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Serum uric acid in traditional Pacific Islanders and in Swedes

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Abstract. Lindeberg S, Cordain L, Råstam L, Ahrén B (Lund University, Lund, Sweden; and Colorado State University, Fort Collins, CO, USA). Serum uric acid in traditional Pacific Islanders and in Swedes. *J Intern Med* 2004; **255**: 373–378.

Background. In some western populations, increased serum uric acid has been positively associated with cardiovascular disease, possibly because hyperuricaemia could be an untoward part of the insulin-resistant metabolic syndrome. However, there is evidence that uric acid is a free radical scavenger capable of inhibiting LDL oxidation. Amongst the traditional horticulturalists of Kitava, Trobriand Islands, Papua New Guinea, cardiovascular disease, hypertension, hyperinsulinaemia and abdominal obesity are absent or rare. In contrast, serum triglycerides are similar to Swedish levels.

Objective. To compare serum uric acid between nonwesternized and westernized populations.

Methods. Fasting levels of serum uric acid were measured cross-sectionally in 171 Kitavans aged

20–86 years and in 244 randomly selected Swedish subjects aged 20–80 years.

Results. There were small differences in serum uric acid between the two populations, although a slight increase with age was found only in Swedish males ($r = 0.20$; $P = 0.03$) and females ($r = 0.36$; $P < 0.0001$). Above 40 years of age, uric acid was approximately 10% lower in Kitavans, a difference which was statistically significant only in males, possibly because of the limited number of females. Regarding hyperuricaemia, two Kitavan males had uric acid above $450 \mu\text{mol L}^{-1}$ whilst none of the females was above $340 \mu\text{mol L}^{-1}$. Amongst the Swedish subjects, five of 117 males and 19 of 127 females had hyperuricaemia according to these definitions.

Conclusion. The rather similar uric acid levels between Kitava and Sweden imply that uric acid is of minor importance to explain the apparent absence of cardiovascular disease in Kitava.

Keywords: diet, epidemiology, humans, insulin resistance, Papua New Guinea, uric acid.

Introduction

The role of uric acid in the development of cardiovascular disease has not been established, although some epidemiological studies have suggested that serum uric acid is an independent cardiovascular risk factor [1, 2], particularly amongst high-risk subgroups [3]. In westernized populations, serum uric acid tends to be higher in subjects with obesity, dyslipidaemia, hypertension or glucose intolerance [4–6]. This raised level of serum uric acid parallel to an increased risk of cardiovascular disease could be either primary or secondary. However, there is some evidence suggesting that the increase is protective because uric acid acts as an endogenous antioxidant

[7, 8]. This circumstance would be beneficial if, for example, oxidative modification of LDL is important in the atherosclerotic process.

Serum uric acid concentrations are highly dependent on endogenous production [9] as well as renal excretion [10]. Both these mechanisms have been suggested as causes of hyperuricaemia in the metabolic syndrome [9, 11].

In our health survey of the people of Kitava, Trobriand Islands, Papua New Guinea, we have found this population free from overweight, hypertension, hyperinsulinaemia, ischaemic heart disease, stroke and malnutrition [12–14]. The influence of imported food is negligible and staple foods are tubers, fruit, coconut, fish and vegetables [15].

Table 1 Clinical characteristics (means \pm SD) of the study populations

	Males			Females		
	Kitava (<i>n</i> = 125)	Sweden (<i>n</i> = 117)	<i>P</i>	Kitava (<i>n</i> = 46)	Sweden (<i>n</i> = 127)	<i>P</i>
Age (years)	48 \pm 19	50 \pm 17	0.4	48 \pm 18	50 \pm 18	0.5
Weight (kg)	52 \pm 7	76 \pm 11	<0.0001	42 \pm 6	65 \pm 12	<0.0001
Height (cm)	161 \pm 7	176 \pm 6	<0.0001	150 \pm 5	163 \pm 6	<0.0001
Body mass index (kg m ⁻²)	20 \pm 2	25 \pm 4	<0.0001	18 \pm 2	24 \pm 5	<0.0001
Systolic blood pressure (mmHg)	116 \pm 15	144 \pm 20	<0.0001	122 \pm 16	147 \pm 27	<0.0001
Diastolic blood pressure (mmHg)	70 \pm 6	87 \pm 9	<0.0001	71 \pm 7	86 \pm 10	<0.0001
S-Cholesterol (mmol L ⁻¹)	4.7 \pm 1.0	5.1 \pm 1.1	0.0003	5.7 \pm 1.3	6.0 \pm 1.2	0.12
HDL-C (mmol L ⁻¹)	1.1 \pm 0.2	1.1 \pm 0.3	0.5	1.3 \pm 0.3	1.2 \pm 0.3	0.7
Triglycerides (mmol L ⁻¹)	1.1 \pm 0.4	1.1 \pm 0.4	0.5	1.3 \pm 0.6	1.1 \pm 0.5	0.052
Insulin (IU mL ⁻¹)	4.0 \pm 2.9	NA		4.8 \pm 4.7	NA	
Leptin (ng mL ⁻¹)	1.6 \pm 0.5	NA		5.0 \pm 4.3	NA	
S-Glucose (mmol L ⁻¹)	3.7 \pm 0.6		NA	3.9 \pm 0.7	NA	
Smokers (%)	77	34	<0.0001	78	24	<0.0001

