Journal of Internal Medicine 2001; **249**: 553–558

Large differences in serum leptin levels between nonwesternized and westernized populations: the Kitava study

S. LINDEBERG[1], S. SÖDERBERG[2], B. AHRÉN[3] & T. OLSSON[2]
From the [1]Department of Community Medicine, Lund University, [2]Department of Medicine, Umeå University, and [3]Department of Medicine, Lund University, Malmö; Sweden

Abstract. Lindeberg S, Söderberg S, Ahrén B, Olsson T (Lund University; and Umeå University, Malmö, Sweden). Large differences in serum leptin levels between nonwesternized and westernized populations: the Kitava study. *J Intern Med* 2001; **249:** 553–558.

Objectives. To compare serum leptin between nonwesternized and westernized populations.
Setting. (i) The tropical island of Kitava, Trobriand Islands, Papua New Guinea and (ii) the Northern Sweden MONICA study population.
Design. Cross-sectional survey.
Methods. Fasting levels of serum leptin were analysed in 163 randomly selected Kitavans aged 20–86 years and in 224 Swedes aged 25–74.
Main outcome measures. Mean and determinants of serum leptin.
Results. Geometric mean of serum leptin in Kitavan males and females were 1.5 and 4.0 vs. 4.9 and 13.8 ng mL^{-1} in Swedish male and females ($P < 0.0001$ for both sexes). In Kitavans, observed geometric mean were close to predicted levels (1.8 ng mL^{-1} for males and 4.5 ng mL^{-1} for females) based on multiple linear regression equations including body mass index (BMI), triceps skinfolds (TSF) and age from the Swedish population-based sample. In Kitavans serum leptin was positively related to TSF amongst both sexes and, amongst females, to BMI. In Kitavans leptin was not related to fasting serum insulin. TSF explained 55% of the variation of leptin amongst females. There was a slight age-related increase of leptin amongst males. In Kitava leptin was not related to fasting serum insulin which was substantially lower than in Sweden.
Conclusion. The low concentrations of serum leptin amongst Kitavans probably relates to the absence of overweight and hyperinsulinaemia. At a population level serum leptin can apparently be predicted from simple measures of adiposity.

Keywords: diet, epidemiology, humans, leptin, obesity, Papua New Guinea.

Introduction

Leptin is produced in adipocytes and has been shown to suppress appetite and increase energy expenditure with resulting reduction of adiposity and weight loss in animals [1, 2]. In some western populations high leptin is related to increased fat mass [3] and to high circulating levels of insulin, blood pressure and plasminogen activator inhibitor-1 activity [4]. Other studies did not find leptin to be increased in insulin resistant individuals [5]. Recently, hyperleptinaemia was shown to be associated with an increased risk of cardiovascular disease in a Caucasian population [6]. Leptin may, therefore, be involved in the different characteristics of the insulin resistant syndrome. It is not known, however, whether different leptin levels can explain the variations of body weight and insulin sensitivity between different populations.

The subsistence horticulturalists of Kitava, Trobriand Islands, Papua New Guinea are practically uninfluenced by western dietary habits and staple foods are tubers, fruit, fish, coconut and vegetables. A moderately high level of physical activity is another characteristic feature [7, 8]. The population is free from overweight and, apparently, from hypertension, cardiovascular disease and malnutrition [9, 10]. Interestingly, the Kitavans have low fasting serum insulin concentrations which do not increase with age [8], and also low plasma plasminogen activator inhibitor-1 activity levels [11], which altogether suggests high and intact insulin sensitivity throughout life in this very lean population. This would be associated with low leptin levels as insulin is known to increase the expression of leptin [2]. In this study, we therefore analysed leptin levels in the Kitava population.

Our hypothesis was that the absence of abdominal obesity and other markers of insulin resistance in Kitava would be accompanied by low levels of serum leptin.

