CLINICAL STUDY

Thyroid hyperactivity with high thyroglobulin in serum despite sufficient iodine intake in chronic cold adaptation in an Arctic Inuit hunter population

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Abstract

Objective: Adult man hosts brown adipose tissue with the capacity to consume energy and dissipate heat. This is essential for non-shivering thermogenesis and its activation depends on sympathetic activity and thyroid hormones. This led us to evaluate the impact of chronic cold exposure on thyroid activity and thyroid hormones in serum in Arctic residents.

Design: Comparative, population-based study ($n=535$) performed in Greenland.

Methods: Hunters were compared with other men, and Inuit in remote settlements in East Greenland with no modern housing facilities were compared with the residents of the capital city in West Greenland and residents of a major town in East Greenland in a cross-sectional study. We used interview-based questionnaires, measured TSH, free thyroxine, free triiodothyronine (fT₃), thyroglobulin (TG) antibody and TG (a measure of thyroid activity) in serum, and iodine and creatinine in spot urine samples.

Results: Serum TG was the highest among hunters ($P=0.009$) and settlement dwellers ($P=0.001$), who were most markedly exposed to cold, even though they had the highest urinary iodine excretion (hunters, $P<0.001$; settlement dwellers, $P<0.001$). Hunters and settlement dwellers also had the lowest fT₃ (hunters, $P<0.001$; settlement dwellers, $P<0.001$) after adjusting for gender, age, smoking habits, alcohol intake and iodine excretion in multivariate linear regression models. TSH was not influenced by measures of cold exposure (hunter, $P=0.36$; residence, $P=0.91$).

Conclusions: Cold exposure influenced thyroid hormones and TG in serum in Arctic populations consistent with consumption of thyroid hormone and higher thyroid hormone turnover. Findings emphasise that changes in thyroid activity are essential in cold adaptation in Arctic residents.

European Journal of Endocrinology 166 433–440

Introduction

The presence and role of brown adipose tissue (BAT) in adult man was previously much discussed (1, 2), but recently BAT with temperature-dependent activity has been demonstrated in man (3, 4, 5). BAT has gained considerable interest because it has the capacity to deplete energy rather than store it (1, 2, 6). It dissipates heat in the energy consumption and this is essential for non-shivering thermogenesis in cold adaptation (1, 2, 6, 7, 8).

Heat production in brown adipocytes is regulated via the sympathetic nervous system, and it has an absolute requirement for thyroid hormone (9, 10). BAT contains abundant amounts of type II iodothyronine deiodinase (1, 6, 8, 10). Type II deiodinase is a local source of triiodothyronine (T₃) production (11), and cold exposure enhances T₃ production from thyroxine (T₄) locally in BAT (8, 9, 10).

Thyroglobulin (TG) is a large glycoprotein that provides a matrix for the synthesis and storage of thyroid hormones in the follicular lumen of the thyroid gland (12). Small amounts of TG are released from the thyroid into the blood (13), and measurement of TG in serum has found its greatest use as an indicator of thyroid tissue remnants in patients treated for differentiated thyroid carcinoma (14). However, serum TG is raised in patients with goitre (13, 15), in pregnancy (16, 17) and hyperthyroidism (18, 19, 20) where thyroid hormone production is increased. Moreover, elevated serum TG is a sign of iodine deficiency in population studies (21, 22). Thus, serum TG is a marker of overall thyroid gland activity.

Field studies on cold adaptation in man are hampered by man's behavioural adaptations to cold (23). Human cold exposure increased thyroidal iodide turnover in an environmental chamber study (24) and plasma clearance rate of T₃ in Antarctic expeditioners (25). This was

associated with a small decline in T_3 in serum in Antarctic visitors (26, 27) and subarctic inhabitants (28), and was in keeping with an increased requirement for thyroid hormone during winter in hypothyroid individuals (29). None of the studies included data on iodine excretion, though this is a major environmental factor that influences thyroid activity, and Arctic residents remain to be investigated.

This led us to study thyroid hormones and TG in serum and urinary iodine excretion in residents of Greenland with markedly different environmental cold exposure.

