 0.153 mg SCN^-/l
- between day CV: $\pm 3.0\%$, within day CV: $\pm 4.2\%$
- linear region of the calibration straight line: determination limit to 50 mg SCN^-/l
- functional sensitivity: 0.02 l/ μmol SCN^-
- retrieval rate in urine: $< 1 \text{ mg}/192.1\text{--}106.9\% > 1 \text{ mg}/96.0\text{--}104.0\%$
- interfering anions: from the anions in biological materials only CN^- interferes.

However, in urine, CN^- has a 100–1000-fold lower concentration than SCN^- . SCN^- excretion and I^- excretion were correlated with creatinine excretion in every spot urine sample to minimize bias through kidney function and variable 24-hour urinary volume (19). To reduce statistical bias, probands with I^- contamination defined as urinary I^- excretion $> 300 \mu\text{g}$ I^-/g creatinine (20, 21) were excluded from further analysis.

Ultrasound was performed using a high resolution real-time instrument (7.5 MHz) (Siemens Sonoline® Adara Siemens Medical Systems, Erlangen, Germany). Thyroid volumes were calculated according to the spherical ellipsoid formula: volume = $\pi/6 \times \text{anteroposterior diameter (cm)} \times \text{width (cm)} \times \text{length (cm)}$ (22, 23). Thyroid volumes greater than 18 ml were considered to be enlarged in adult women and thyroid volumes greater than 25 ml were considered to be enlarged in adult men, which corresponds to the mean $+3 \text{ s.d.}$ in I^- sufficient populations (24) and guaranteed, that gender specific values for goiter are above the 97th percentile of thyroid volumes found in I^- replete control population (21).

Statistical analyses were performed using SPSS software, version 10.0 (SPSS GmbH Software, Munich, Germany). We used means instead medians for statistical analysis of I^- and SCN^- excretion levels because there was a symmetrical distribution of the data. Moreover, the statistical bias in large cohorts (> 500 probands) is lower when using mean values than median values as mean values better describe metric variables than the median values (25, 26). Multivariable comparisons between the groups were performed with ANOVA (end-points thyroid volume and urinary I^- excretion). Adjustments were made for age, smoking and gender. A value of $P < 0.05$ was considered statistically significant.

Results

Correlations between urinary SCN^- excretions of subpopulations and thyroid volume

Urinary SCN^- excretion (mg SCN^- /g creatinine) correlated positively with thyroid volume (Pearson correlation coefficient 0.097, significant at the 0.01 level, [2-tailed]) and was similar in men and women (male: 2.9 ± 2.6 vs female: 3.3 ± 3.5 mg SCN^- /g creatinine). Probands with (nodular) goiter ($n = 79$) had significantly higher urinary thiocyanate/creatinine excretion ratios in comparison to probands with normal thyroid volume (t -test, $P < 0.05$, [2-tailed]) (Table 2). Gender specific statistical analysis revealed a significantly elevated SCN^- excretion for females with goiter in comparison to females without (t -test, $P < 0.05$, [2-tailed], Table 2). Moreover, the SCN^- excretion is significantly elevated in pregnancy and lactation period (Table 2).

Correlations between urinary I^- excretions of subpopulations and thyroid volume

Hence urinary I^- excretion levels alone did not correlate with thyroid volume of the study population (sex and age corrected analysis). Mean urinary I^- excretion levels were lower in probands with (nodular) goiter than in probands with normal thyroid volume (Table 2) without reaching statistical significance. The mean urinary I^- excretion (108 ± 81 μ g I^- /g creatinine, i.e. 102 μ g/l, Table 2) in our cohort was within the lower range of adequate I^- intake (100 – 200 μ g/g) (20, 21). Of 79 probands with goiter only 15 showed moderate (25 – 49 μ g I^- /g creatinine) to severe (< 25 μ g I^- /g creatinine) I^- deficiency (20, 21).

Urinary I^-/SCN^- ratios and goiter

The I^-/SCN^- ratio of the total study population was negatively correlated with thyroid size (Pearson correlation coefficient -0.079 significant at 0.05 level [2-tailed], Table 2). Probands with (nodular) goiter ($n = 79$) had significantly lower urinary I^-/SCN^- ratios in comparison to probands with normal thyroid

volume (Table 2, t -test, $P < 0.05$, [2-tailed]). Gender specific analysis revealed significant differences in urinary I^-/SCN^- ratios between probands with and without goiter. Females with goiter (Table 2) showed lower urinary I^-/SCN^- ratios than females without ($n = 506$; 63 ± 75 μ g I^- /mg SCN^- /l). Equally, males with goiter (Table 2) had lower urinary I^-/SCN^- ratios than males without ($n = 123$; 49 ± 50 μ g I^- /mg SCN^- /l) (t -test, $P < 0.05$, [2-tailed]).