Methods

The survey was given ethical approval by the National Medical Research Advisory Committee of Papua New Guinea. It was approved by other national and provincial bodies and at the community level by the inhabitants and their chiefs. From a total population of 2300 Kitavans, all subjects older than 50 years ($n = 206$) and 20% of those aged 20–49 ($n = 41$) were eligible. Informed consent was obtained through personal contact. Ages were calculated from known historical events and were considered accurate to within 3 years for most subjects. The acceptance rate for serum sampling was only 42% and, therefore, self-selected subjects below 50 years were included. These consisted of persons excluded by the random generator but willing to take part. Individual subjects did not receive payment for their participation. Serum samples from 120 male- and 43 female-subjects aged 20–86 years, 30% of which were self-selected subjects below 50 years, were thus available for leptin analysis.

A random subsample of 224 subjects aged 25–74 from the population-based Northern Sweden MONICA study served as controls [4]. In both populations blood samples were taken before 9.00 a.m., after 9–15 hours of fasting. Blood was centrifuged and serum was frozen in liquid nitrogen within 60 min. Serum samples were stored in −70°C until analysis.

Serum leptin analysis was performed in the same laboratory for the two populations using a double-antibody radioimmunoassay (RIA) with rabbit antihuman leptin antibodies, 125I-labelled human leptin as tracer and human leptin as standard (Linco Res., St Louis, MO, USA). Serum insulin was determined by radioimmunoassay (Phadeseph Insulin RIA; Pharmacia Diagnostics, Uppsala, Sweden) in the same laboratory for the two populations. Standard methods were used for measurements of sitting blood pressure, weight, standing height, waist circumference, triceps skinfold (TSF) thickness and mid-arm circumference. Clinical characteristics of the two study populations are presented in Table 1.

Kitavan dietary habits were investigated by use of diet history, weighing of ready-to-eat foods and sharing of food habits by one of the authors (SL) who lived with the people for 7 weeks [7], during which time patterns of physical activity were observed and supplemented with nonsystematic interviews.

Tubers (yam, sweet potato, taro and maniok), fruit, fish and coconut were dietary staples with a negligible intake of western foods like margarine, oil, milk products, cereals and refined sugar.

The level of physical activity of Kitavan males was roughly estimated at 1.7 multiples of basal metabolic rate (BMR). BMR multiples for westerners with

Table 1 Clinical characteristics (mean ± SD) of the study populations

	Kitava	Sweden	P
Males	(n = 120)	(n = 107)	
Age (years)	49 ± 18	52 ± 15	0.2
BMI (kg m^{-2})	20 ± 2	26 ± 3	0.0001
TSF (mm)	7 ± 2	14 ± 6	0.0001
Waist (cm)/height (m)	46 ± 2	53 ± 6	0.0001
Systolic BP (mmHg)	116 ± 15	132 ± 20	0.0001
Diastolic BP (mmHg)	70 ± 6	82 ± 11	0.0001
Serum insulin (IU mL^{-1})	4.0 ± 2.9	8.3 ± 7.0	0.0001
Smoking rates (%)	76	16	0.0001
Females	(n = 43)	(n = 117)	
Age (years)	52 ± 16	48 ± 14	0.2
BMI (kg m^{-2})	18 ± 2	25 ± 5	0.0001
TSF (mm)	10.5 ± 3.8	22.4 ± 7.8	0.0001
Waist (cm)/height (m)	46 ± 4	51 ± 8	0.0001
Systolic BP (mmHg)	120 ± 18	128 ± 24	0.046
Diastolic BP (mmHg)	71 ± 7	79 ± 11	0.0001
Serum insulin (IU mL^{-1})	4.8 ± 4.7	7.8 ± 4.9	0.0001
Smoking rates (%)	76	24	0.002

TSF: triceps skinfold thickness; BMI: body mass index; BP: blood pressure; sitting BP in Kitavans and supine BP in Swedish subjects.

low occupational activity level who are nonactive at leisure time is 1.4 for both sexes, whilst moderately active persons at work as well as during leisure time is 1.7 for males and 1.6 for females [12]. Median BMR as predicted from weight at age 18–30 was 5.5 MJ day^{-1} in males and 4.9 MJ day^{-1} in females. For 18–30-year-old Kitavan males the estimated energy expenditure was 9.4 MJ, whilst their estimated total daily calorie intake from diet history was 9.2 MJ.

