

# Heart rate is associated with markers of fatty acid desaturation: the GOCADAN study

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**Objectives:** To determine if heart rate (HR) is associated with desaturation indexes as HR is associated with arrhythmia and sudden death.

**Study design:** A community based cross-sectional study of 1214 Alaskan Inuit.

**Methods:** Data of FA concentrations from plasma and red blood cell membranes from those  $\geq 35$  years of age ( $n = 819$ ) were compared to basal HR at the time of examination. Multiple linear regression with backward stepwise selection was employed to analyze the effect of the desaturase indexes on HR, after adjustment for relevant covariates.

**Results:** The  $\Delta^5$  desaturase index ( $\Delta^5$ -DI) measured in serum has recently been associated with a protective role for cardiovascular disease. This index measured here in plasma and red blood cells showed a negative correlation with HR. The plasma stearoyl-CoA-desaturase (SCD) index, previously determined to be related to cardiovascular disease (CVD) mortality, on the other hand, was positively associated with HR, while the  $\Delta^6$  desaturase index ( $\Delta^6$ -DI) had no significant effect on HR.

**Conclusion:** Endogenous FA desaturation is associated with HR and thereby, in the case of SCD, possibly with arrhythmia and sudden death, which would at least partially explain the previously observed association between cardiovascular mortality and desaturase activity.

**Keywords:** *Inuit; diet; fatty acid metabolism; CVD risk factors.*

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Growing interest in the role of diet in cardiovascular disease (CVD) has recently led to research showing relationships between consumption of a variety of specific fatty acids (FAs) that associate differently with CVD and associated risk factors. For example, presence of plaque is not inversely associated with consumption of fish oil omega-3 fatty acids ( $\omega$ -3 FAs) in Inuit as previously thought (1), but is positively associated with palmitic (16:0) and stearic (18:0) acid intake (2). The cardioprotective affect from  $\omega$ -3 FAs observed in several longitudinal studies (3–6) appears

therefore not to be associated with plaque, but with decreased risk of arrhythmia (7) and improved plaque stability (8). A recent 20-year prospective study of 2,000 Swedish men has recently shown an association between desaturase indexes, as specific markers of fatty acid synthesis, and cardiovascular mortality (9). Since HR is associated with arrhythmia and sudden death (3,4), we are here testing the hypothesis that the same desaturase indexes are associated with HR.

The Inuit participants in the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study

(10,11) are an advantageous population in which to undertake this analysis because it is currently undergoing a forced acculturation involving decreased utilization of traditional foods and a variable shift among community members to a diet containing more saturated and *trans* fats (2,12). This allows the study of the effects of a wide range of dietary intakes on health.

The objective of this study was to determine if HR, a risk factor for arrhythmia and sudden death (3,4), is affected by the fatty acid desaturases that are related to cardiovascular mortality (9).

## Material and methods

### Study population

A total of 1,214 predominantly Inupiat Inuit (men and women) >17 years of age from 9 villages in the Norton Sound Region of Alaska were examined in 2000–2004 for CVD and associated risk factors as part of the GOCADAN study (10). In 7 of the 9 villages, an average of 82.6% of the eligible residents participated (11). Screenings were terminated early in an additional village, when it was determined that the village was not able to support the data collection due to absent villagers for the fishing season, and in Nome when the study reached its total recruitment goal. From the sample of 1,214 participants, those ≥35 years of age with available HR and red cell and plasma FA measurements (361 men and 458 women) were included in the present analysis to allow a comparison with the same age group as in previous studies (2,13).

### Study examination

The GOCADAN exam (10) consisted of a personal interview (including medical history and medication use), physical examination including ultrasound assessment of atherosclerosis in the carotid artery system, blood pressure measurements, ECG and a Rose questionnaire, blood sampling and a nutritional interview using a validated food frequency questionnaire (FFQ; 12). Energy expenditure was estimated by metabolic equivalents.