Smoking and thyroid volume

Four hundred ninety one (69.4%) probands answered the question for a history of smoking. 217 probands (30.6%) failed to give an answer. Three hundred sixty seven from 491 probands (74.7%) were non-smoker and 124/491 (25.3%) were smoker. Mean thyroid volume was higher in smokers than in non-smoking probands without reaching statistical significance (Table 3, t -test, $P = 0.085$, [2-tailed]). Thyroid volume correlated positively with the reported pack years of the smokers (Pearson correlation coefficient 0.124 significant at the 0.01 level [2-tailed]). Renal SCN^- excretion in mg SCN^- /g creatinine did not correlate with thyroid volume in smokers ($P = 0.6$) and showed a correlation in non-smokers ($P = 0.068$). Urinary I^-/SCN^- ratios correlated negatively with thyroid volume in 124 smokers (Pearson correlation coefficient -0.183 significant at the 0.05 level [2-tailed]). Additionally, smokers showed significantly elevated urinary SCN^- /creatinine ratios and lower urinary I^-/SCN^- ratios in comparison to non-smokers (t -test, $P < 0.001$, [2-tailed], Table 3).

Prediction of thyroid volume through single parameters

Moreover, we performed ANOVA to investigate which of the single parameters: age, smoking, gender, body weight, body height, pregnancy or nursing period, urinary I^- excretion, urinary SCN^- excretion and urinary I^-/SCN^- ratio, can predict the dependent variable thyroid volume. ANOVA reveals a prediction of thyroid volume through: age ($P < 0.001$), gender ($P < 0.001$), smoking ($P < 0.05$) and body weight ($P < 0.05$). Because the hypothesis is that smoking generates SCN^- , that causes goiter we have to define SCN^- as an intermediate variable that can therefore not be included in the same model as tobacco smoking without providing misleading results. We have to consider different effects: 1. The within-subjects mean effect: the influence of SCN^- on thyroid volume, and 2. The between-subjects interaction effect: does the influence of SCN^- on thyroid volume depend on smoking? For those reasons we did not include SCN^- in the same ANOVA model as tobacco smoking. ANOVA did not show a prediction of thyroid volume through SCN^- .

Discussion

Despite considerable improvements in the iodide supply in Saxony, 11% of the probands in our study showed goiter (Table 1). In this context the urinary I^-/SCN^- ratios were significantly lower in probands with goiter compared with probands without thyroid enlargement (Table 2). Previous investigations have suggested an increased risk for the development of goiter in probands with low urinary I^-/SCN^- ratios (1, 10). In these studies thyroid volumes were more often found to be in the upper normal limit, if probands had urinary I^-/SCN^- ratios below $4 \mu\text{g}/\text{mg}$ (1, 10). In the beginning of the 90s, probands with goiter in the industrial area of Halle/Leipzig were found to have such a risk constellation with urinary I^-/SCN^- ratios of $3.5 \mu\text{g}/\text{mg}$ (10). Our present investigation in the same area demonstrated a marked increase in mean urinary I^-/SCN^- ratios ($41 \mu\text{g } I^-/\text{mg } SCN^-$) in probands with thyroid enlargement (Table 2). This finding is most likely due to the increased urinary I^- excretion in Saxony (14) based on a rise in the ambient I^- supply. Contrary to the results of a previous investigation in Italy, which stated that the prevalence of goiter is restricted to I^- deficiency (based on urinary I^- excretion level), but is not correlated to SCN^- (27). Our results demonstrate that SCN^- is a cofactor or indicator for goiter in non-smokers (SCN^- is an independent determinant) as well as smokers. SCN^- , a major component of tobacco smoke, inhibits I^- uptake by the thyroid gland and SCN^- correlates with the intensity of smoking (10, 28). Based on the WHO criteria for urinary I^- excretion, only 15 of 79 probands with goiter showed moderate to severe I^- deficiency ($< 50 \mu\text{g } I^-/\text{g creatinine}$) (20, 21). The remaining participants with goiter showed urinary I^- excretion levels within the lower range of adequate I^- intake ($100 \mu\text{g } I^-/\text{g creatinine}$) (20, 21). The I^- status of probands, determined by urinary I^- excretion measurements or by I^- intake estimation using a questionnaire, may modulate the response to smoking (3, 28–30). Smoking has antithyroid properties, especially if the I^- status is low (28, 30). Moreover, recommendations for the I^- intake levels, have to consider different incidences of malignant and immunogenic

