Serum lipids and dehydroepiandrosterone excretion in normal subjects

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ABSTRACT Serum levels of cholesterol, phospholipids, β-lipoproteins, and free fatty acids were correlated with urinary dehydroepiandrosterone (DHEA) excretion in healthy blood donors. An indirect dependence was found for cholesterol and phospholipids that was more important in persons with a low DHEA excretion. The correlation seems to be more a function of the dependence of both DHEA excretion and serum lipid levels on age than a direct relationship between these factors.

SUPPLEMENTARY KEY WORDS cholesterol · phospholipids · β-lipoproteins · free fatty acids · age · 17-ketosteroids · glucose 6-phosphate dehydrogenase

THE INHIBITORY EFFECT of dehydroepiandrosterone (DHEA) on glucose 6-phosphate dehydrogenase was reported by Marks and Banks in 1960 (1). Šonka and coworkers (2, 3) and Lopez and Krehl (4) found an enhanced pentose cycle in the erythrocytes of persons with a very low DHEA excretion. It was suggested that the lack of DHEA may stimulate NADPH-dependent biosyntheses, the most important being the synthesis of lipids. Subsequently, a very low DHEA excretion was found in patients with a syndrome characterized by obesity, diabetes, hypertension, hypercholesterolemia, and hyperuricemia (5–8).

The present study provides data concerning the correlation of DHEA excretion with serum lipid levels in healthy persons.

MATERIALS AND METHODS

Blood and urine for analysis were taken from 94 healthy persons—blood donors as they presented themselves consecutively to the blood bank for periodical examination. This group was composed of 47 men and 47 women, of ages ranging from 19 to 58 yr. Blood serum, obtained by immediate centrifugation of blood, was analyzed within 60 min for total cholesterol (9), phospholipid phosphorus (10), β-lipoproteins by turbidimetry (11), and free fatty acids (FFA) (12). 17-ketosteroids (17-KS) were estimated in a 24 hr sample of urine. The total 17-KS were analyzed by the method of Callow, Callow, and Emmens (13); for the estimation of DHEA the chromatographic method of Stárka and Brabencová (14) was used. The results were analyzed by Student's "t" test; linear correlation and regression analysis were calculated by the method of Ezekiel and Fox (15).

RESULTS

Table 1 shows the values of serum lipids and urinary DHEA in blood donors. The differences between men and women in their mean values for cholesterol, phospholipids, FFA, and β-lipoproteins are not statistically significant. On the other hand there is a difference in DHEA excretion ($P < 0.005$), although it has generally been found that there is no sex difference in DHEA excretion.

Regression equations and statistical significance of their coefficients were calculated for the evaluation of the potential influence of DHEA on serum lipids. As cholesterol and some other serum lipids rise with age, analogous calculations were also performed in order to evaluate the role of the latter factor. It is apparent (Table 2) that both DHEA excretion and age are correlated

Abbreviations: DHEA, dehydroepiandrosterone (3β-hydroxyandrost-5-en-17-one); FFA, free fatty acids; 17-KS, 17-ketosteroids.

with cholesterol and phospholipid levels; FFA are unaffected and only age influences β-lipoproteins. On the other hand there is only a slight correlation between age and DHEA excretion, which suggests among other things that there are several mechanisms that stimulate the rise in serum cholesterol and phospholipids. The p values suggest that the relation of age to serum lipids is more important than the postulated relation of DHEA.

Another presentation of our results gives some explanation to this finding (Fig. 1). In our blood donors, DHEA excretion rises up to 30 yr of age and afterwards declines. This is in good agreement with the findings of Keutmann and Masson (16). If the correlation equations were employed for blood donors older than 30, an identical statistical significance for age and DHEA would be obtained.

