Iodine Excess is a Risk Factor for Goiter Formation

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Abstract

Background: Goiters have been associated with iodine deficiency. Although universal salt iodization in Uganda achieved a household coverage of 95% by 2005, goiter rates are still high. This study investigated the association between iodine excess and goiter. **Methods**: In a case control study, urinary iodine levels, complete blood count, T3, T4 and TSH levels were determined. **Results**: We recruited, 60 goiter and 63 non goiter patients. The median urine iodine level for goiter patients was significantly higher than in non-goiter controls. Urinary iodine excretion was sufficient in 43%, more than sufficient in 31% and excess in 10% of cases. There was an association between excess urinary iodine levels and goiter. **Conclusion**: Urinary iodine excess was significantly associated with occurrence of goiter.

Key Words: Iodine excess, Goiter, Sub Saharan Africa

Introduction

Goiter refers to an enlarged thyroid gland. Biosynthesis defects and iodine deficiency are associated with reduced efficiency of thyroid hormone synthesis leading to increased thyroid stimulating hormone (TSH) which stimulates thyroid growth and enlargement as a compensatory mechanism to overcome a block in hormone synthesis (1).

Goiters are still common in Uganda despite majority (>90%) of people having excess iodine in urine. After mandatory iodine fortification of salt, goiter rates reduced to 14% from 74% in 1991, even though, it was expected according to WHO that fortifying salt would reduce this to less than 5% (2–4). It is unclear why the goiter rate is indeed still high despite the successful iodine fortification program and a 95% households' coverage (5). Some reasons advanced for this include pockets of iodine deficiency, other causes of goiter such as cancer or goitrogens ingestion, selenium deficiency and vitamin A deficiency. Some studies have suggested that excess iodine may be the cause of reactive goiters (5–15). Thus, the aim of this study was to explore the association between goiter and iodine excess at a surgical endocrine unit in Uganda.

Methods

This case control study took place at Mulago, a 1500 bed national referral teaching hospital for Makerere University, Kampala, Uganda. The surgical endocrine unit conducts an outpatient clinic weekly where an average of 10 new thyroid patients are seen. Patients with goiter attending this endocrine clinic were recruited as cases. The controls were recruited from other outpatient surgical units.Cases were matched with controls for age and sex. Exclusion criteria included pregnancy, lactating mothers, chronic renal failure, those receiving radioiodine therapy, presence of goiter for >15 years, and those who had received intravenous contrast or were using drugs that alter thyroid function.

Study variables collected included urinary iodine levels, dietary goitrogens, serum creatinine, age, sex, address (district/regions), occupation, place of residency, duration of symptoms, use of iodized salt, thyroid size and thyroid hormonal levels. A standardized pretested questionnaire was administered. Patients were interviewed and underwent a thorough physical examination to establish the presence of goiter and its size according to WHO grading (16,17).

Urine specimens were collected in sterile containers (Falcon tubes), acidified, labeled and wrapped with aluminum foil and kept in a cool, dark container whilst awaiting analysis. All urine samples were taken for analysis using the wet digestion method. In this method, the change in color of cerric ammonium sulfate by arsenious acid accelerated by iodine, which acts as a catalyst. The rate of this colour change, which depends upon the amount of iodine present, was measured by a colorimeter. The amount of iodine in the urine was calculated by a comparison with standard solutions of known iodine content, and expressed as mcg iodine per 100ml urine. Blood samples were taken for thyroid function tests, complete blood count and renal function tests. The renal functions tests were done by measuring the serum creatinine levels.

Data captured was entered to SPPS version 16 for analysis. Conditional logistic regression analysis was performed to assess the relationship between excess urinary iodine levels and the presence of goiter. P values of <0.05 were considered significant. Adjusting for confounding and interaction (goitrogens, age and sex, renal functions, district of residence etc): Variables found to have p-values <0.2 were entered into a multivariate logistic for analysis. Confounding was reported by the percentage difference when a given variable was in or out of the model as less than 10%.

Permission was obtained from the College of Health Sciences, School of Medicine Research and Ethics Committee (SOMREC) at Makerere University. A voluntary informed written consent was obtained from all study participants.

Results

One hundred and twenty three (60 cases, 63 controls) patients were recruited between March and May 2012. Sixteen were males (4 cases, 12 controls) and 107 (56 cases, 51 controls) were females. The mean age among the cases was 41.8 year (SD 14) whereas among the controls the mean age was 40 (SD 14). The majority of the participants were in the age group 30-39 (cases 37%, controls 36%). The least in both cases and controls were in the age above 50 years as indicated in Table 1.

