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Intake of traditional Inuit diet vary in parallel with inflammation as estimated from YKL-40 and hsCRP in Inuit and non-Inuit in Greenland

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ABSTRACT

Background: Chronic low-grade inflammation is involved in the initiation and progression of atherosclerosis and ischemic heart disease. This was rare in pre-western Inuit who lived on a diet that consisted mainly of marine mammals rich in n-3 fatty acids.
Objectives: To assess the association between biomarkers of inflammation and the intake of traditional Inuit diet in addition to Inuit ethnicity.
Methods: YKL-40 and hsCRP were measured in serum from 535 Inuit and non-Inuit living in the capital city Nuuk in West Greenland or in the main town or a settlement in rural East Greenland. Dietary habits were assessed by an interview-based food frequency questionnaire.
Results: The participation rate was 95%. YKL-40 was higher in Inuit than in non-Inuit ($p < 0.001$), in Inuit with a higher intake of traditional Inuit diet ($p < 0.001$), and in Inuit from rural compared to urban areas ($p < 0.001$). It also rose with age ($p < 0.001$), alcohol intake (0.019) and smoking ($p < 0.001$). Inuit had higher hsCRP compared to non-Inuit ($p = 0.003$) and hsCRP increased in parallel with intake of traditional Inuit foods ($p < 0.001$). Alcohol associated with a decrease in hsCRP in Inuit ($p = 0.004$). YKL-40 and hsCRP increased with higher intakes of traditional Inuit diet after adjusting for ethnicity, gender, age, smoking, alcohol intake and BMI.
Conclusions: Biomarkers of inflammation vary in parallel with the intake of traditional Inuit diet. A diet based on marine mammals from the Arctic does not reduce inflammatory activity and it may be speculated that markers of inflammation reflect the disease rather than the cause of the disease.

1. Introduction

Chronic low-grade inflammation is involved in the initiation and progression of atherosclerosis [1] and the severity of atherosclerosis associates with markers of inflammation [2]. Atherosclerosis and inflammation have been linked to n-3 fatty acid consumption [3]. High intakes of n-3 fatty acids associate with lower inflammatory activity via suppression of proinflammatory cytokines [4]. A lower risk of inflammatory diseases such as rheumatoid arthritis has been found in subjects with a high intake of n-3 fatty acids [5]. Consequently, decreasing inflammation may be speculated to reduce atherosclerosis and hence the risk of ischemic heart disease [6].

Low occurrence of ischemic heart disease in pre-western Inuit was confirmed recently [7] and high physical activity influenced their cardiovascular risk profile [8]. Also, pre-western Inuit had a high intake of traditional Inuit foods that consist mainly of marine mammals [9–11] rich in n-3 fatty acids. These were linked to the low occurrence of ischemic heart disease [11]. It may thus be speculated that the traditional Inuit diet rich in n-3 fatty acids influences inflammation and biomarkers of inflammation.

YKL-40 and hsCRP are markers of inflammation [12]. YKL-40 participates in inflammatory processes, angiogenesis and apoptosis that are important for the risk of ischemic heart diseases [12]. YKL-40 is independently associated with the presence of cardiovascular disease [12] and may be an indicator of presence and progression of coronary artery disease [13]. Also, YKL-40

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concentrations are associated with cardiovascular and all-cause mortality [14]. This supports a role of YKL-40 in cardiovascular disease similar to hsCRP [15,16].

The aim of the present study was to investigate the association between biomarkers of inflammation and the intake of traditional Inuit diet in addition to ethnicity in non-Inuit and in Inuit living in urban and rural areas of Greenland with markedly different dietary habits.

2. Subjects and methods

2.1. Area of investigation

Fig. 1 shows the areas included in the study. Nuuk (64.15N 51.35W) in West Greenland is the capital of Greenland with 16,000 inhabitants of whom 75% were Inuit (Eskimo) and 25% non-Inuit (Caucasians). Nuuk is a modern city with access to a wide variety of imported foods supplementary to traditional Greenlandic food items.