NA, not available.

Total fat intake in Kitava is very low (roughly 20% of dietary energy, *E*%) and fibre intake is high, but the estimated intake of saturated fat from coconut is similar to that in Sweden (17 *E*%) [15]. Accordingly, serum lipoproteins were not as favourable in Kitava as would be expected from the apparent absence of atherosclerotic heart and brain disease. Considerable overlapping of serum cholesterol were found between Kitava and Sweden, and 40% of Kitavan males and 60% of Kitavan females had LDL cholesterol \geq 3.4 mmol L⁻¹ [13] (Table 1). Furthermore, serum HDL cholesterol (HDL-C) and triglycerides (TG) were similar to Swedish levels.

Based on these collective findings, our aim was to study if there was a difference in serum uric acid levels between Kitavans and Swedish subjects which could contribute to the understanding of the different prevalences of cardiovascular disease. The hypothesis to be tested is the null hypothesis of serum uric acid not being independently related to the risk of cardiovascular disease.

Study populations and methods

The survey in Kitava was given ethical approval by the Medical Research Advisory Committee of Papua New Guinea. The inhabitants and their chiefs also approved it by national and provincial bodies and at the community level. From a total population of 2300 Kitavans, all subjects older than 50 years (*n* = 206) and 20% of those aged 20–49 years (*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 response rate for serum sampling was only 42% and therefore self-selected subjects below 50 years were included. We thus recruited 125 males and 46 females aged 20–86 years, of which 29% were self-selected. Throughout the island, nonattending subjects were systematically screened for visible signs of overweight, disease or sedentism. An age- and gender-matched subsample of 244 Swedish males and females aged 20–80 years, constituting 82% of 296 eligible subjects, served as controls. This Swedish control population was randomly selected from complete population registers [16]. In both populations serum was sampled before 09.00 hours, after 9–15 h of fasting. They were centrifuged within 60 min, immediately frozen in liquid nitrogen and later stored in -70 °C until analysis.

Assays

Serum uric acid was determined by the uricase-peroxidase method [17] at the same laboratory for the two study populations. Conventional methods, validated for precision and accuracy, were used for serum analyses of total cholesterol, HDL-C, TG, apolipoprotein A1, lipoprotein(a), glucose, insulin and leptin, as already described [13, 14, 18, 19]. Measures of muscular content or renal function were not available. Standard methods were also

used for measurements of sitting blood pressure, weight and standing height. 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 Kitavans for 7 weeks [15]. Tubers (yam, sweet potato, taro and manioc), fruit, fish and coconut were dietary staples and the intake of western food was negligible. The estimated proportions of energy derived from total, saturated, monounsaturated and polyunsaturated fatty acids (PUFA) were 21, 17, 2 and 2 E% compared with 37, 16, 16 and 5 E% in Sweden [20]. Median basal metabolic rate as predicted from weight at age 18–30 was 5.5 and 4.9 MJ day⁻¹ in males and females, respectively.

The level of physical activity of Kitavans was roughly estimated at 1.7 multiples of basal metabolic rate. Basal metabolic rate multiples for westerners with 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 [21]. 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 of four Kitavan males and females were daily smokers and the rest were nonsmokers. The difference in serum lipoproteins and apolipoproteins between smokers and nonsmokers was of the same magnitude as in western populations [13]. The prevalence of smokers in the Swedish population was 23% in men and 27% in women. Estimated life expectancy was 45 years at birth and 75 years at age 45. Major causes of death in Kitava were infections, trauma and complications of pregnancy.

