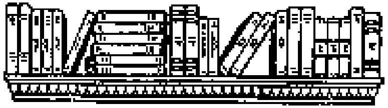

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Age-related patterns of DHEAS among Turkana males of northern Kenya

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Abstract

Dehydroepiandrosterone sulphate (DHEAS) has been widely associated with aging, but little is known about age-related decline of DHEAS in non-western populations. To determine the age-related pattern of DHEAS and its relationship to nutritional status in a subsistence population, we sampled Turkana nomads from northern Kenya. Subjects were 108 nomadic and 90 settled Turkana males, estimated ages 20 to 80+. Measures included blood DHEAS, height, weight, skinfolds, and waist circumference. Overall nomads exhibited less adiposity ($5.7 \pm 1.8\%$ versus $9.0 \pm 3.3\%$ body fat) and higher blood DHEAS levels (5.2 ± 3.3 μM versus 4.1 ± 3.1 μM; $p = 0.03$). Age pattern of DHEAS was curvilinear, peaking in the 30s and 40s. General linear models (GLM) showed that blood DHEAS levels among men over 70 years of age were significantly lower than those in their 30s and 40s. Controlled for age, blood DHEAS was not related to adiposity. These results suggest that DHEAS levels were higher in those individuals who were calorie restricted. In addition, DHEAS levels rose more slowly than described in other populations, peaking in the fourth decade of life.

Keywords: *DHEAS, aging, males, Africa, body composition, pastoral nomads*

Introduction

Dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) are the most common steroids in the human body [1], yet their function remains largely a mystery [2]. DHEAS has effects on a wide variety of physiological systems including neurological [3], immunological [4], and metabolic [5], suggesting that it may play an important role in general health. Furthermore, after the mid-20s DHEAS shows a steady decline with age [6,7], which parallels an increasing incidence of age-related diseases making it of great interest in the study of aging.

Endogenous DHEAS has been associated with a variety of conditions associated with aging including depression [8,9], heart disease [10,11], sexual function [12] and mortality [10,13,14]. However, despite initially promising results [15,16] more recent DHEA supplementation studies in the well elderly have failed to produce compelling results on body composition, physical performance, insulin sensitivity or quality of life [17,18] leading to the question of how important a role DHEA actually plays in normal aging.

In addition to its well-documented decline with age, DHEAS has been related to body composition [19]. In men, serum DHEA and/or DHEAS have been inversely related to BMI [20], body fat [21], and abdominal fat [22]. Among men, central adiposity has been associated with greater decline in DHEA with age [23] indicating that metabolic factors may play an important role in age-related changes in DHEA, and confound the relationship between DHEA and health.

In primates, caloric restriction has been associated with increased circulating DHEA [24], and inversely related to insulin levels [25], directly implicating a role for nutritional status. In humans, DHEAS has also been inversely related to insulin and blood glucose levels in healthy men [26,27]. DHEA administration has also been shown to improve insulin sensitivity in hypoadrenal women [5], though similar results were not obtained in elderly men and women [15].

Yet, despite evidence for a relationship between metabolic status and DHEAS, the impact of reduced caloric intake and low adiposity on age-related changes in DHEAS among non-western populations has received almost no attention. Adrenopause has been shown to occur earlier among high altitude women in Peru compared to their lowland counterparts [28], which may reflect the impact of hypoxia on adrenal function [29]. However, the role of adiposity was not investigated.

Thus we chose to look at the role of nutritional status in age-related changes in DHEAS among Turkana males. The Turkana, pastoral nomads of northern Kenya, exhibit low % body fat [30], low caloric intake [31] and late attainment of adult

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stature [32] indicative of chronic undernutrition. Previous results demonstrate the lack of an age-related decline in blood testosterone (T) [33] among male nomads together with an age profile of decreasing adiposity with age [30], and elevated urinary cortisol [34] suggestive of negative energy balance. In addition, a settled sub-population of Turkana with higher levels of adiposity that increase with age [30] provides a comparison with a better nourished but genetically similar group.

Given the previously demonstrated inverse association of DHEA with both caloric restriction and adiposity, we hypothesized that 1) DHEAS levels among nomadic males will be higher than those among their settled counterparts, and 2) DHEAS will show less of an age-related decline among nomadic males. In addition, we expect differences in DHEAS within both settled and nomadic males to be most directly related to measures of abdominal fat.