Subjects and methods

Areas of investigation

Ammassalik district (65.35N) in East Greenland was isolated until 1884 and is still difficult to access by sea due to pack ice from the northern icecap. It is sparsely populated with 2800 inhabitants (93% Inuit) in an area of 243 000 km². Tasiilaq is the main town of Ammassalik district, which holds seven settlements with almost half of the population.

Nuuk (64.15N) in West Greenland is the capital of Greenland with 13 000 inhabitants of whom 75% are Inuit (Eskimo) and 25% non-Inuit (Caucasian Danes). Nuuk is the northernmost capital in North America and indeed in the whole world and is the commercial and administrative centre of Greenland with modern housing facilities, shopping and transport.

Subjects

Participants were 50- to 69-year-old men and women. Subjects in this age range included a group of Inuit who had been hunters for many decades. Hunters were selected because they hunt and fish using small open boats in the Arctic seas and fjords throughout the year (Fig. 1) except during sea ice. Then, they use dog sledges or walk. Hence, they cannot avoid extensive cold exposure. Whether being a hunter or not, cold exposure is, in general, mandatory for residents in remote settlements where no modern housing facilities, roads or transport are available. Thus, people collect water from a central tap in the settlement, carry petrol from the store for heating and use a dry toilet with bags for disposal throughout the year.

The study population was collected from three areas: the capital city of Nuuk in West Greenland, the town Tasiilaq in East Greenland, and the four settlements Tiniteqilaq, Sermiligaaq, Kulusuk and Kuummiut in Ammassalik district in East Greenland (Fig. 2). Settlements with <15 inhabitants in the selected age group were not included for practical reasons. Comparisons were made between inhabitants of these three areas as well as between Inuit hunters, other Inuit men and non-Inuit men. We excluded seven subjects of

Figure 1 An Inuit fisherman working from a small open boat in the Arctic sea.

mixed ethnicity, one on anti-thyroid drug therapy and one receiving levothyroxine following thyroidectomy.

In Nuuk, names and addresses were obtained from the hospital registration system that maintains records of all inhabitants of the city. A random sample of 480 (25% of the total population aged 50–69 years) was selected. It turned out that the hospital registration system had not been regularly updated. Thus, we obtained names and addresses from the National Civil Registration System for investigation in Ammassalik district. This register maintains records of every person living in Denmark, the Faeroe Islands and Greenland. We included persons who were selected and confirmed to be living on the address recorded in the National Civil Registration System.

Ethical approval by the Commission for Scientific Research in Greenland was obtained before the commencement of this study (j. number 505-31). All subjects gave informed written consent in Danish or Greenlandic by participant choice.

Investigational procedures

The local hospital porter or the nursing station attendant delivered a letter of invitation to each subject, and three invitations were delivered to non-responders. The investigation took place at the local hospital or nursing station or, by request, during home visits. A physical examination was performed by one of the investigational doctors (S A, P L or B H) by examining the neck and recording goitre and any major disability. Participants were interviewed by an interpreter or by one of the investigational doctors who completed the

Figure 2 Map of Greenland indicating sites included in the survey. Nuuk in west Greenland is the capital of Greenland, whereas Tasiilaq is the major town in east Greenland. Tiniteqilaq, Sermiligaaq, Kuummiut and Kulusuk are settlements with a population of <500.

questionnaire in either Danish or Greenlandic as appropriate for the subject. Questions were asked as written in the questionnaires. The same interpreter interviewed the participants in Nuuk, Tasiilaq and all settlements. Information on hunting and other lifestyle patterns was obtained by questionnaires. Hunting is a distinct trade in Greenland and being a hunter associates with the highest esteem. Only subjects who reported to be hunters were categorised as such. A Greenlandic (Inuit) was defined as a person who was born in Greenland and whose parents were also born in Greenland. Information on residence, age and gender was obtained from the National Civil Registration System.

Sample collection and assays

A blood sample was drawn using minimal tourniquet, and a non-fasting spot urine sample was collected in

iodine-free polyethylene containers from all participants at the interview. Serum was separated and samples were stored at -20°C until analysis.

Iodine content in urine was determined by the Sandell–Kolthoff reaction modified after Wilson & van Zyl (30) as described in detail previously (31, 32). Urinary creatinine was determined by a kinetic Jaffé method (33). Urinary iodine excretion was corrected for dilution by calculating the iodine:creatinine ratio (32, 34). Median urinary iodine excretion above $150\text{ }\mu\text{g/g}$ in a population is recommended.