### Blood pressure measurements

Following a 5-minute rest, sitting blood pressure was measured on the right brachial artery 3 times with a Baum mercury sphygmomanometer (10; W. A. Baum, Copiague, NY, USA), with the mean of the 2nd and 3rd measurements used for analysis.

### Heart rate measurement

Heart rate was measured from computerized ECGs performed using a GE Systems MAC 1200 electrocardiograph. Heart rate was calculated from the mean interval between QRS complexes over a period of 10 seconds.

### Fatty acid analyses

The method for total plasma fatty acids has been described elsewhere (14). Recent modifications are noted: methanol is used instead of ethanol, the internal standard is now C21, a standard mix was added (Supelco 37; a standard with 37 FAME of known mass) and 20% of the samples were run by mass spectrometry for compound conformation. The method for red blood cell fatty acid composition has also been described elsewhere (15).

### Fatty acid desaturation indexes

We have examined the association between HR and the activity indexes of the fatty acid desaturases previously shown to be related to cardiovascular mortality in Swedish men (9). These enzymes, the stearoyl-CoA-desaturase (SCD),  $\Delta^6$  desaturase (D6D) and  $\Delta^5$  desaturase (D5D) relate to specific enzymatic activity, partly dependent on consumption of specific FAs. The estimates of FA composition and desaturase indices reflect not only endogenous metabolism and diet, but genetic variation which affects the regulation of the desaturase activity as estimated by the desaturase indices (9). The desaturase indexes were calculated as follows from FA concentrations (9) in plasma and red blood cells (RBC):

$$SCD = \frac{16 : 1}{16 : 0} \cdot \Delta^5 \text{ desaturase} = \frac{20 : 4\omega 6}{20 : 3\omega 6} \cdot \Delta^6 = \frac{18 : 3\omega 6}{18 : 2\omega 6}$$

### Statistical analysis

The statistical analysis was defined a priori and carried out with SPSS (version 15.0; Statistical Package for the Social Sciences). Comparison between sexes was made with Student t-test corrected by variances. Variables with right skewed distributions were  $\log_{10}$  transformed.

Pearson product-moment correlation was used to compare desaturase indexes between plasma and red blood cells. Multiple linear regression with backward stepwise was employed to analyze the effect of the desaturase indexes adjusted by age, sex, BMI, waist, HOMA, Mets of physical activity, hypolipidemic medication, glucose intolerance, and diabetes. Variables with p value greater than 0.10 were dropped from the model.

## Results

We included the 458 females and 361 males ≥35 years of age. Table I shows differences by gender. Women had higher BMI, HR, triglycerides, plasma insulin, HOMA index, HDL-cholesterol, plasma SCD index, and  $\Delta^6$  desaturase index ( $\Delta^6$ -DI), but lower diastolic BP, and Mets than men.

### Correlation between plasma and RBC fatty acids

The  $\Delta^5$  desaturase index ( $\Delta^5$ -DI) from plasma FAs was highly correlated with the RBC index ( $r = 0.61$ ,  $p < 0.001$ ) with no comparable correlation with