Ammassalik district (65.35N 38.00W) in East Greenland is difficult to access by sea due to pack ice from the northern icecap. It is sparsely populated with 2943 inhabitants (93% Inuit) in 243,000 km^2. The main town Tasiilaq has one store with a limited selection and five minor shops. Each of the settlements has one store with a limited selection depending on access by sea and air. City, town and settlements are situated on fjords with access to the sea.

2.2. Subjects

Participants were 50–69 years of age, men and women, Greenlanders (all Inuit) and not Greenlanders (Caucasians). We included individuals registered, selected, and living on the address. The places selected for investigation were Nuuk, Tasiilaq, and the settlements Tiniteqilaaq, Sermiligaaq, Kulusuk and Kuummiut in Ammassalik district (Fig. 1). For practical reasons, settlements with less than 15 inhabitants in the selected age group were not included. In Nuuk, names and addresses were obtained from the hospital registration system. A random sample of 480 (25% of the total population aged 50 to 69 y) was selected. The hospital registration system had not been regularly updated and for the subsequent investigation in Ammassalik district names and addresses were obtained from the National Civil Registration System in which every person living in Denmark, the Faeroe Islands and Greenland is recorded.

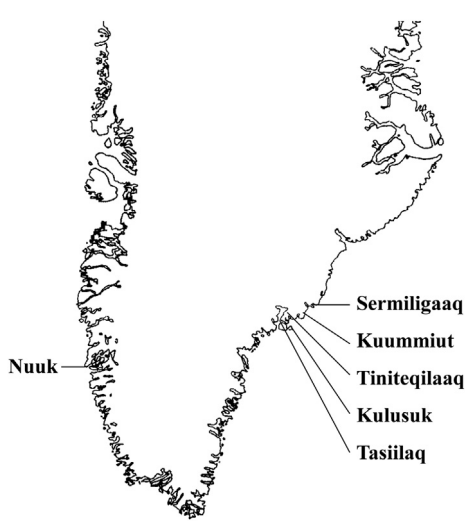

Fig. 1. Map of Greenland that indicates sites included in the survey. Nuuk is the capital of Greenland and is situated on the more heavily populated west coast of Greenland while Tasiilaq is the major town in the sparsely populated East Greenland. Tiniteqilaaq, Sermiligaaq, Kuummiut and Kulusuk are settlements with a population of less than 500.

The local hospital porter or the nursing station attendant delivered a letter of invitation. Non-responders were invited three times.

A Greenlander (Inuit) was defined as an individual born in Greenland with both parents born in Greenland.

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

2.3. Investigational procedures

The investigation took place at the local hospital or nursing station or at request as home visits. One of the investigational doctors performed a physical examination that included height without shoes, weight in indoor clothing and recording of major disabilities. Participants were interviewed by a Greenlandic interpreter or by one of the investigational doctors completing a questionnaire in either Danish or Greenlandic as appropriate for the participant. Information regarding age and gender was obtained from the National Civil Registration System. Information on lifestyle patterns and dietary habits was obtained by interview-based questionnaires. An alcohol unit was defined as 12 g of alcohol. The same interpreter was used in Nuuk, Tasiilaq and all settlements.

A venous blood sample was drawn at the visit during normal working hours using minimal tourniquet, separated and stored at minus 20° Celsius until analysis. Serum was lacking in five participants.

2.4. Dietary habits

Recording of dietary habits has been described in details previously [9,10]. In brief, an interview based food frequency questionnaire (FFQ) was used to assess the dietary habits based on seven traditional Inuit and seven imported food items. For each food item, six different frequency categories were given from never to daily intake. The food item was given a frequency score calculated as the average number of days per month it was ingested. Frequency scores were summed and each participant was categorised into: Diet group 1: >80% Inuit food item scores; 2: 60–80%; 3: 40–60%; 4: 20–40%; 5: <20% Inuit food item scores on a scale where 100% was Inuit foods only and 0% was imported foods only. These evaluations were validated by crosscheck questions [9,10].