Continuous variables were checked for or transformed into apparent normality by use of normal probability plots [22]. Serum uric acid had a skewed distribution, whilst the logarithm of serum uric acid showed a perfect normal distribution in males and females of both study populations. Group comparisons were made by use of the two-sample *t*-test. Simple and forward stepwise multiple linear regressions were applied with log serum uric acid as dependent variable and weight, height and insulin as independent variables. Standardized residuals in

the stepwise regression models were plotted against standard *z* scores in normal plots for final quality control.

Results

There was a slight increase with age of serum uric acid in Swedish males ($r = 0.20$; $P = 0.03$) and females ($r = 0.36$; $P < 0.0001$) but not in Kitavan males ($r = 0.07$; $P = 0.4$) or females ($r = -0.04$; $P = 0.08$) (Fig. 1; Table 2). The age relation in Swedish males, but not in Swedish females, disappeared after adjustment for body mass index (BMI) (data not shown). Amongst 20–39-year-old males and females serum uric acid did not differ between Kitava and Sweden (Table 2). Above 40 years of age, uric acid was approximately 10% lower in Kitavans, a difference which was statistically significant only in males, possibly because of the limited number of females. After adjustment for BMI, none of the age groups differed with regard to serum uric

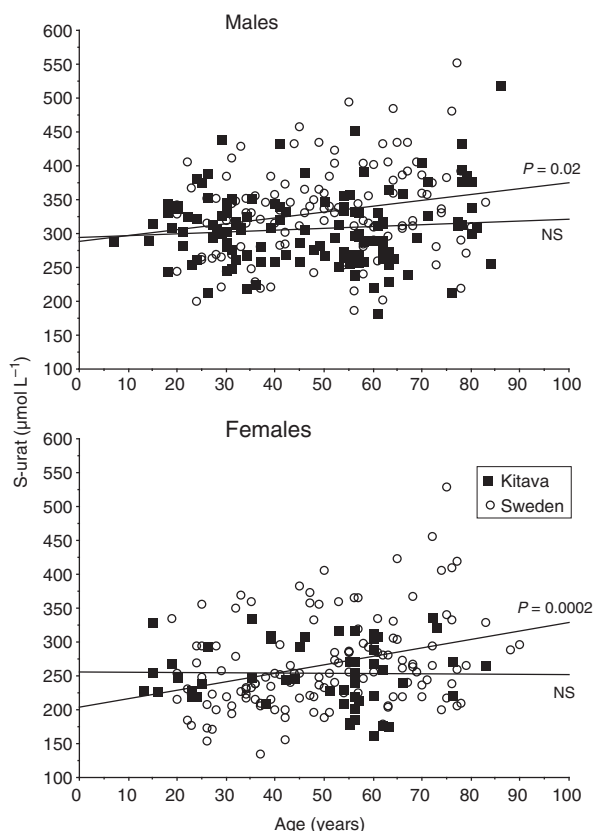


Fig. 1 Serum uric acid in Kitavan and Swedish males and females. NS, not significant.

Table 2 Geometric means (interquartile ranges) of serum uric acid ($\mu\text{mol L}^{-1}$) in males and females from the Kitavan and Swedish populations

Age (years)	Kitava	<i>n</i>	Sweden	<i>n</i>	<i>P</i>
Males					
20–39	301 (277–330)	45	303 (263–351)	37	0.9
40–59	302 (267–335)	41	327 (285–365)	42	0.049
≥60	305 (268–361)	39	343 (296–393)	38	0.019
Females					
20–39	257 (222–303)	11	231 (208–258)	41	0.15
40–59	239 (210–273)	19	262 (225–298)	43	0.12
≥60	253 (221–306)	16	280 (237–330)	43	0.16

acid between Kitava and Sweden. Further adjustment for height did not essentially change the results. Regarding hyperuricaemia, two Kitavan males had uric acid above $450 \mu\text{mol L}^{-1}$ whilst none of the females was above $340 \mu\text{mol L}^{-1}$. Amongst the Swedish subjects, five of 117 males and 19 of 127 females had hyperuricaemia according to these definitions. In the age group 40–65 years, uric acid differed by the same magnitude as the LDL/HDL ratio and there was considerable overlapping between the two populations (Fig. 1).

In Kitavan males, but not in Swedish males or any of the female groups, serum uric acid was negatively associated with standing height ($r = -0.29$; $P = 0.0014$). In Kitavan females, serum uric acid was positively related to serum insulin, which explained 10% of its variation ($r = 0.32$; $P = 0.040$). In forward stepwise regression for Kitavan males and females combined, only gender was independently related to log serum uric acid with Kitavan males having 22% higher levels than females. Amongst Swedish subjects males had 25% higher levels than females.