Methods

Study site

The Turkana are a subsistence population of pastoral nomads in the Turkana district of northern Kenya, where they depend primarily on animal products, including milk, blood and meat [35]. As with other African pastoralists, caloric intake is limited (estimated caloric intake of <1500 kcal/day), while protein intake is thought to be more than adequate (estimated protein intake $>150\%$ of FAO requirements) [31]. The Turkana are known to have a high rate of hydatid cysts [36] and malaria appears to be widespread [37]. Reports of diarrhoeal disease and acute respiratory infection (ARI) are common and appear to be an important cause of infant mortality [38].

The Turkana are traditionally nomadic, but some Turkana have come to live in settlements, as a result of loss of animals to drought or raiding [39]. The settled men in this study live in Morulem, an agricultural scheme which dates from the 1960s. There is evidence for reduced meat and increased grain consumption, as well as greater exposure to malaria in Morelum relative to the nomads [39]. The altitude of Morelum, at approximately 600 m does not differ from that of the surrounding area by more than 50 m [40]. Thus the settled men share their genealogy, early experience and oxygen content of the air with the nomads, but differ in current diet and disease exposure.

The data presented here were collected in July and August 1992 during a time of drought, with nomads sampled preceding the distribution of food relief, and the settled population sampled in March–April of 1993, 3 months after the food relief became available [41]. Thus differences in nutritional status between the two sub-populations reflect both short-term and long-term conditions.

Subjects

A total of 222 men, 132 nomads and 90 settled men participated in the study. Human subjects clearance was obtained from the UNC institutional review board. Permission to conduct the study was obtained from the Kenyan government and the local chiefs. Oral consent was obtained from each subject. Subjects were given a modest gift for their participation.

Anthropometric measures

Nutritional status was assessed using standard anthropometric measures, including height, weight, mid upper arm, waist, and hip circumference. Six skinfold measures were obtained: triceps, subscapular, mid-axillary, periumbilical, suprailliac and mid-calf. Derived measures include Body Mass Index (BMI) calculated as (wt (kg)/ht^2 (m)), and total lean mass ((1% body fat) $\star$ weight). Body fat was determined using the Durnin-Worsley equations [42]. Two BMI values, 3 waist circumference measures and 3% body fat measures were more than 3 SDs from the mean and were removed from the data set.

Age estimates of the participants, which ranged from 20 to 80+, were obtained based on an event calendar [43] and comparison with subjects of similar but better established ages. In order to minimize the effect of uncertainty in the age estimates we group men into 10-year age groups for the purpose of statistical analysis.

Hormonal determinations

Blood. A finger prick blood sample of 250 μl was collected from each subject using a capillary tube and dried and stored on filter paper in the field and brought back for assay at the University of Massachusetts–Boston (K.L. Campbell). Samples (available for 182 of the men) were reconstituted and analysed using slightly modified standard assays that have been revalidated for use on paper extracts [44,45]. Blood DHEAS was determined using a radioimmunoassay from ICN Diagnostics (Costa Mesa, CA). Interassay variability was $10 \pm 4\%$, with a sensitivity (defined as mean of zero standards $\pm$ 2SD) of 80 ± 10 nM.

The antibody used in this assay does not distinguish between DHEA, DHEAS and 4–5, androstendione. Because the circulating levels of DHEAS in blood are 200 times greater than that of DHEA and over 1,000 times greater than that of androstenedione [46] this assay reflects circulating DHEAS levels. Furthermore, though all three hormones are interconvertible, in men the adrenal gland is the overwhelming source of all three hormones [46], suggesting the assay here should serve as index of adrenal function.

The age distribution of subjects for whom both anthropometric and hormonal values are available are shown in Table I. Sample collection time ranged from 7:20 a.m. to 12:40 p.m. with an average of 9:00. However, blood DHEAS value was not related to time of sample collection ($\beta = 0.052$; $p = 0.50$) and hence time of collection was not used in subsequent analyses.

Statistical analysis

Differences in anthropometric and hormones values between settled and nomadic groups were compared using standard two-tailed, unpaired *t*-tests. Age-related changes in blood DHEAS were analysed using general linear models (GLM) based on ten-year age groups. Post-hoc comparisons using the Bonferroni correction were used to test for differences between specific age-groups. Separate linear regression models were run to determine the relationship between blood DHEAS and various anthropometric measures, with age as a control.