2.5. Assays

Analyses of the following inflammations markers were done: 1) Plasma YKL-40 was measured using an ELISA method (Quidel, USA). Measuring range of the assay was 20–300 ng/ml, with intra- and interassay coefficients of variation of 5.8% and 6.0%, respectively; 2) hsCRP was measured with a highly sensitive, latex-particle-enhanced immunoturbidimetric assay (DAKO, Glostrup, Denmark) with a measuring range of 0.2–80 mg/L and with a lower detection limit of 0.03 mg/L. All assays were performed with serum from participants mixed in random order with participant characteristics blinded to the laboratory.

2.6. Statistics

Results are given as median and interquartile range (IQR). Groups were compared using Mann–Whitney *U* test for

comparison of levels between two groups, Kruskal–Wallis test for levels between several groups, and Kendall's tau for a relation between groups. Data with a non-Gaussian distribution was logarithmically transformed using the natural logarithm for calculations for Fig. 2 and for the multiple linear regression analyses. YKL-40 and hsCRP were entered as dependent variables in linear regression analyses. Explanatory variables entered were: ethnicity, gender, age, smoking, alcohol, BMI, and diet groups. Random selection of participants in Nuuk was performed using MedStat (Astra, Albertslund, Denmark). Data were processed and analysed using Corel Quattro Pro 8 (Corel Corporation, Ottawa, Ontario, Canada) and the Statistical Package for the Social Sciences version 13.0 (SPSS Inc., Chicago, Illinois). A p-value of less than 0.05 was considered significant.

3. Results

The participation rate was 95%. Table 1 shows the characteristics of the study population. More non-Inuit were men and they were generally younger since non-Inuit tend to move back to Denmark when they retire. Inuit counted more smokers and had a higher intake of traditional Inuit food items than non-Inuit, which is in accordance with markedly more Inuit hunting (Table 1).

3.1. YKL-40

Details on the levels of YKL-40 are given in Table 2. Inuit had markedly higher YKL-40 levels than non-Inuit ($p < 0.001$), and it was higher among Inuit participants in East Greenland compared to Inuit participants from the capital Nuuk in West Greenland ($p < 0.001$). There was no difference in YKL-40 levels between residents of town and settlements in East Greenland (Table 2). YKL-40 levels increased with rising intake of traditional Inuit food items (Fig. 2, $p < 0.001$) and the levels differed markedly between diet groups (Table 2). Similarly, markedly higher YKL-40 levels were seen among subjects living on foods from local hunt than among subjects living on imported foods ($p < 0.001$). YKL-40 was higher in participants who were 60 through 69 years than in those aged 50 through 59 years ($p < 0.001$). Present smokers had higher levels of YKL-40 than past smokers and even higher levels than never smokers ($p < 0.001$). Similarly, YKL-40 levels were higher in subjects with the higher alcohol intake compared to those with a daily alcohol intake of two units or less (Table 2).

Ethnicity, diet, alcohol, BMI and age influenced YKL-40 in the adjusted analysis (Table 3).

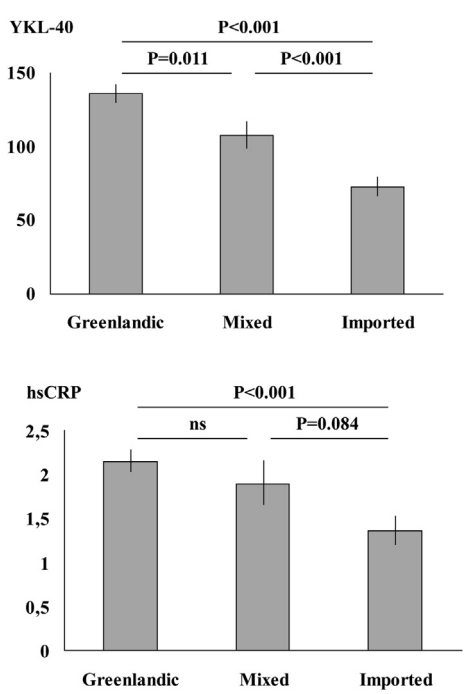

Fig. 2. Higher serum concentrations of the markers of inflammation YKL-40 and hsCRP in subjects living in Greenland with a high intake compared to those with a low intake of traditional Inuit food items. Data shown are mean and standard error of the mean calculated on ln-transformed data. Overall differences were distinct for both YKL-40 and hsCRP ($p < 0.001$) with pairwise comparisons shown on the figures.