Three out of four Kitavan males and females were daily smokers and the rest were nonsmokers. The difference in TSF and serum lipoproteins and apolipoproteins between smokers and nonsmokers was of the same magnitude as in western populations [10]. Estimated life expectancy was 45 years at birth and an additional 25 years or more thereafter. Major causes of death were infections, trauma and complications of pregnancy whilst atherothrombotic disorders were absent or rare [9].

Continuous variables were checked for normality by use of normal probability plots [13]. After logarithmic transformation serum leptin showed near normal distribution. Geometric mean of leptin (the antilog of the mean of log leptin) were calculated. Group mean and distributions of log-leptin were compared by use of the two sample *t*-test. $P < 0.05$ was chosen for statistical significance. Simple and forward stepwise multiple linear regressions were applied with log-leptin as dependent variable.

Results

At all ages, fasting serum leptin concentrations were markedly lower in Kitavans than in Swedish subjects (Figs 1 and 2; Table 2). Nearly all of this difference was explained by measures of adiposity. In Swedish males and females, body mass index (BMI) and TSF were each positively and independently associated with leptin (Table 3). When Kitavan levels of age, BMI and TSF were entered into the Swedish regression equations, the predicted geometric mean of leptin for Kitavan males and females were, respectively, 1.8 and 4.5 ng mL^{-1}, close to the observed geometric mean of 1.5 and 4.0 ng mL^{-1}. In Swedish males and females the observed geometric mean of leptin were 4.9 and 13.8 ng mL^{-1}. After adjustment for age, BMI and TSF the difference in leptin between Sweden and Kitava was still statistically significant in males ($P < 0.0001$) but not in

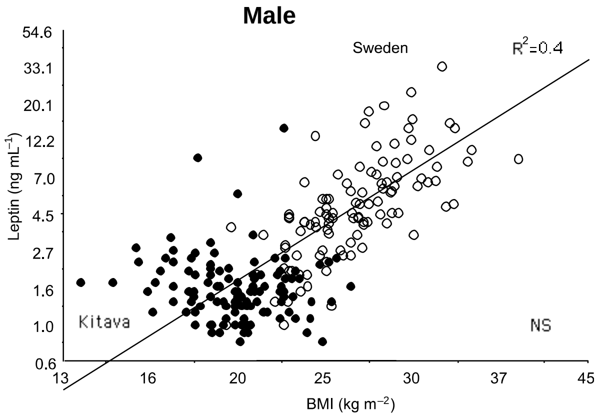

Fig. 1 Serum leptin versus body mass index (BMI) in males from Kitava and Sweden. Note the log scales.

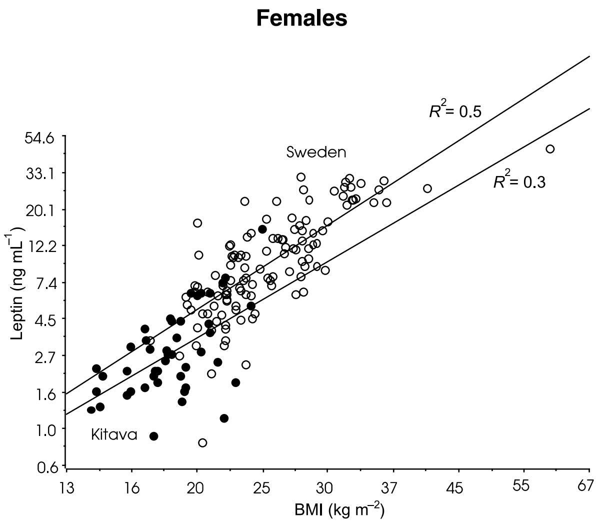

Fig. 2 Serum leptin versus body mass index (BMI) in females from Kitava and Sweden. Note the log scales.