Table 1: The overall baseline characteristics of the study participants

Variable	Case (n=60	Control (n=63)	Total (n=123)	OR	95% CI	p-value
Age						
Mean	41	39	40	-	-	-
SD	14	14	14			
Age group						
<30	12 (20%)	15 (24%)	27 (22%)			0.885
30 – 39	21 (35%)	23 (37%)	44 (36%)	1.0	0. 4-2.6	0.978
40 – 49	15 (25%)	12 (19%)	27 (22%)	0.7	0.3-2.0	0.503
≥50	12 (20%)	13 (21%)	25 (20%)	1.0	0.3-2.7	0.921
Sex						
Female	56 (93%)	51 (81%)	107 (87%)	3.3	1 - 11	0.050
Male	4 (7%)	12 (19)	16 (13%)			
Thyroid size						
Stage 0	0 (0%)	0	0 (0%)	-	-	-
Stage 1	15 (25%)	0	15 (12.2%)	-	-	-
Stage 2	45 (75%)	0	45 (33.8%)	-	-	-
Main diet of the study participant						
Cassava	33 (58	24 (42)	2.0	1.0-4.1	0.061	
Maize	41 (53)	36 (47)	1.6	0.8-3.4	0.201	
Matooke	52 (50)	53 (51)	1.2	0.5-3.4	0.961	
Sweet potatoes	27 (43)	36 (57)	0.6	0.1-1.2	0.210	
Cabbage	12 (50)	12 (50)	1.1	0.4-2.6	0.894	
Family history of Goitre	15(25)	9(14)	-	-	-	>0.25
Others*	18 (48)	19 (51)	1.0	0.5-2.2	0.985	

*(includes rice, Irish potatoes and beans)

The main presenting symptom was a neck swelling. Most patients (40%) had the symptoms for 1-5 years. The mean duration of goiter was 2.8 years (Table 1). Positive family history of goiter was reported in 15(25%) cases and 9(14%) controls. Use of iodized salt was reported in 28% of the cases and 30% of the controls. The main diet was rice (18% cases and 16% controls). There was no significance association between diet and goiter (p-value 0.944).

The majority of the goiter patients (72%) presented with goiter stage 2, which is both palpable and visible (Table 1). Most patients (52%) had nodular/ multinodular non-toxic goiters followed by diffuse non-toxic goiters (20%). All study participants had normal renal function tests (Table 2). Seven percent of the cases had previous thyroidectomy. Normal T3, T4 and TSH were found in 83%, 85% and 78% respectively.

Table 2: Clinical diagnosis of study subjects various lab test results

Clinical diagnosis	**Cases (n=60)** n (%)	**Control (n=63)** n (%)	**Total (n=123)** n (%)	**P values**
Diffuse non toxic goiter	12 (20)	0	12 (10)	-
Diffuse toxic goiter	3 (5)	0	3 (2)	-
Nodular/multinodular non toxic goiter	32 (53)	0	31 (25)	-
Solitary nodule	1 (2)	0	1 (1)	-
Physiological goiter	0	0	0	-
Thyroiditis	4 (7)	0	4 (3)	-
Thyroid malignancy	3 (5)	0	3 (2)	-
Others	5 (8)	63	68 (55)	-
Renal Function test				
Normal†	60 (100)	63 (100)	123 (100)	-
Abnormal	0	0	0	-
Urinary Iodine levels				
<100	7 (12)	13 (21)	20 (16)	0.162
100 – 199	25(42)	28 (45)	53 (43)	0.352
200 –299	19 (32)	19 (31)	38 (31)	0.278
>300	9 (15)	3 (5)	12(10)	0.035
Mean (Urine)	216	171		0.016
Standard deviation (Urine)	119	82		-
Median (urine)	194	162		-
Mean (Urine)	216	171		-
Iron Deficiency Anemia(IDA) ††				
Present	6 (10)	6 (10)	12 (10)	
Absent	54 (90)	57 (91)	111 (90)	
Serum T 3				**0.003**
Low	3 (5)	0	3 (2)	
Normal*	50 (83)	63 (100)	113 (92)	
High	7 (12)	0	7 (6)	
Serum T 4				0.006
Low	3 (5)	0	3 (2)	
Normal**	51 (85)	63 (100)	114 (93)	
High	6 (10)	0	6 (5)	
Serum TSH				<0.001
Low	12 (20)	0	12 (10)	
Normal***	47 (78)	63 (100)	110 (89)	
High	1 (2)	0	1 (1)	

† (Serum creatinine 44-106 µmol/L); †† (Hb < 11g/dL, MCV <80fL, MCHC <31 g/dL);
*(Serum T_3 1.3-3.1 nmol/L); ** (Serum T_4 66-181 nmol/L), *** (Serum TSH 0.27-4.20µIU/mL).

The mean urine iodine level among the goiter patients and controls was 216.1µ/L (SD 119) and 171.3µ/L (SD 81.5) respectively (Table 2). The differences observed between the cases and controls were statistically significant (p =0.016). Most (43%) of the study participants had sufficient urinary iodine excretion while 31% had more than adequate urinary iodine excretion (Table 2).