Discussion

This is the first study comparing mean serum uric acid levels between traditional subsistence horticulturalists and Caucasians. The Kitavans have a low incidence of cardiovascular disease and are thus suitable for comparative studies. They also differ from westernized populations by low levels of insulin and leptin [14, 19]. We found only small differences of uric acid between Kitava and Sweden, although the absent age increase of serum uric acid and the low prevalence of hyperuricaemia in Kitava are noteworthy. We do not consider our findings ham-

pered by selection bias. The eligible Kitavan population is 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 (age-adjusted) serum variables differed between randomized and self-selected subjects. Different selection criteria preclude any strict comparisons, but our methods permit us to exclude any major differences in serum uric acid between Kitava and Sweden.

If hyperuricaemia is an important factor in the insulin-resistant metabolic syndrome, as inferred by previous reports [4–6, 23], it is of relevance that uric acid did not increase with age in Kitavan males or females. Nevertheless, one would, according to that hypothesis, expect uric acid to be still lower in the Kitavans, who had very low levels of diastolic blood pressure, plasma plasminogen activator inhibitor-1 activity and serum glucose, and whose low insulin and leptin could be accurately predicted from their marked leanness and absence of abdominal overweight [14, 19]. However, the slightly unfavourable LDL/HDL ratios and TG levels [13] suggest that the Kitavans are not the ideal ethnic group in studies of the effects of a traditional lifestyle on cardiovascular risk factors. In Kitava, carbohydrate intake is high, almost 70 E% compared with 48 E% in Sweden. Protein intake is 10 E%, which is similar to that in Sweden (12 E%). Fat intake is low, slightly above 20 E%, compared with more than 30 E% in most Caucasian populations. Due to the high intake of coconut, saturated fat intake is around 17 E% which is similar to that in Sweden (16 E%).

It could be argued that the Kitavan high-carbohydrate, low-protein, high-saturated-fat diet is not optimal and that this has some bearing on the slightly unfavourable uric acid, lipoproteins, and systolic blood pressure, findings which were most prominent in the females. It is well known that a high-protein diet lowers TG [24] and is satiating [25], has a three times greater thermic effect than either carbohydrate or fat [26], and promotes weight loss [27], and increasing evidence supports the notion that it may increase insulin sensitivity [28]. Dessein *et al.* showed that increasing protein and unsaturated fat intake whilst restricting carbohydrates markedly decreased uric acid, serum cholesterol, TG, weight and frequency of gouty attacks [23], and similar results were found by Jenkins *et al.* [29]. The old concept of treating hyperuricaemia

with a low purine diet [30] could thus be challenged on these grounds, and it finds no support from the high uric acid in Kitava despite a very low intake of purines.

It is of relevance to the present findings that fractional excretion rate of uric acid is diminished in hypertriglyceridaemic individuals [31] and that dietary changes which lower TG seem to be able to reverse this process [32]. Garbagnati and Boschetti found that the increase of serum uric acid during female puberty was related to decreased renal clearance in lean girls (BMI 16) but not in those who were obese (BMI 26), suggesting enhanced uric acid production in the latter group [33]. Leyva *et al.* proposed a disturbance in the glycolytic pathway as a key factor behind increased uric acid synthesis [9], but their suggestion that it is related to insulin resistance is not supported by our data.

If the notion is correct that uric acid acts as an endogenous antioxidant [34], serum uric acid could possibly be increased in the Kitavans as a reaction to the slightly unfavourable LDL/HDL ratios and TG levels. Rosell *et al.* noted strong positive correlations between serum uric acid and total serum antioxidant capacity (TAOC) at baseline, and between changes in antioxidant capacity and serum uric acid during lifestyle intervention [35]. The fact that glucose, insulin and lipoproteins were unrelated to TAOC in that study suggests that serum uric acid is a more sensitive marker of antioxidant capacity. Uric acid may increase at an early stage before the presence of other markers of insulin resistance, and Selby *et al.* showed that high serum uric acid levels precede the development of hypertension in US adults [36]. This could hypothetically explain the much lower BMI, glucose, insulin and leptin in Kitava than in Sweden despite similar uric acid levels.

In conclusion, it is possible that the Kitavan high-carbohydrate, low-protein, high-saturated-fat diet raises serum lipoproteins enough to cause an elevation of uric acid. Nevertheless, the different rates of cardiovascular disease in Kitava and Sweden are not reflected by serum uric acid. Apparently, uric acid seems to be of minor importance to explain the virtual absence of cardiovascular disease in the Trobriand Islands.

Conflict of interest statement

No conflict of interest was declared.

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