Results

The blood DHEAS values reported here must be adjusted for haematocrit concentrations for comparison with western clinical serum standards. Haematocrit values are not available for the individual samples here. However, previous comparison of blood spot and serum results suggests an average conversion factor of 2.2 for DHEAS [47]. Thus conversion of blood DHEAS values which range from 0.10 to 24.90 μM with an overall mean of 5.88 ± 5.57 μM, yields serum values of 0.22 to 54.78 μM with an average of 12.94 ± 12.25 μM. Comparison with a serum reference range of 3.0 to 18.7 μM [48] suggests that DHEAS values among the Turkana are in the normal range for western clinical samples.

Table II compares hormone values and anthropometric measures among nomadic and settled Turkana males. Average blood DHEAS is significantly greater among the nomadic males. In addition, the settled males are significantly shorter and exhibit a significantly higher BMI. The difference in BMI is unlikely to be biologically significant. However, while both of these groups are quite lean, all of the skinfold measures are significantly higher among the settled males at the $p < 0.001$ level, suggesting substantially greater current energy stores.

Table I. Age composition of participants with blood DHEAS values.

	Group	
Age group	Nomadic	Settled
20–29	22	15
30–39	23	13
40–49	28	17
50–59	14	14
60–69	11	9
70+	5	6
Total	103	74

Figure 1 show the age-related pattern for blood DHEAS by 10-year age groups for nomadic and settled males. Blood DHEAS appears to peak in the 30s for the nomads and the 40s for the settled males and then decline. GLM shows a significant overall difference by group and age group, but no interaction between the two, indicating no difference in the age pattern between the two sub-populations. ($n = 177$; adj. $r^2 = 0.086$; group $F = 4.6$; $p = 0.032$; age group $F = 3.8$; $p = 0.003$; group $\star$ age group $F = 0.7$; $p = 0.654$). *Post hoc* tests indicate that values for the 70-year-old age group are significantly lower than those from the 30s (mean difference $= -3.8$; $p = 0.009$) and 40s (mean difference $= -3.4$; $p = 0.02$).

Table III shows the relationship of blood DHEAS with various anthropometric measures controlled for age. Blood DHEAS show no significant association with any of the anthropometric measures, including suprailliac skinfolds, a measure of subcutaneous abdominal fat related to central obesity.

Discussion

The results presented here indicate that while levels of blood DHEAS among Turkana males are within the range of those exhibited in serum by western populations, the age pattern differs by showing a peak in the 30s and 40s rather than the 20s [6,7]. DHEAS is higher among the nomadic males as hypothesized on the basis of lower adiposity, but does not show less of an age-related decline. Furthermore, individual variation in DHEAS is not related to adiposity as predicted. These results suggest an overall delay in maturation of the adrenal

Table II. Anthropometric measures and DHEAS among settled and nomadic males.

Variable	Nomads	Settled
Blood DHEAS (uM)	5.2 ± 3.1	4.1 ± 3.3*
Height (m)	174.5 ± 7.2	172.2 ± 7.5*
Weight (kg)	53.0 ± 6.9	53.4 ± 6.9
Body mass index (kg/m^2)	17.4 ± 1.7	17.9 ± 1.7*
Arm muscle plus bone	35.9 ± 13.8	35.0 ± 8.3
Waist circumference (cm)	71.5 ± 4.7	75.5 ± 4.9***
Body fat (%)	5.7 ± 1.8	9.0 ± 3.3***
Fat free mass (kg)	50.0 ± 6.1	48.6 ± 5.6***
Triceps skinfold (mm)	4.0 ± 0.7	5.4 ± 1.7***
Subscapular skinfold (mm)	5.7 ± 0.9	7.3 ± 1.9***
Mid axillary skinfold (mm)	4.5 ± 0.7	4.8 ± 1.0*
Periumbilical skinfold (mm)	5.4 ± 1.0	9.1 ± 3.3***
Suprailliac skinfold (mm)	4.6 ± 0.9	6.1 ± 2.4***

Values reported are means ± standard deviation. Statistically different by *t*-test. *$p < 0.05$; ***$p < 0.001$.