Urinary iodine versus thyroid size

Most (37%) of the study subjects had stage 2 goiters (WHO classification), 49% of whom had sufficient urinary iodine excretion. The largest proportion (40%) of those who had stage 1 goiter had more than adequate urinary iodine excretion. There was no statistical significance between levels of urinary iodine excretion and the size of goiter (p = 0.404).

Urinary iodine levels versus thyroid function

Three out of seven participants who had high T3 serum levels had excess iodine level (Table 3). Of the six people who had high T4 serum levels only two had excess urinary iodine. Only one participant had high TSH levels and insufficient urinary iodine levels.

Table 3: Urinary iodine levels versus thyroid functions

Thyroid Function	Urinary iodine				P values
	Iodine deficiency	Sufficient Iodine	More than sufficient	Excess Iodine	
T_3					0.165
Low	1(33%)	1(33%)	1(33%)	0	
Normal	18(16%)	50(44%)	35(31%)	10(9%)	
High	1(14%)	2(29%)	1(14%)	3(43%)	
T_4					0.332
Low	1(33%)	1(33%)	0	1(33%)	
Normal	18(16%)	50(44%)	36(32%)	10(9%)	
High	1(17%)	2(33%)	1(17%)	2(33%)	
TSH					0.000
Low	1(8%)	2(17%)	3(25%)	6(50%)	
Normal	18(16%)	51(46%)	34(31%)	7(6%)	
High	1(100%)	0	0	0	

Urinary iodine levels versus age

Most of the participants with either excess iodine or iodine insufficiency were more than 50 years old. The peak age of those who had excess iodine was between 20 and 40 years. The age differences observed were not statistically significant (p= 0.778).

Discussion

We found that there was an association between goiter and urinary iodine excess. Iodine excess may be occurring following universal salt iodization. In Uganda, there are indications since 2000 that median urinary iodine excretion exceeds the WHO recommended level of 300µg/L (5,9,17,18). Studies elsewhere have reported that taking in food or medicine with too much iodine causes thyroid dysfunction (3,6–8). Our study has shown that 10% of the study subjects exceed this level.

The difference between the median urinary iodine levels among goiter patients (194µg/L) and the controls (162µg/L) was significant. A community study done in Uganda revealed a similar picture with median urinary iodine levels of 150µg/L (5). The fact that 31% of the study population had more than adequate urinary iodine excretion raises concern as levels above 200µg/L might cause thyroid dysfunctions among susceptible individuals (18,19). In Uganda, in 1991, before Universal Salt Iodinization (USI), 36% of the population had severe iodine deficiency with urinary iodine below 50µg/L. USI in Uganda was implemented in 1994, five years later the median urinary iodine was 310µg/L, an excess by WHO set standards (5).

Excess urinary iodine levels in this study had an association with goiter (p= 0.035) which was comparable to other studies (6,8). The safety levels however differ from one study to study. Some Authors have found significant association only when the levels exceed 500µg/L (8). The findings of this study however differ from those in a similar study done 12 years ago in Uganda which found no association and the largest proportion of participants had iodine deficiency (11). The explanation to the change of trend is USI. The risk of developing iodine induced thyroid dysfunction depends on how quickly the uptake of iodine is and the severity of the pre-existing iodine deficiency(19).

In the non- goiter patient there was none with thyroid dysfunction signifying that there was no subclinical thyroid dysfunction in the study participants which could have confounded the results if not dealt with. Among the goiter patients, 12% were hyperthyroid, 5% hypothyroid with 83% euthyroid, the results were almost similar to those in a study done four years ago in the same hospital (20).

Most of goiters in this study were multinodular (73%) followed by the diffuse type (22%); 48% of those with nodular goiter and 45% with diffuse goiters had iodine levels >200 µg/L, replicating the finding in other studies (6). Most of the goiter patients had goiter stage 2 according to WHO classification and 11% of them had excess iodine, 31% more than adequate and only 9% had insufficient iodine. This showed an association between the goiter size and urinary iodine levels similar to the findings by Zimmerman who related the thyroid volume increase with excess iodine levels >5008 (8). This study however, did not demonstrate a significant statistical correlation.

It is well known that dietary goitrogens are found in food like cassava, cabbage, sweet potatoes and some cereals like maize (1). This study did not show any

significant association, probably due to recall bias amongst the participants.

Limitation of the study

The effects of goitrogens and other micronutrients such as selenium, vitamin A and folic acid were not measured. However, the presence or absence of night blindness was used to rule out vitamin A deficiency. Thyroid autoantibody tests were not done. Graves's disease is known to alter urinary iodine excretion. However, the incidence of Graves disease is thought to be low <1% of the general population. The diagnosis of Goitre was by physical examination sub clinical ones could have been missed as US Scans were not used as a screening tool for the controls. Total T4 values may be affected by thyroid binding globulin. This being a hospital based study; the results may not fully reflect the true national picture, though Mulago hospital receives patients from all over the country.

Conclusion

Urinary iodine excess was associated with goiter occurrence.

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