thyroid disorders in different age groups (30, 31). Therefore, the I^- intake level should be brought to the lowest levels (not the higher levels) to avoid I^- deficiency disorders. However, the optimal I^- intake level remains to be determined (30). Mean SCN^- excretion levels ($3.2 \text{ mg } SCN^-/\text{g creatinine}$) in our probands were lower than in a previous investigation ($6.8 \text{ mg } SCN^-/\text{g creatinine}$) by Kramer *et al.* (10) conducted in the same area in 1990. This was expected and mostly based on the elimination of industrial waste products and a decreased CN^- pollution (13). CN^- , is detoxified to SCN^- when inhaled (polluted air or smoking) or absorbed (polluted foods), especially in industrial areas (1, 10, 12). CN^- has goitrogenous properties and may be relevant in the aetiology of thyroid disorders, particularly in I^- deficient regions (1, 10). Moreover, the serum half-lives for SCN^- of approximately 6 days is important, as SCN^- persists for more than 20 times longer in the human serum than other goitrogenes, i.e. perchlorate or nitrate (32). Therefore the I^- uptake inhibition by SCN^- at the sodium–iodide symporter is most likely relevant in the etiology of goiter (32). In this context Delange *et al.* (1) described an increased risk for developing goiter in patients with urinary I^-/SCN^- ratio < 4 . The authors investigated SCN^- -sources and measured urinary I^-/SCN^- ratios in patients with goiter and excessive consumption of cabbage in an area of moderate to severe I^- deficiency (Sicily, Italy) and compared them with healthy probands from Belgium. The environmental SCN^- exposure through food, industrial waste products and smoking was not investigated in this study, because there are considerable geographic differences between both regions. A bias due to CN^- incorporation via air pollution or other foods than cabbage can not be excluded. The causes for the differences in urinary SCN^- and I^- excretion levels, between probands in Italy and Belgium and the role of SCN^- in the etiology of goiter in both regions remain unclear. Moreover, the authors suggested, that the increased prevalence of goiter in Sicily is most likely based on severe I^- deficiency and secondarily associated with goitrogenous properties of SCN^- (1). In contrast Costa *et al.* (27) did not find any correlation between urinary SCN^- excretion and goiter prevalence in Italy.

Table 1 Characteristics of the overall study population.

	Males	Females	Study population
Probands*	132 (19%)	576 (81%)	708 (100%)
Age** (years)	31 ± 12	36 ± 13	35 ± 13
Goiter*	9 (7%)	70 (12%)	79 (11%)
Thyroid nodules*	26 (20%)	179 (31%)	205 (29%)
Nodular goiter*	7 (5%)	49 (9%)	56 (8%)
Previous thyroidectomy*	2 (2%)	14 (2%)	16 (2%)
Pregnancy/lactation period*		23 (4%)	23 (4%)

*Number of probands; **Mean $\pm$ s.d.

Table 2 Urinary SCN⁻ and I⁻ excretions and urinary I⁻/SCN⁻ ratios of the overall study population.

	Urinary SCN ⁻ excretion** (mg SCN ⁻ /g creatinine)	Urinary I ⁻ excretion** (μg I ⁻ /g creatinine)	Urinary I ⁻ /SCN ⁻ ratio** (μg I ⁻ /mg SCN ⁻)/l	Thyroid volume** (ml)
Study population (n = 708*)	3.2±3.3 [f]	108±81	58±68 [f]	13±7
Normal thyroid volume (n = 629*)	3.1±3.4 [a, b]	102±96	61±71 [c]	11±4
(Nodular) goiter (n = 79*)	3.9±2.8 [a]	96±74	41±38 [c]	28±11
Males with goiter (n = 9)	4.0±3.0	75±21	26±13 [e]	45±18
Males with normal thyroid volume (n = 123)	2.8±2.6	76±45	49±50 [e]	13±5
Females with goiter (n = 70)	4.0±2.8 [b]	114±92	43±40 [d]	26±8
Females with normal thyroid volume (n = 506)	3.2±3.5	117±86	63±75 [d]	10±4
Thyroid nodules (n = 205*)	3.5±3.5	108±115	57±62	16±10
Males (n = 132*)	2.9±2.6	79±44	47±49	15±10
Females (n = 576*)	3.3±3.5	120±127	61±72	12±7
Pregnancy/lactation period (n = 23*)	4.1±3.7 [f]	145±272	41±68 [f]	13±6

SCN⁻ excretion and I⁻ excretion were correlated with creatinine excretion in every spot urine sample to minimize bias through kidney function and variable 24-hour urinary volume. Alphabetical characters in brackets [a–f] demonstrate the corresponding differences at the significant $P < 0.05$ level.

*Number of probands; **Mean±s.d.