Table 1
Descriptives of participants in the study among populations in East- and West Greenland living on traditional Inuit food and imported food items.

		Ethnicity			P^a
		Inuit	Mix	Non-Inuit	
		n	*n*	*n*	
Gender	Men	229	5	75	
	Women	205	2	19	<0.001
Age	50–59	259	6	79	
	60–69	175	1	15	<0.001
Smoking	Never	56	1	25	
	Past	49	1	17	
	Present	328	5	52	0.002
Alcohol[b]	0–7	274	5	51	
	8–14	95	1	24	
	15+	57	1	18	0.45
BMI	<30 kg/m^2	331	7	77	
	>30 kg/m^2	73	0	17	0.46
Diet	Greenlandic	343	5	3	
	Mixed	66	1	13	
	Imported	25	1	78	<0.001
Hunting	Trade	75	2	0	
	Leisure	149	2	37	
	Never	203	3	57	<0.001

[a] Compared using chi-squared test.
[b] Units per week.

3.2. hsCRP

Table 2 details that Inuit had higher hsCRP than non-Inuit in the crude comparison ($p = 0.003$) while this difference disappeared after adjustment for diet and alcohol intake (Table 3). A higher intake of traditional Inuit diet associated with higher hsCRP (Fig. 2, $p < 0.001$) and the levels differed in the crude (Table 2) as well as in the adjusted analysis (Table 3). Similarly, a more frequent intake of foods from their own hunting and catching associated with higher hsCRP (Table 2). An influence of age on hsCRP in the crude analysis (Table 2) disappeared after adjustment for covariates (Table 3). The same applied to BMI with a higher hsCRP in the obese in the crude comparison only (Tables 2 and 3). A higher alcohol intake associated with a lower hsCRP (Table 2). This differed with ethnicity as it was marked in Inuit ($p = 0.001$) while not in non-Inuit ($p = 0.77$). Also, alcohol influenced hsCRP in the adjusted analysis (Table 3).

4. Discussion

This is the first study of the inflammatory marker YKL-40 in Inuit. It comprised 95% of invited Inuit and non-Inuit in selected geographical areas in Greenland in an age group with increased risk of cardiovascular disease. We found both inflammatory markers YKL-40 and hsCRP higher in Inuit compared to non-Inuit although only YKL-40 remained higher in Inuit in the adjusted analysis. Interestingly, YKL-40 and hsCRP increased with higher intakes of traditional Inuit diet after adjusting for ethnicity, gender, age, smoking, alcohol intake and BMI.

Table 2
Serum concentrations of YKL-40 and hsCRP among persons living in the capital Nuuk in West Greenland and rural Ammassalik district in East Greenland.

		n	YKL-40			hsCRP		
			Median	25;75 percentile	*p*[a]	Median	25;75 percentile	*p*[a]
Ethnicity[c]	Inuit	432	124	77;219	<0.001	1.68	1.07;4.06	0.003
	Non-Inuit	91	59	45;109		1.47	0.91;2.71	
Gender	Men	308	103	64;188	ns	1.68	1.07;3.63	ns
	Women	222	121	69;213		1.58	1.02;3.80	
	Inuit men	228	120	77;220	ns	1.68	1.04;4.00	ns
	Inuit women	204	127	77;217		1.49	0.90;3.62	
Age	50–59 years	340	97	59;182	<0.001	1.49	1.00;3.17	<0.001
	60–69 years	190	129	79;245		1.95	1.15;5.02	
Smoking	Never	81	74	51;150	<0.001	1.36	0.86;4.02	ns
	Past	66	103	62;175	0.07[b]	1.62	0.99;4.84	
	Present	382	121	76;219	ns[b]	1.68	1.07;3.49	
Alcohol[d]	0–7	326	107	62;203	0.019	1.79	1.07;4.38	0.004
	8–14	120	97	64;170	ns[b]	1.50	0.99;2.45	0.002[b]
	15+	76	154	92;221	0.004[b]	1.42	0.92;2.95	ns[b]
BMI	<30	411	109	66;211	ns	1.51	1.00;3.18	0.039
	>30	89	107	64;166		2.27	1.20;4.84	
Greenlandic diet	80%+	241	129	81;225	<0.001	1.68	1.14;3.92	<0.001
	60–79%	110	133	74;217	ns[b]	1.64	0.91;4.24	ns[b]
	40–59%	78	95	64;196	0.07[b]	1.75	0.99;3.81	ns[b]
	20–39%	61	68	46;128	0.004[b]	1.54	0.82;3.38	ns[b]
	<20%	40	59	45;122	ns[b]	1.41	0.78;2.04	ns[b]
Diet from own catch	Weekly	197	130	79;220	<0.001	1.61	1.04;3.81	0.038
	Monthly	147	111	62;234	ns[b]	2.03	1.17;4.41	ns[b]
	Rarely	179	86	57;164	0.019[b]	1.47	0.93;3.14	0.012[b]
Residence[e]	City	149	94	64;165	<0.001	2.04	0.87;4.91	0.017
	Town	140	151	93;246	<0.001[b]	1.70	1.20;3.76	0.008[b]
	Settlement	143	143	83;239	ns[b]	1.49	0.96;3.91	0.08[b]