Serum TG, TSH, estimated free T_4 (fT_4) and estimated free T_3 (fT_3) were analysed using LUMitest (BRAHMS, Berlin, Germany). The functional sensitivity of the TSH assay was 0.01 mU/l . Reference intervals were $0.3\text{--}4.5\text{ mU/l}$ for TSH, $9.8\text{--}20.4\text{ pmol/l}$ for fT_4 and $3.6\text{--}6.9\text{ pmol/l}$ for fT_3 . The TG assay had a working range from 1 to $500\text{ }\mu\text{g/l}$, and median values of around 9, 10 and $15\text{ }\mu\text{g/l}$ are seen in iodine-replete, mild and moderately deficient Caucasian Danes respectively (21, 22). TG antibodies (TGAb) were measured using Dynotest RIA (BRAH-MS Diagnostica) with a functional sensitivity of 20 kU/l for TGAb (35). Individuals with TGAb above 100 kU/l ($n=39$) were excluded from calculations including serum TG, as TGAb above this level influenced measurements of TG. All assay runs included samples from different groups investigated in random order.

Statistical analysis

Frequencies among populations were compared using χ^2 test, and medians were compared using Mann–Whitney U test or Kruskal–Wallis test. Dependent variables included in linear regression models were serum TG, fT_3 and fT_4 after logarithmic transformation because the distributions were positively skewed. Explanatory variables included were gender, age, smoking habits, alcohol use, urinary iodine excretion and participant group. The latter was for men with occupation split by Inuit hunter, other Inuit men and non-Inuit men, and for women by place of living according to settlements, town or city.

Random selection of participants in Nuuk was performed using MEDSTAT software (version 2.12; Astra, Albertslund, Denmark). Data were processed and analysed using Corel QuattroPro X3 (Corel Corporation, Ottawa, ON, Canada) and the Statistical Package for the Social Sciences version 11.0 (SPSS, Inc., Chicago, IL, USA) software. A P value of <0.05 was considered significant.

Results

One per cent of the population of Greenland was invited and the participation rate was 95% (Table 1). Hunters were all men and included more Inuit in settlements

Table 1 Participant selection and inclusion.

	Populations recorded		Cohort selected	No contact on the address	Invited	Non-attenders	Investigated	%
	Total	Aged 50–69 years						
Nuuk ^a	12 909	1920	480 ^b	255 ^c	225	14	211	94
Tasiilaq ^d	1724	197	197 ^e	13 ^f	184	11	173	94
Settlements ^g	1093	161	161	9 ^f	152	1	151	99
Total			838		561		535	95

^aNuuk is the capital of Greenland and is situated on the relatively more populated west coast of Greenland.

^bSelected at random from the hospital register.

^cThe hospital register was not updated for years and some individuals had died or moved (house/town/country).

^dTasiilaq is the main town of Ammassalik county in the sparsely populated East Greenland (0.01 inhabitant per square kilometre).

^eNames and addresses obtained from the National Civil Registration System which maintains records of every person living in Denmark, the Faroe Islands and Greenland.

^fSome individuals had died or moved out of the district but their records were still in the National Civil Registration System due to late reporting.

^gOnly settlements in Ammassalik district with more than 15 inhabitants in the selected age group were included in the study: Tiniteqilaq ($n=19$, aged 50–69 years), Sermiligaaq ($n=28$), Kulusuk ($n=52$) and Kuummiut ($n=53$).

(51%) than in town (16%) or city (4%). The characteristics of the study populations are listed in Table 2. Seven participants had one parent born in Greenland while 94 had neither parent born in Greenland. Non-Inuit were skilled labourers from Denmark and the group included more men than women ($P<0.001$). There were relatively fewer non-Inuit than Inuit aged 60–69 years because some Caucasian Danes leave Greenland when they retire. Inuit men were iodine replete whereas non-Inuit men had urinary iodine considerably below the recommended level (Table 3).