The authors found highly variable levels of SCN⁻ excretion, ranging from 1.24 ± 0.57 mg/l to 8.08 ± 5.5 mg/l in different regions, which may have compromised the statistical analysis. In this study the inverse correlation between urinary I⁻/SCN⁻ excretion levels and goiter was exclusively based on lower I⁻ excretion in patients with increased thyroid volume (27). Up to now, a relationship between goiter and increased SCN⁻ excretion (in patients with similar I⁻ status) could only be demonstrated in epidemiological surveys in Africa (33). In contrast to our study population, these African populations showed severe I⁻ deficiency (33). Based on the analyses of non-smokers, the SCN⁻ excretion correlated ($P = 0.068$) with thyroid volume. However, a general causal thyrostatic effect of SCN⁻ could not be identified. As expected the individual risk for developing goiter increases with tobacco smoking (3). Smoking increases the CN⁻ absorption of the human body (4, 10, 11). In our study smokers had a tendency towards higher values

for thyroid volume in comparison to non-smokers, without reaching statistical significance (Table 3). Because prevalence of goiter increases with age and decreases with increased I⁻ intake (3, 29, 34, 35), the younger mean age of our population as well as the elimination of severe I⁻ deficiency in Saxony (14) may obscure to the (insignificant) difference between smokers and non-smokers. We are aware that the 30% non-response regarding smoking behaviour could cause some selection bias. Previous investigators found an increased risk for developing a goiter due to elevated SCN⁻ concentrations of 8–12 mg/l (normal 2–4 mg/l) in the serum of smokers in comparison to nicotine abstinence (11, 36, 37). Our results show an elevated risk for developing a goiter beginning with urinary SCN⁻ concentrations > 3.5 mg SCN⁻/g creatinine.

The population based Study of Health in Pomerania (35) in a formerly I⁻-deficient region showed, that thyroid enlargement is associated with advanced age and

Table 3 Urinary SCN⁻ and I⁻ excretions and urinary I⁻/SCN⁻ ratios of 491 probands with known smoking behaviour.

	Urinary SCN ⁻ excretion** (mg SCN ⁻ /g creatinine)	Urinary I ⁻ excretion** (μg I ⁻ /g creatinine)	Urinary I ⁻ /SCN ⁻ ratio** (μg I ⁻ /mg SCN ⁻)/l	Thyroid volume** (ml)
Smoker (n = 124*)	4.3±4.3 [j, l]	114±79 [1]	45±47 [k, l]	14±8
Smoker with normal thyroid volume (n = 99*)	4.2±4.6	124±83	51±51	11±6
Smoker with goiter (n = 25*)	4.8±3.1 [l]	79±44 [l]	21±13 [l]	26±7
Smoker with thyroid nodules (n = 37*)	4.0±3.3	101±63	42±43	18±8
Nonsmoker (n = 367*)	2.4±2.1 [j]	113±88	60±61 [k]	13±8
Nonsmoker with normal thyroid volume (n = 324*)	3.1±3.4	113±87	61±63	11±4
Nonsmoker with goiter (n = 43*)	3.0±1.9	114±94	51±48	28±12
Nonsmoker with thyroid nodules (n = 116*)	3.2±3.9	133±113	67±71	15±10

SCN⁻ excretion and I⁻ excretion were correlated with creatinine excretion in every spot urine sample to minimize bias through kidney function and variable 24-hour urinary volume. Alphabetical characters in brackets [j–l] demonstrate the corresponding differences at the significant $P < 0.05$ level.

*Number of probands; **Means±s.d.

current smoking. Völzke *et al.* found higher urinary SCN^- excretion in males with goiter in comparison to men without, but no correlation of renal SCN^- excretion with goiter of the overall study population ($n = 3,915$). The authors (35) suggested a role of environmental SCN^- (smoking) in the development of thyroid enlargement, but could not exclude a misclassification of smokers due to information bias. Our investigation conducted in an area with borderline I^- deficiency indicates a significant correlation of urinary SCN^- excretion of the overall study population with the thyroid volume and probands with goiter had higher urinary SCN^- excretions than probands without. Moreover, the SCN^- effects on the thyroid volume depend on SCN^- concentrations, urinary I^- and urinary I^-/SCN^- ratios (10, 11, 35, 38) as well as environmental and individual risk factors, especially the intensity of smoking (10, 11, 35, 37). Surprisingly, in contrast to SCN^- excretion, the urinary I^- excretion of our probands did not correlate with thyroid volume, because the prevalence of goiter increases with age (3, 29, 34). The small mean thyroid volume in our probands, especially in young male probands with moderate to severe I^- deficiency, most likely prevented an inverse correlation between urinary I^- and thyroid volume.

In summary, our investigation shows that age, gender, body weight and smoking (increased SCN^- levels by CN^- inhalation) were predicting factors for thyroid volume. The urinary I^-/SCN^- ratio was able to detect probands with an increased risk for goiter, in contrast to urinary I^- excretion levels alone. However, the etiology of goiter is an interplay between environmental, individual and genetic factors. Further research is needed to understand how factors such as smoking and SCN^- influence the genetic susceptibility to develop goiter.

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Received 19 April 2005

Accepted 19 October 2005