Table 2 Geometric mean (interquartile ranges) of serum leptin (ng mL^{-1}) in males and females from the Kitavan and Northern Sweden MONICA populations

Age (years)	Kitava	*n*	Sweden	*n*	*P*
Males					
<40	1.4 (1.1–1.7)	42	3.4 (2.2–4.5)	29	<0.0001
40–59	1.5 (1.3–1.8)	39	5.2 (3.8–7.0)	38	<0.0001
≥60	1.7 (1.3–2.4)	39	6.3 (4.2–10.0)	40	<0.0001
Females					
≥40	5.7 (3.3–8.8)	11	11.3 (7.1–16.0)	33	<0.0001
40–59	3.2 (2.0–3.9)	18	13.2 (8.6–21.7)	54	<0.0001
≥60	3.9 (2.7–5.7)	14	18.8 (12.5–41.6)	30	<0.0001

females ($P = 0.7$). BMI was identical in smoking and nonsmoking Kitavans.

Serum leptin was strongly and independently associated with TSF in Kitavans of both sexes (Tables 3 and 4). In multivariate analysis of the total Kitavan study group, most of the sex difference of leptin was explained by TSF (Table 3). Leptin levels were 25% lower in Kitavan males who were smokers compared with nonsmokers ($P = 0.1$), but this difference disappeared after adjustment for TSF.

In Kitavans, leptin was not related to fasting serum insulin (Tables 3 and 4) which was substantially lower than in Sweden [8]. Leptin increased with age in Kitavan males ($P < 0.0001$) even after adjustment for TSF which was not age-related. In Kitavan females, a nonsignificant negative relation between leptin and age ($r = -0.20$; $P = 0.2$) disappeared after adjustment for TSF.

Table 3 Variables independently related to serum leptin in the two populations[a]

	Independent variables	Std β in final step	Cumulative adj R^2 (%)
All Kitavans	TSF	0.73***	54
	Sex	0.41***	65
	Age	0.11*	66
All Swedes	TSF	0.31***	51
	Insulin	0.22***	64
	Sex	0.46***	71
	BMI	0.33***	77
	Glucose	0.08*	77
Kitavan males	Age	0.36***	13
	TSF	0.36***	26
Kitavan females	TSF	0.75***	57
Swedish males	BMI	0.69***	48
	TSF	0.26***	53
	Age	0.23***	58
Swedish females	BMI	0.76***	58
	TSF	0.35***	66

[a] Significant ($P < 0.05$) independent variables, standardized regression coefficients (std β) and cumulative adjusted R squared (adj R^2) in stepwise multiple linear regression analysis including age, log BMI and log TSF as independent variables and log leptin as dependent variable; *P < 0.05; ***$P < 0.001$.

Discussion

In this study, very low mean serum leptin was noted cross-sectionally amongst the lean Kitavans of Papua New Guinea, amongst whom cardiovascular diseases are absent or rare.

We do not consider our findings hampered by selection bias. The eligible population was homogeneous, and randomized and nonattending subjects did not differ by appearance in body composition, agility or level of physical activity. In addition, none of the measured variables differed between randomized and self-selected subjects.