**Table I.** Comparison of general phenotypes between sexes in Alaskan Inuit

	Female			Male			p-value
	n	Mean	CI 95%	n	Mean	CI 95%	
Systolic BP	458	120.51	(119, 122)	360	122.14	(121, 124)	0.13
Diastolic BP	459	75.32	(74, 76)	361	78.54	(77, 80)	<0.001
BMI	458	28.62	(28, 29)	358	26.67	(26, 27)	<0.001
Age (years)	460	51.36	(50, 53)	364	50.38	(49, 52)	0.249
HOMA Index	440	2.15	(2, 2.3)	348	1.73	(1.6, 1.87)	<0.001
Waist	450	35.11	(34.6, 35.6)	351	34.89	(34.4, 35.4)	0.544
Waist/hip ratio	448	0.85	(0.84, 0.86)	351	0.88	(0.88, 0.89)	<0.001
Hdl-C mg/dL	439	66.36	(64.6, 68.1)	350	57.52	(55.5, 59.5)	<0.001
Ldl-C mg/dL	439	121.83	(118, 125)	350	123.38	(119, 127)	0.546
Triglyceride mg/dL	439	118.65	(113, 124)	350	111.49	(105, 117)	0.07
Glucose mg/dL	441	95.41	(94, 97)	350	95.03	(93, 97)	0.722
Insulin uU/mL	440	9.14	(8.7, 9.6)	348	7.37	(6.8, 7.9)	<0.001
Heart rate (beats/min)	460	73.81	(72.8, 74.8)	362	71.18	(69.8, 72.5)	0.002
Mets	311	4.26	(4.0, 4.5)	260	4.87	(4.5, 5.2)	0.004
Plasma SCD index	414	0.6	(0.60, 0.61)	328	0.56	(0.55, 0.57)	<0.001
Plasma D <sup>5</sup> desat index	244	0.81	(0.79, 0.83)	188	0.81	(0.79, 0.83)	0.843
Red cell SCD index	416	0.1	(0.09, 0.10)	330	0.09	(0.09, 0.10)	0.138
Red cell D <sup>6</sup> desat index	416	0.12	(0.11, 0.12)	330	0.11	(0.10, 0.11)	<0.001
Red cell D <sup>5</sup> desat index	416	2.42	(2.38, 2.45)	330	2.43	(2.39, 2.46)	0.677

SCD-DIs. The  $\Delta^5$  DI had the highest correlation, and the explained percentage of the variance between the 2 sources of fatty acids was 37%.

The correlation coefficients for desaturases with other phenotypes can be seen in Table II. Age was the only variable with statistical significant positive correlation with all desaturase indexes, but was negative for RBC  $\Delta^6$  desaturase.

#### Effects of $\Delta^5$ -DI on the studied phenotypes

The  $\Delta^5$ -DI, measured in serum, had been associated with a protective roll for cardiovascular disease (9). This index measured in plasma and red blood cells showed a negative correlation with HR. This association remained significant after adjustment for gender, age, BMI, waist, HOMA, hypolipemic medication, glucose intolerance, diabetes, and Mets of physical activity (Table III).

In addition, the plasma desaturase index, but not the RBC desaturase indexes, was associated with C-reactive protein (Table II). The RBC desaturase index showed an inverse association with BMI, waist circumference, diastolic BP and triglycerides concentration. Interestingly, LDL cholesterol was positively associated with both the plasma and the RBC desaturase indexes.

#### Effects of SCD and $\Delta^6$ -DI on the studied phenotypes

The plasma SCD index (SCD-DI) was positively associated with HR; moreover, the adjusted linear regression model showed that both measurements from plasma and red blood cells, had significant associations with HR, but

in the opposite directions. The  $\Delta^6$  DI had no significant association with HR (Table III).

Other phenotypes were positively associated with SCD (systolic BP), and with  $\Delta^6$  desaturase (waist circumference, HOMA index, and triglycerides).

### Discussion

A longitudinal study of Swedish men (9) has recently shown that 3 enzymes related to fatty acid metabolism are associated with cardiovascular mortality. Positive associations of cardiovascular mortality with activity indexes of stearoyl-CoA-desaturase (SCD) and D6D and a negative association with D5D implicates, for the first time, that these enzymes as potential factors in cardiovascular mortality. Since the activity indexes for SCD and D5D are associated with higher and lower HR, respectively, the data presented here suggests that these 2 desaturases influence HR, which is known to be associated with arrhythmia and sudden death. The GOCADAN study results thus identify specific enzymes affecting HR, a potential contributor to cardiovascular mortality.