TG in serum

Thyroid activity as evaluated from serum TG was higher among Inuit in settlements compared with Inuit in town and city in the crude comparison ($P=0.003$) and after correction for age, gender, smoking habits, alcohol intake and iodine excretion in multivariate linear regression ($P=0.001$). Serum TG was highest among Inuit women living in settlements (univariate analysis, $P=0.01$) and among Inuit men living in settlements ($P=0.04$), as was found after adjusting for age, smoking habits, alcohol intake and iodine excretion (Table 3).

Serum TG tended to be higher among hunters compared with other men in the crude comparison ($P=0.07$), while hunters had the highest serum TG ($P=0.009$) after adjusting for age, smoking habits, alcohol intake and iodine excretion (Table 3). Being a hunter remained an important factor for serum TG when including only Inuit men in the multivariate analysis ($P=0.04$).

Thyroid hormones

Serum fT₃ was lower among Inuit living in settlements compared with Inuit living in town and city in the crude

comparisons ($P<0.001$) as well as after adjusting for gender, age, smoking habits, alcohol intake and iodine excretion ($P<0.001$). This difference was marked for both men and women in the crude as well as in the adjusted analysis (all, $P<0.001$; Table 3). Place of living also influenced fT₄ both in the crude comparison ($P<0.001$) and after adjustment for the above-mentioned variables ($P=0.005$), though the influence in women was limited (Table 3). No significant difference in serum TSH was found between groups (Table 3).

Serum fT₃ was markedly lower in hunters compared with other men in the crude comparison ($P<0.001$) as well as after adjusting for age, smoking habits, alcohol intake and iodine excretion (Table 3). Also, fT₃ was lower in hunters than in other Inuit men ($P<0.001$). Serum fT₄ was the lowest in hunters in the crude comparison ($P=0.027$) while this difference was not significant after adjustment for the above-mentioned variables (Table 3).

Discussion

The influence of cold exposure on circulating thyroid hormone concentrations has been studied using a variety of study set-ups (24, 25, 26, 27, 28, 29, 36, 37, 38, 39, 40). A slight decrease in thyroid hormone concentrations in serum (26, 27) has been observed. None of the previous studies included Arctic residents exposed to cold for decades and none included evaluation of iodine intake. Thus, serum TG was included in one study on Antarctic visitors, but iodine excretion was not measured (41). Also, none studied the association between habitual cold exposure and TG, a measure of thyroid gland activity and iodine deficiency, in circumpolar residents.

Urinary iodine excretion differed markedly between the groups investigated in Greenland. Inuit in settlements and town were in the recommended

Table 2 Participant descriptives.

	Inuit men				Non-Inuit				P ^c	
	Hunters		Non-hunters ^a		Inuit women ^a		Men			
	n	%	n	%	n	%	n	%		
Residence									<0.001	<0.001
City	3	5.4	67	38.7	80	39.0	47	62.7	12	63.2
Town	13	23.2	67	38.7	61	29.8	23	30.7	7	36.8
Settlements	40	71.4	39	22.6	64	31.2	5	6.7	0	0.0
Age (years)										0.58
50–59	35	62.5	101	58.4	123	60.0	61	81.3	18	94.7
60–69	21	37.5	72	41.6	82	40.0	14	18.7	1	5.3
Smoker ^d										0.99
Present	43	76.8	134	77.5	151	74.0	44	58.7	8	42.1
Past	7	12.5	21	12.1	21	10.3	14	18.7	3	15.8
Never	6	10.7	18	10.4	32	15.7	17	22.7	8	42.1
Alcohol use (units) ^e										0.71
<7	12	21.4	29	17.1	16	8.0	18	24.0	0	0.0
7–21	13	23.2	46	27.1	36	18.0	20	26.7	4	22.2
>21	31	55.4	95	55.9	148	74.0	37	49.3	14	77.8
Thyroid disease ^f										0.19
SH	0	0.0	1	0.6	3	1.5	0	0.0	0	0.0
Hyperthyroidism	1	1.8	0	0.0	6	2.9	1	1.3	2	10.5
Goitre	0	0.0	1	0.6	5	2.4	1	1.3	2	10.5
Visible goitre ^g	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
										0.31
										0.81
										NA

NA, not applicable. SH, Spontaneous hypothyroidism.