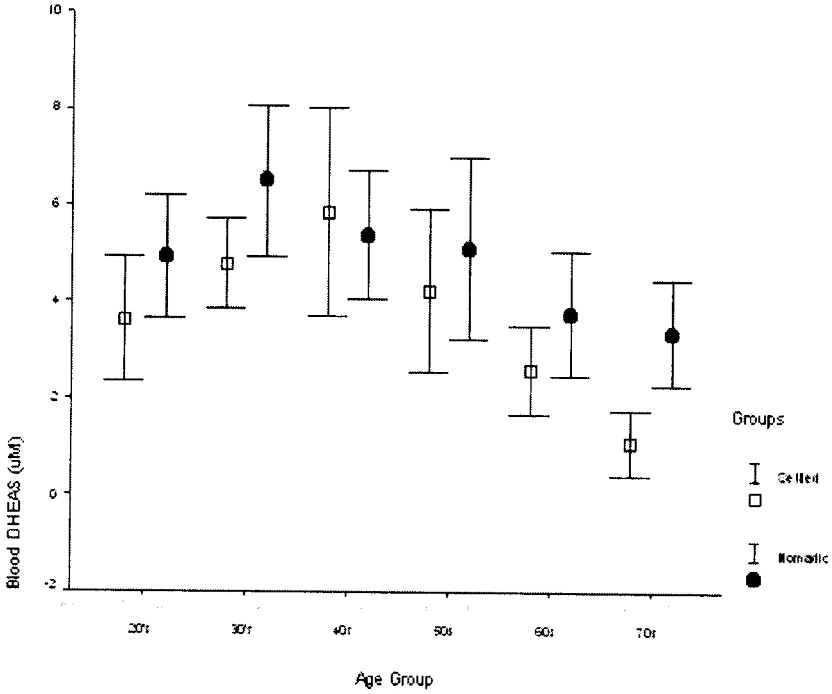

Figure 1. Blood DHEAS by age group among turkana males. Average blood DHEAS values peak in the 30s for the nomads and the 40s for the settled males and then declines. Error bar represents the standard error of the mean. Analysis by GLM shows a significant overall difference by group and age group, but no interaction between the two. (adj. $r^2 = 0.086$; group $F = 4.6$; $p = 0.032$; age group $F = 3.8$; $p = 0.003$; group $\star$ age group $F = 0.7$; $p = 0.654$). *Post hoc* tests indicate that values for the 70-year-old age group are significantly lower than those from the 30s (mean difference $= -3.8$; $p = 0.009$) and 40s (mean difference $= 3.4$; $p = 0.02$).

gland in this chronically undernourished population, along with an elevation of DHEAS in response to current caloric restriction among the nomadic males.

The significant decline in blood DHEAS among the oldest age group of Ariaal men is consistent with the well-documented decline in DHEAS among men in western samples [6,7,49], as well as reports of age-related declines in DHEAS among men in a Chinese population [50]. Furthermore the extent of the decline appears similar to that in western samples. Here the average value for men over 70 years old (2.11 μM) is 35% of the peak average in the 30s (5.88 μM), roughly similar to the decline reported in other studies [6,7,18].

More importantly, the peak of blood DHEAS among Turkana men is the 30s and 40s is delayed compared to that reported in western samples in the 20s [6,7]. Given evidence among the Turkana of late pubertal maturation [51] and extended somatic growth into the early 20s [32], the late peak in DHEAS suggests that adrenal maturation may also be delayed. Puberty is strongly related to IGF-1 [52,53] which is also thought to be involved in the growth of the adrenal gland [54]. Thus under-nutrition, which has been associated with low levels of IGF-1 [55] may result in delayed pubertal maturation, extended somatic growth and late maturation of the adrenal gland.

Table III. Relationship between blood and urinary DHEAS and body composition.

Variable	DHEAS β
Height (cm)	0.01
Weight (kg)	0.03
Body mass index (kg/m^2)	0.05
Muscle plus bone area (cm^2)	0.02
Waist (mm)	−0.05
Fat free mass (kgs)	0.01
Body fat (%)	0.04
Triceps skinfold (mm)	0.07
Subscapular skinfold (mm)	0.06
Midaxillary skinfold (mm)	0.02
Suprailliac skinfold (mm)	−0.08
Periumblical skinfold (mm)	−0.02

Results represent β-coefficients controlled for age. $+p < 0.10$; $^*p < 0.05$. β = standardized regression coefficient for variable shown, controlled for age.

Sub-group comparison

Blood DHEAS levels were higher among the nomadic males compared to the settled males, as predicted on the basis of lower adiposity among the nomads and reduced food intake. This group difference is consistent with the results of caloric restriction in primates [24]. However, the age-related decline in DHEAS was not less pronounced among the nomads as we had expected on the basis of age-related patterns of adiposity. Furthermore, variation in DHEAS levels within our sample is not associated with abdominal fat as expected on the basis of previous results linking DHEA to central obesity [23]. The reason for the lack of an association is not clear; it may be that the Turkana men sampled here are sufficiently lean that there is either not enough abdominal fat or enough variation in adiposity to show a significant relationship with DHEAS.