The Kitavans are unusual amongst traditional populations of today because of food surplus in combination with a negligible influence of western diet. They are also unique in their leanness: for

Table 4 Pearson correlation coefficients for the analysed variables in the Kitavan population

	Leptin	Age	BMI	TSF	MAC	Waist	Insulin
Males							
Age	0.38***	1					
BMI		−0.58***	1				
TSF	0.35***		0.25**		1		
MAC	−0.22*	−0.60***	0.79***	0.28**	1		
Waist			0.58***	0.37***	0.54***	1	
Insulin		−0.20*	0.22*		0.28**	0.21*	1
Glucose	0.29**						0.27**
Females							
Age	1						
BMI	0.62***	−0.44**		1			
TSF	0.76***		0.71***		1		
MAC	0.60***		0.78***	0.72***		1	
Waist	0.64***			0.67***	0.63***	0.64***	1
Insulin						0.34*	1
Glucose							

Only statistically significant ($P < 0.05$) correlations are shown. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

comparison, in the Tokelau Island Migrant study the mean BMI was 27 amongst 40-year-old nonmigrant males [14], compared with only 22 in Kitavans of the same age, suggesting a markedly different lifestyle in Tokelau. Similarly, a group of allegedly traditional Mexican Pima Indians recently studied regarding serum leptin had a mean BMI of 25 (equal to the 99th percentile in Kitava), a diabetes prevalence of 7% [15] and a regular intake of sugar, refined cereals and milk [16]. The difference in leptin between these relatively traditional Mexican Pimas and a group of US Pimas with a North American lifestyle (mean BMI 34) [15] was of the same magnitude as that between Kitava and Northern Sweden.

Compared with populations of northern European ancestry, traditional ethnic groups in general and Pacific Islanders in particular seem more prone, not less, to develop obesity after adopting a western lifestyle [17]. Obesity and diabetes are increasingly common amongst urbanized Melanesian populations of Papua new Guinea [17, 18] and our own preliminary observations of obese Kitavans in the cities suggest that they are no exception, once they become westernized.

Leptin did not correlate with BMI in Kitavan men (Fig. 1), probably because most of the variation of BMI in lean populations like the Kitavans is explained by variation of muscle mass. It has been proposed that TSF is the single best indicator of body fat percentage in females and that BMI is the best indicator in males [19]. This notion agrees with the fact that TSF alone explained 57% of the variation of BMI in Kitavan females but only 8% in Kitavan males (data not shown).

A possible explanation of the positive correlation between leptin and arm circumference in Kitavan females (Table 4) is that arm circumference is largely related to regional fat mass, at least in postmenopausal white women [20]. This notion is further supported by the fact that leptin was not related to arm circumference in Kitavan females after adjustment for TSF (data not shown).

This is the first study to compare serum leptin levels between a truly traditional and a western population. Measures of adiposity explained most of the difference in leptin between Kitavans and the Northern Sweden MONICA population. Our findings support the notion that leptin is a marker for excess adipose tissue with its associated metabolic disorders. The possibility of direct links between hyperleptinaemia and cardiovascular disease remains to be studied further [6, 21]. The apparent absence of coronary heart disease in Kitava may largely be explained by absent obesity, as mirrored by low levels of serum leptin, BMI, diastolic blood pressure, serum insulin and plasma plasminogen activator inhibitor-1.

Acknowledgements

The technical assistance of Lilian Bengtsson is gratefully acknowledged. The study was supported by the Swedish Medical Research Council (14X-6834), Novo nordisk and Albert Påhlsson Foundations, the Swedish Diabetes Association, and the Faculty of Medicine, Lund University.