p-value less than 5% considered significant.
[a] Overall comparison of groups unless otherwise specified.
[b] Compared with the group above (pairwise comparisons).
[c] Excluding 7 with mixed ethnicity and 5 without serum samples.
[d] Units (of 12 g of alcohol) per week.
[e] Including only Inuit.

YKL-40 and hsCRP are serum biomarkers of inflammation [12] and biomarkers of vascular inflammation have been associated with the severity of atherosclerosis [2]. Hence, the inflammatory marker YKL-40 participates in inflammatory processes, angiogenesis and apoptosis that are important for the risk of ischemic heart diseases [12] and has been linked to cardiovascular mortality [12,14].

The notion that Inuit living on a traditional marine diet had a low occurrence of ischemic heart disease was based on early clinical evidence and uncertain statistics [17]. However, the low occurrence of ischemic heart disease in historic Inuit was confirmed recently [7]. The cause was speculated to be a high intake of marine food items from local hunt rich in n-3 fatty acids [11]. This has led to a host of studies on n-3 fatty acids and cardiovascular morbidity and mortality but the findings are not unequivocal [18]. Moreover, the risk of cardiovascular disease in Greenland Inuit has increased [19] and a different contribution to the previously low occurrence of ischemic heart disease was suggested recently [8]. Hence, the link between Inuit diet and cardiovascular disease may be complex and needs to be detailed.

Table 3
Factors important to YKL-40 and to hsCRP among populations in the capital Nuuk in West Greenland and in rural Ammassalik district in East Greenland in multivariate linear regression model.

	YKL-40[a]		hsCRP[b]	
	Beta	*p*-value	Beta	*p*-value
Ethnicity	−0.18	0.001	−0.06	ns
Gender	0.01	ns	−0.04	ns
Age	0.20	<0.001	0.07	ns
Smoking	0.07	ns	0.02	ns
Alcohol	0.14	0.001	−0.14	0.001
BMI	−0.11	0.007	0.03	ns
Diet	−0.13	0.019	−0.15	0.001

Dependent variables entered were YKL-40 and hsCRP after ln-transformation because they were positively skewed.
Explanatory variables were gender, age, smoking, alcohol intake, BMI, diet and ethnicity.
[a] Model $p < 0.001$; $r^2 = 0.17$.
[b] Model $p < 0.001$; $r^2 = 0.06$.

A high level of n-3 fatty acids suppresses proinflammatory cytokine generation and associates with lower inflammatory activity [4]. This could reduce the risk of inflammatory diseases such as rheumatoid disease, and it may reduce the risk of cardiovascular disease [5,20]. We hypothesised that a high intake of marine diet rich in n-3 fatty acids associated with a low inflammatory activity. Interestingly we found quite the opposite. This unexpected finding was similar for both markers of inflammation even though they are produced and secreted independently.