^aExcluding two women and five men with mixed ethnicity.^b χ^2 test for comparing proportions among all groups.^c χ^2 test for comparing proportions among Inuit men.^dInformation missing for one participant.^eEstimated units of alcohol per week. Information missing for nine participants.^fPrevious or present thyroid disease in the participant.^gThe woman with goitre had hyperthyroidism.

Table 3 Thyroglobulin (TG), thyroid function tests and urinary iodine excretion among groups in Greenland with different cold exposure due to either occupation (hunters) or residence. Outdoor activity is mandatory in settlements because housing is without tap water, flush toilets and central heating.

	TG ^a (μg/l)			TSH (μU/l)			fT ₄ (pM)			fT ₃ (pM)			Iodine/creatinine ^b (μg/g)		
	Median	25.75%	P ^c	Median	25.75%	P ^c	Median	25.75%	P ^c	Median	25.75%	P ^c	Median	25.75%	P ^{c,d}
By residence (only Inuit)															
Women															
Settlement	26.1	(16.3–35.4)	0.002												
Town	21.3	(15.6–30.5)		0.96	(0.67–1.60)	0.65	14.5	(12.7–17.1)	0.17	4.58	(4.10–5.02)	<0.001	181	(122–334)	0.003
City	18.6	(13.3–26.3)		0.98	(0.63–1.58)		16.9	(15.5–18.6)		5.08	(4.71–5.48)		185	(118–313)	
Men			0.010	0.99	(0.62–1.45)		15.7	(14.3–17.4)		5.90	(5.33–6.38)		137	(83–227)	
Settlement	20.2	(13.5–26.6)				0.38	14.1	(12.7–15.7)	0.005	4.55	(4.17–5.05)	<0.001	164	(94–344)	<0.001
Town	18.2	(10.6–23.3)		1.10	(0.71–2.00)		16.6	(15.4–18.8)		5.10	(4.63–5.52)		163	(103–267)	
City	13.7	(9.9–21.8)		1.30	(0.84–1.90)		15.9	(13.5–17.9)		5.95	(5.49–6.51)		105	(75–183)	
By hunting and ethnicity (only men)			0.009	1.34	(0.91–2.18)	0.36			0.19			<0.001			<0.001
Inuit hunter	20.3	(14.3–26.5)					14.8	(12.9–17.0)		4.76	(4.29–5.22)		169	(93–314)	
Other Inuit men	17.2	(10.5–23.8)		0.97	(0.66–1.87)		15.9	(13.9–17.9)		5.22	(4.63–5.85)		133	(87–243)	
Caucasian men	13.9	(7.9–27.3)		1.30	(0.90–2.00)		15.9	(14.2–17.7)		5.62	(5.19–6.08)		69	(46–118)	

^aExcluding 39 with interfering TGAb (> 100 kU/l).^bCalculated as an iodine/creatinine ratio in a non-fasting spot urine sample.^cAdjusted for age, smoking habits, alcohol intake and iodine excretion in multivariate linear regression models: TG, TSH, fT₄, fT₃ and iodine/creatinine included after logarithmic transformation as distributions were positively skewed.^dExplanatory variables include age, smoking habits and alcohol intake except iodine excretion.

range, while Inuit in the capital city were slightly below the range and non-Inuit were mildly iodine deficient. The traditional Inuit diet consists of mainly sea mammals and fish that have high iodine content, whereas imported food items are low in iodine (32). The intake of the traditional Inuit food items decreases with increasing Westernisation and explains the rather marked differences in iodine excretion between the participant groups (32).

In populations, serum TG increases with increasing iodine deficiency (16, 21, 22). We would thus expect lower TG among hunters and settlement dwellers. Paradoxically, we found quite the opposite. Serum TG was high in the population groups with sufficient iodine intake. These groups were exposed to cold because of their occupation or place of living.

Cold exposure activates non-shivering thermogenesis. The principal organ of non-shivering thermogenesis is BAT which generates heat in the energy consumption. BAT has been found convincingly in adult man recently (3, 4, 5). It is highly vascularised and innervated by sympathetic nerve endings (1, 2, 9), and initiation of the adaptive thermogenesis requires adrenergic signalling in complex interaction with thyroid hormone action involving T₄ to T₃ deiodination (7, 8, 10).