These desaturases catalyze the endogenous synthesis of long-chain FAs, which mediate and modulate metabolic functions and physical properties of the cell (16,17). The measures of activity indexes, derived from ratios of the relative proportion of individual FAs, reflect metabolic changes of specific FAs that are not only known to be associated with cardiovascular risk factors, but have been related to metabolic diseases and coronary heart disease

**Table II.** Correlations (p-values) between the desaturases and biological variables associated with CVD in Alaskan Inuit

Variables	Plasm $\Delta^5$	Plasm SCD	Rbc SCD	Rbc $\Delta^6$	Rbc $\Delta^5$
Age (years)	0.122*	0.168*	0.127*	-0.102*	0.243*
	-0.011	(<0.001)	-0.001	-0.005	(<0.001)
BMI	0.076	0.041	-0.042	0.246*	-0.131*
	-0.116	-0.272	-0.253	(<0.001)	(<0.001)
Waist circumference (cm)	0.123*	0.027	-0.061	0.227*	-0.087*
	-0.011	-0.472	-0.099	(<0.001)	-0.019
Waist/hip ratio	0.083	0.031	-0.089*	0.085*	-0.028
	-0.087	-0.409	-0.016	-0.021	-0.446
Diastolic BP (mmHg)	-0.092	-0.023	-0.033	0.057	-0.147*
	-0.056	-0.541	-0.37	-0.117	(<0.001)
Systolic BP (mmHg)	-0.061	0.112*	-0.06	0.049	-0.011
	-0.209	-0.002	-0.099	-0.184	-0.76
Heart rate (beats/min)	-0.182*	0.232*	-0.014	0.059	-0.176*
	(<0.001)	(<0.001)	-0.711	-0.106	(<0.001)
HOMA (Log <sub>10</sub> )	0.028	0.059	-0.015	0.196*	-0.051
	-0.557	-0.111	-0.681	0	-0.161
HDL-cholesterol (mg/dL)	0.048	0.099*	-0.042	-0.07	0.05
	-0.318	-0.007	-0.257	-0.055	-0.172
C-reactive protein	-0.107*	0.088*	0.01	-0.003	0.063
	-0.027	-0.017	-0.795	-0.937	-0.084
LDL-cholesterol (mg/dL)	0.159*	-0.064	0.113*	-0.104*	0.118*
	-0.001	-0.084	-0.002	-0.004	-0.001
Triglycerides (Log <sub>10</sub> mg/dL)	-0.075	0.071	-0.115*	0.400*	-0.275*
	-0.121	-0.052	-0.002	(<0.001)	(<0.001)
Glucose (Log <sub>10</sub> mg/dL)	0.082	0.061	-0.017	0.104*	0.012
	-0.09	-0.098	-0.64	-0.004	-0.754
Mets (Log <sub>10</sub> )	-0.015	-0.007	-0.047	-0.039	-0.041
	-0.789	-0.88	-0.282	-0.365	-0.342

\*p-values lower than 0.05.

(CHD; 18). It is known that estimated SCD activity is independently associated with cardiovascular disease risk factors, including insulin resistance and low grade inflammation (19,20). The present study also showed a variety of associations of desaturase indexes and cardiovascular disease risk factors (Table II). Although the role of estimated desaturase activities in CVD and subsequent mortality is largely unknown (9), our data support the concept that higher HR and subsequent arrhythmia and sudden death may be possible effects of desaturase activity.

Increased saturated fat consumption increases desaturase activity (9,21) and thus contributes to higher HR. It is known that high SCD and D6D indexes and low D5D index can be induced by a diet high in saturated fat compared to a diet rich in unsaturated fat (rapeseed oil; 21). Thus the shift in dietary fat from relatively low to high saturated fat content currently experienced by Inuit (12) appears to result in increased HR via changes in desaturase activity in addition to having the known detrimental associations with increased carotid artery

plaque (2), impaired glucose metabolism (22) and the contributions to the metabolic syndrome (13).