References

1 Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998; **395**: 763–70.
2 Ahren B, Larsson H, Wilhelmsson C, Nasman B, Olsson T. Regulation of circulating leptin in humans. *Endocrine* 1997; **7**: 1–8.
3 Considine RV, Sinha MK, Heiman ML *et al.* Serum immunoreactive-leptin concentrations in normal-weight and obese humans [see comments]. *N Engl J Med* 1996; **334**: 292–5.
4 Soderberg S, Olsson T, Eliasson M, Johnson O, Ahren B. Plasma leptin levels are associated with abnormal fibrinolysis in men and postmenopausal women. *J Intern Med* 1999; **245**: 533–43.
5 Bluher M, Kratzsch J, Paschke R. Plasma levels of tumor necrosis factor-alpha, angiotensin II, growth hormone, and IGF-I are not elevated in insulin-resistant obese individuals with impaired glucose tolerance. *Diabetes Care* 2001; **24**: 328–34.
6 Soderberg S, Ahren B, Jansson JH *et al.* Leptin is associated with increased risk of myocardial infarction. *J Intern Med* 1999; **246**: 409–18.
7 Lindeberg S, Vessby B. Fatty acid composition of cholesterol esters and serum tocopherols in Melanesians apparently free from cardiovascular disease – the Kitava study. *Nutr Metab Cardiovasc Dis* 1995; **5**: 45–53.
8 Lindeberg S, Eliasson M, Lindahl B, Ahrén B. Low serum insulin in traditional Pacific Islanders – the Kitava Study. *Metabolism* 1999; **48**: 1216–9.
9 Lindeberg S, Lundh B. Apparent absence of stroke and ischaemic heart disease in a traditional Melanesian island: a clinical study in Kitava. *J Intern Med* 1993; **233**: 269–75.
10 Lindeberg S, Nilsson-Ehle P, Terént A, Vessby B, Scherstén B. Cardiovascular risk factors in a Melanesian population apparently free from stroke and ischaemic heart disease – the Kitava study. *J Intern Med* 1994; **236**: 331–40.
11 Lindeberg S, Berntorp E, Carlsson R, Eliasson M, Marckmann P. Haemostatic variables in Pacific Islanders apparently free from stroke and ischaemic heart disease. *Thromb Haemost* 1997; **77**: 94–8.

12 Department of Health. *Dietary Reference Values for Food, Energy and Nutrients for the United Kingdom*. London: HMSO, 1991.
13 Afifi AA, Clark V. *Computer-Aided Multivariate Analysis*, 2nd edn. New York: Van Nostrand Reinhold Co., 1990.
14 Prior IA, Davidson F, Salmond CE, Czochanska Z. Cholesterol, coconuts, and diet on Polynesian atolls: a natural experiment: the Pukapuka and Tokelau island studies. *Am J Clin Nutr* 1981; **34**: 1552–61.
15 Fox C, Esparza J, Nicolson M *et al.* Plasma leptin concentrations in Pima Indians living in drastically different environments. *Diabetes Care* 1999; **22**: 413–7.
16 Ravussin E, Valencia ME, Esparza J, Bennett PH, Schulz LO. Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care* 1994; **17**: 1067–74.
17 King H. The epidemiology of diabetes mellitus in Papua New Guinea and the Pacific: adverse consequences of natural selection in the face of sociocultural change. In: Attenborough RD, Alpers MP, eds. *Human Biology in Papua New Guinea. The Small Cosmos*. Oxford: Clarendon Press, 1992; 363–72.
18 Sinnett PF, Kevau IH, Tyson D. Social change and the emergence of degenerative cardiovascular disease in Papua New Guinea. In: Attenborough RD, Alpers MP, eds. *Human Biology in Papua New Guinea. The Small Cosmos*. Oxford: Clarendon Press, 1992; 373–86.
19 Cronk CE, Roche AF. Race- and sex-specific reference data for triceps and subscapular skinfolds and weight/stature. *Am J Clin Nutr* 1982; **35**: 347–54.
20 Reid IR, Evans MC, Ames R. Relationships between upper-arm anthropometry and soft-tissue composition in postmenopausal women. *Am J Clin Nutr* 1992; **56**: 463–6.
21 Soderberg S, Ahren B, Stegmayr B *et al.* Leptin is a risk marker for first-ever hemorrhagic stroke in a population-based cohort. *Stroke* 1999; **30**: 328–37.

Received 19 October 2000; revision received 19 March 2001; accepted 20 March 2001.

Correspondence: Staffan Lindeberg, Primary Health Care Centre, S-275 23 Sjöbo, Sweden (e-mail: staffan.lindeberg@smi.mas.lu.se).