Our findings suggest that chronic cold exposure in the Arctic environment leads to high thyroid gland activity and thyroid hormone consumption. This is compatible with brown fat activation and high thyroid hormone turnover. The T₃ produced by type II deiodinase-catalysed T₄ deiodination is mostly confined to the cellular compartment and not released into the blood (42), and chronic cold exposure is associated with a decrease in serum T₃. Interestingly, Reed *et al.* (25) found an increased T₃ production and clearance in people travelling to the Antarctic, which is consistent with our findings. They found that the increased consumption of T₃ is associated with low T₃ in serum. The mechanism for the increase in T₃ clearance in cold exposure is not known, but the high consumption of thyroid hormones matched the high activity of the thyroid gland reflected by the high levels of TG in serum in the groups with chronic cold exposure.

We did not quantify cold exposure in the individual participants. However, all of Greenland is Arctic and cold exposure is mandatory when everyday life requires outdoor undertakings (43). Hunters use small open boats and dog sledges for hunting and fishing, and even today, most of Greenland outside the major towns remains a hunter society (43). Moreover, life in a settlement depends on daily outdoor activities throughout the year because of a lack of modern conveniences. This accounts to some degree for residents in the town and not for residents in the city. Thus, the groups selected were exposed to different intensities of cold.

Traditional Inuit food items have high contents of environmental contaminants (44, 45). However, no studies in animals or man have suggested that exposure

to environmental contaminants should lead to high serum TG levels as observed in the cold-exposed Inuit. Cold-exposed Inuit have an increased requirement for energy, and hence a need for higher food intake. Still, the influence hereof on thyroid hormone metabolism is limited and cannot explain our findings. It might be speculated that BAT in the hunters was activated not only by the cold exposure but also by their diet. There are, however, no data to support such a mechanism.

Some overlap between hunter occupation and residence in settlements could match the findings in the two analyses including men. However, half of the men in settlements were not hunters, about one-third of the hunters did not live in settlements, and the use of women in the residence analysis excluded such an effect. Thus, the two measures of cold exposure may be considered separately.

The same interpreter interviewed in all areas and among all population groups to ensure equal understanding and interpretation of the questionnaire among the regions and the participant groups. Also, the participation rate of 95% was high and the selection of elderly subjects contributed to a valid representation of the participant groups with decades of cold exposure, and migration between areas was low.

Seasonal variation did not contribute to the marked differences between Inuit in settlements and town in East Greenland as these data were collected in parallel. However, data were collected in early autumn in the capital city in West Greenland before the collection in East Greenland, which was carried out further into the autumn. A slight difference in time of year could not be avoided for practical reasons but should not be sufficient to corrupt our results.

In conclusion, our findings match high thyroid hormone consumption in brown fat activated by chronic cold exposure in the Arctic environment. They emphasise a key role of the thyroid axis in adaptation to cold in the Arctic. The finding of increased thyroid activity and thyroid hormone consumption urges further studies to clarify the interaction of sympathetic stimulation of BAT and the thyroid during cold exposure.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

Greenland Home Rule, Aalborg City Christmas Lottery, Obel Family Foundation, Northern Jutland Research Foundation, and Danish Hospital Foundation for Medical Research, Region of Copenhagen, the Faroe Islands and Greenland.

Author contribution statement

Conception of idea, study design, raising of funds, data collection, analysis and interpretation of data and writing of the manuscript: S Andersen; design, translations and explanations, techniques to

improve Inuit participation rate, and reviewing of the manuscript: K Kleinschmidt; data collection and reviewing of the manuscript: B Hvingel; conception of idea, design of the study, raising of funds, data collection, interpretation of data and writing of the manuscript: P Laurberg.

Acknowledgements

The authors thank Karoline Berglund for her enthusiasm and thorough interviewing of Inuit, the invaluable support from lægeklinikken in Nuuk, from Hans Chr. Florian Sørensen and from the hospital in Tasiilaq and the nursing stations in Tiniteqilaq, Sermiligaaq, Kuummiut and Kulusuk.

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Received 13 October 2011

Revised version received 7 December 2011

Accepted 14 December 2011