Diet influenced YKL-40 and hsCRP independently. Our findings suggest that a higher intake of traditional Inuit foods caused higher levels of inflammation. This intriguing finding could be explained by the content of persistent organic pollutants in marine mammals, known to be high in Greenland [21]. These pollutants have been shown to influence the development of inflammatory diseases such as atherosclerosis [22]. Thus, Hennig and colleagues have demonstrated that polychlorinated biphenyls contribute to an inflammatory response in endothelial cells [22]. Such mechanism might contribute to our findings of high levels of YKL-40 and hsCRP with high intake of marine food items. Consequently, it may be speculated that the high levels of persistent organic pollutants have contributed to the increase in cardiovascular disease among Inuit in Greenland demonstrated recently by signs of coronary heart disease in ECG in 13% of the population [19].

Factors important to YKL-40 and hsCRP in serum differed slightly in our study. This may be caused by differences between the two markers of inflammation. YKL-40 is an inflammatory protein [23] that originates from activated cells of the innate immune system [24] whereas CRP is produced mainly by hepatocytes in response to inflammation mediated by for example interleukin-6.

Ethnicity influenced YKL-40 in the adjusted analysis. This is a novel finding. It was present both in the direct comparisons and in the adjusted analysis for YKL-40 while not in the adjusted analysis for hsCRP. This could be explained by a difference in YKL-40 metabolism among Inuit rather than a genetic predisposition to inflammation in Inuit.

The risk of cardiovascular disease is influenced by age, obesity, smoking and alcohol intake. These factors may influence inflammation and thus affect our findings. Advancing age is a major risk factor for inflammatory diseases [25] and we found an influence of age on YKL-40. Obesity is characterised by low-grade inflammation and obese people have higher levels of inflammatory markers in serum [5,12]. Still, YKL-40 was previously found to be elevated only in the morbidly obese [12]. Hence, we found that BMI influenced YKL-40 and not hsCRP in the direct comparison while the opposite was seen when also adjusted for ethnicity and diet. This finding may be explained by differences in body build between Inuit and non-Inuit [26] or may be contributed by the traditional Inuit diet. The difference in body build may contribute to BMI being a poor descriptor of central obesity in Inuit [27] and YKL-40 associated with measures of central obesity in another ethnic group with type-2 diabetes [28]. Still, BMI associated with lipids in serum and supported the importance of ethnicity [29].

Smoking influences the inflammatory response [30] and YKL-40 is elevated in patients with chronic obstructive pulmonary disease [31]. Consistent with this we found a gradual increase in YKL-40 from never to past to present smokers. Alcohol influences YKL-40 mainly via fibrosis of the liver [32], but fibrosis has not been demonstrated in Inuit [33,34]. We found a higher level of YKL-40 in the group with the highest alcohol intake and lower levels of hsCRP. This corresponds to a low level of inflammation in the liver among Inuit. Thus, in accordance with previous studies, elevated YKL-40 levels were seen in heavy alcohol consumers, smokers and in old age. Furthermore, it associated negatively with BMI.

Our study included only 1% of the population of Greenland and was restricted to two areas in Greenland. However, it was strengthened by a very high participation rate. Smoking habits and alcohol intake were evaluated by questionnaires. Inuit do not conceal these habits, which decreases the bias in reporting. The validity of the dietary assessment was strengthened by the comprehensive dietary food frequency questionnaire and cross-check questions as evaluated previously [9,10].

Markers of inflammation predict vascular risk [12–16]. Still, the causal link between inflammation and cardiovascular disease remains to be confirmed and markers of inflammation may be speculated to reflect the disease rather than the cause of the disease. YKL-40 and hsCRP increased with higher intakes of traditional Inuit diet after adjusting for ethnicity, gender, age, smoking, alcohol and BMI. Hence, our data may support that the disease process itself causes the high levels of markers of inflammation in cardiovascular disease.

Contributions by the individual authors

LHS: conception of idea, analysis of data and writing of the manuscript.

HV: conception of idea, analysis of data and reviewing of the manuscript.

PL: conception of idea, data collection, analysis of data and reviewing of the manuscript.

CNR: conception of idea, analysis of data and reviewing of the manuscript.

SA: conception of idea, data collection, analysis of data and writing of the manuscript.

Disclosures

There are no conflicts of interest.

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