It has been suggested by Warensjö et al. (9) that “desaturases may affect metabolic processes either via their product FAs or by their potential capacity to act as proteins that directly or indirectly interact with signal transducer proteins or transcription factors” (23). What variables affect the product-to-precursor FA ratios are to a great extent unknown. Such variables would have an effect on either the product or the precursor.

The findings reported here on desaturases adds to the growing knowledge of the positive association of FAs related to saturated fat consumption and HR (24) and the finding of an opposite association by fish oil  $\omega$ -3 FAs. To what extent the indexes of desaturation activity reflect consumption of specific FAs is not known at this time, and requires investigation. The principal evidence, so far, has been that dietary saturated FAs increase cardiovascular disease by their effects on blood cholesterol concentrations (25,26) and mechanisms related to insulin resistance, inflammation and endothelial function

**Table III.** Multiple linear regressions for association with heart rate in Alaskan Inuit. All models were adjusted by age, sex, BMI, waist, HOMA, Mets of physical activity, hypolipidemic medication, glucose intolerance (GIT) and diabetes. Backward stepwise selection was used to assess the statistical significance of the variables

Variable	Regression coefficient	SE	Standardized $\beta$	p-value
Plasma $\Delta^5$ desat	-11.34	3.28	-0.19	<0.01
HOMA	3.71	0.9	0.22	<0.01
Gender	-4.21	1.27	-0.18	<0.01
Constant	67.87	1.32		<0.01
Plasma SCD	13.22	3.65	0.16	<0.01
Waist	6.24	3.77	0.08	0.1
Gender	-2.23	1.07	-0.1	0.04
GIT	2.43	1.38	0.08	0.08
Constant	57.78	13.51		<0.01
Red cell $\Delta^5$ desat	-19.21	4.09	-0.2	<0.01
Gender	-3.17	1.02	-0.14	<0.01
GIT	3.3	1.33	0.11	0.01
Constant	89.95	3.66		<0.01
Red cell $\Delta^6$ desat	Dropped from the model			
Waist	6.73	3.8	0.08	0.08
Gender	-3.14	1.04	-0.13	<0.01
GIT	2.8	1.4	0.09	0.05
Constant	49.35	13.43		<0.01
Red cell SCD	-8.17	2.64	-0.14	<0.01
Gender	-3.46	1.03	-0.15	<0.01
GIT	3.06	1.35	0.1	0.02
Constant	54.13	6.16		<0.01

(27,28). The finding here of associations between FA enzyme activity (the indexes) and a number of other known CVD risk factors, including HR, further reveals the importance of FAs and associated enzymes in cardiovascular health and pathology.

### Limitations and strengths

The present cohort represents principally Alaskan Inupiat; these data may not necessarily be representative of other ethnic groups. The strengths of the study are the clear results due to the exceptional genetic and cultural homogeneity of this cohort presently undergoing a forced acculturation involving a dietary shift from “healthy” fats to more saturated fats. This allows the identification of the effect of such shifts on health and related phenotypes. Although generally acceptable, and justified (9,19,20), the use of desaturase indexes to estimate desaturase activity does not account for the dietary contributions specifically and therefore presents a potential error in the estimate of desaturase activity which is very difficult to measure. Additional studies are required to ascertain to what extent the diet by itself, affect the estimates of desaturase activity if one uses the now acceptable indexes. The estimates of desaturase indexes used in this study were obtained from total FA concentrations of plasma and phospholipids concentrations of RBC membranes,

whereas the indexes related to cardiovascular mortality (9) were obtained from serum cholesteryl esters. To what extent such different measures correlate with one another and with dietary intake is not known and requires further studies. Nevertheless, all 3 types of estimate show similar, but slightly different associations. At this point the measures appear to provide associations that partially explain the results of the Swedish study.

### Conclusion

The present study suggests that endogenous FA desaturation, partly dependent on diet, is associated with HR and thereby, in the case of SCD, possibly with arrhythmia and sudden death which would at least partially explain the parallel association between cardiovascular mortality and desaturase activity indexes observed in Swedish men (9).

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