Relationship of DHEAS and cortisol

In addition to elevated DHEAS, the nomadic Turkana males exhibit higher urinary cortisol levels compared to their nomadic counterparts [34]. Together with elevated DHEAS this suggests greater stimulation of the adrenal axis by ATCH. Furthermore, urinary cortisol was inversely related to upper arm muscle plus bone area among the nomads, suggesting that elevated cortisol among the nomads reflects a catabolic state [33]. Thus elevated blood DHEAS levels among the nomads may be part of a response to acute undernutrition as seen in young women with anorexia nervosa or bulimia [56].

We can not rule out the effects of the psychosocial stress of poor food availability on elevated cortisol and DHEAS levels among the nomads. However, the nomads are used to fluctuations in food availability and may not find short-term reduction in food availability psychologically stressful. Furthermore, as nomads who are forced to settle because they lost their herds, the settled men may experience more long term psychosocial stress than the nomads [57], suggesting that they would be more likely to exhibit chronically elevated cortisol as a result of psychosocial stress.

In addition to higher DHEAS, nomadic males also exhibit higher blood T and sex hormone binding globulin (SHBG) than their settled counterparts [33]. Elevated levels of T and SHBG among Norwegian men have been suggested to be related to greater insulin sensitivity [58]. Given the close association of DHEAS with both insulin and testosterone [27], it may be that the higher blood DHEAS levels of the nomadic men also reflects greater insulin sensitivity related to acute negative energy balance [34].

Other factors influencing DHEAS

DHEAS levels have been related to differences between normal and lacto vegetarian diet [59], and alcohol consumption [60,61]. It is possible that differences in diet may play some role in the overall differences in blood DHEAS between the two sub-populations. However, analysis of results from 48-hour dietary recall indicate higher caloric intake among the settled males, but no difference in fat or protein intake between the two groups [62]. Furthermore, it is the settled males, not the nomadic males who reported consuming considerably more alcohol [62], meaning that effect of moderate alcohol consumption on increased DHEAS [63] can not explain higher DHEAS in the nomadic men.

Serum DHEAS levels are also known to be strongly heritable [64–66] and it is possible that genetic differences could play a role in overall DHEAS levels among the Turkana as well as differences between nomadic and settled subgroups. However, because the two sub-groups are highly related, any genetic differences between the groups are likely to be quite slight.

Comparison with other populations

The lack of a sub-group difference in age-related patterns of blood DHEAS among Turkana males contrasts with findings of earlier adrenopause among highland Bolivian women compared to their lowland counter part [28]. This difference in findings appears to reflect the greater similarity of the two Turkana sub-groups. Settled Turkana men are almost exclusively former Turkana nomads. Thus the two groups of men share similar developmental histories. Furthermore, there is no difference in DHEAS levels during adolescence among Turkana males from the two sub-populations [51], suggesting that higher blood DHEAS among the nomadic men primarily reflect their current nutritional status – reduced food intake and lower adiposity – and is not a developmentally derived difference.

In contrast, the majority of Peruvian women were life-long residents of either the highlands or lowlands [28], giving the two groups distinctive developmental histories. Furthermore, earlier reports indicate an earlier age at adrenarche among children in the lowland compared to the highland Peruvian population [67] suggesting that differences in DHEAS among women in the two populations may be life-long.

Furthermore, unlike the Turkana men, the two groups of women differed in their exposure to hypoxia. The high altitude women are exposed to hypoxia, while the lowland women are not. Oxygen is essential for the cytochrome P450c17 involved in the production of DHEAS by the zona reticularis of the adrenal cortex [29]. Declines in DHEAS with age are though to reflect atrophy of the adrenal gland [68]. Thus earlier decline in DHEAS levels among the highland women may reflect either earlier atrophy of the zona reticularis related to the effects of hypoxia or a smaller zona reticularis throughout development.

Summary

The Turkana males studied here demonstrate age patterns of blood DHEAS consistent with results from western populations. Blood DHEAS levels are within the normal clinical reference range based on serum and show a clear decline over the age of 70 years. DHEAS levels peak after 30 suggesting delayed adrenal maturation. Furthermore, nomadic men showed higher DHEAS consistent with their lower adiposity and reduced caloric intake. However, age-related patterns of DHEAS did not vary between the two sub-groups and were not related to adiposity as expected.

These results suggest that population variation in DHEA may reflect the effects of nutritional status on both the development of the adrenal gland and the effects of current energetic status on its function. More work is called for to determine the extent of population variation in age-related profiles of DHEAS and their implications for aging in non-western populations.

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