Fig. 2 shows a comparison of the serum levels of cholesterol, phospholipids, β-lipoproteins, and FFA in blood donors who excrete DHEA in very low amounts (below 0.08 mg/24 hr, the limit of sensitivity in our method) and in persons excreting DHEA in larger amounts. The DHEA "excretors" (mean value 1.44 mg/24 hr) have lower values in all four measures of serum lipids and statistical significance was found not only for cholesterol ($P < 0.005$) and for phospholipids ($P < 0.025$) as in the former type of statistical analysis, but also for FFA ($P < 0.05$). This method of calculation partly modifies the parity of age in both groups. The "nonexcretors" (28 persons) are on an average 6 yr older than the group of DHEA "excretors" (66 persons, mean age 34 yr. There is also a sex difference; among the DHEA "nonexcretors" there are 20 women and only 8 men.

TABLE 1 SERUM LIPIDS AND URINARY DHEA EXCRETION IN NORMAL BLOOD DONORS

	All Subjects (n = 94)	Men (n = 47)	Women (n = 47)
Age (yr)	35.5 ± 10.0	34.9 ± 8.81	36.1 ± 11.2
Cholesterol (mg/100 ml)	234.0 ± 51.1	231.9 ± 45.6	236.2 ± 56.8
β-Lipoproteins (turbidity units)*	4.64 ± 1.30	4.70 ± 1.25	4.59 ± 1.37
Phospholipid P (mg/100 ml)	8.98 ± 1.88	8.88 ± 1.74	9.08 ± 2.04
FFA (meq/liter)	0.61 ± 0.19	0.60 ± 0.18	0.62 ± 0.21
Urinary 17-keto-steroids (mg/24 hr)	6.07 ± 3.84	6.44 ± 4.19	5.69 ± 3.44
Urinary DHEA (mg/24 hr)	1.01 ± 1.27	1.36 ± 1.53	0.64 ± 0.78

Values are means ± SD. Differences between men and women were not statistically significant, except for DHEA excretion.

* Values can be converted to mg/100 ml by multiplication by 103 (P. Fassati and M. Fassati, in press).

TABLE 2 REGRESSION EQUATIONS BETWEEN SERUM LIPIDS, DHEA EXCRETION, AND AGE

		DHEA (x)			Age (x)		
y Coordinate		Regression Equation	SR	$P <$	Regression Equation	SR	$P <$
Cholesterol	Σ	$y = 245.3 - 11.2x$	49.4	0.01	$y = 140.7 + 2.6x$	44.0	0.001
	M	$y = 243.5 - 8.4x$	44.1	—	$y = 166.2 + 1.8x$	42.9	0.01
	F	$y = 251.8 - 24.3x$	54.1	0.05	$y = 124.3 + 3.0x$	45.4	0.001
Phospholipid P	Σ	$y = 9.36 - 0.37x$	1.83	0.05	$y = 6.00 + 0.08x$	1.69	0.001
	M	—NS	—	—	—NS	—	—
	F	$y = 9.67 - 0.90x$	1.93	0.05	$= 5.14 + 0.10x$	1.64	0.001
FFA	Σ	—NS	—	—	—NS	—	—
	M	—NS	—	—	—NS	—	—
	F	—NS	—	—	—NS	—	—
β-Lipoproteins	Σ	—NS	—	—	$y = 2.90 + 0.04x$	1.21	0.001
	M	—NS	—	—	—NS		—
	F	—NS	—	—	$y = 2.55 + 0.5x$	1.22	0.01
DHEA excretion	Σ				$= 2.05 - 0.02x$	1.23	0.05
	M				—NS	—	—
	F				—NS	—	—
Urinary 17-keto-steroids	Σ	$y = 3.69 + 2.35x$	2.42	0.001	$y = 9.59 - 0.09x$	3.72	0.05
	M	$y = 3.20 + 2.36x$	2.14	0.001	—NS	—	—
	F	$y = 3.83 + 2.90x$	2.60	0.001	$y = 9.00 - 0.09x$	3.32	0.05

Σ, all subjects; M, men; F, women; SR, residual standard deviation; NS, not significant.

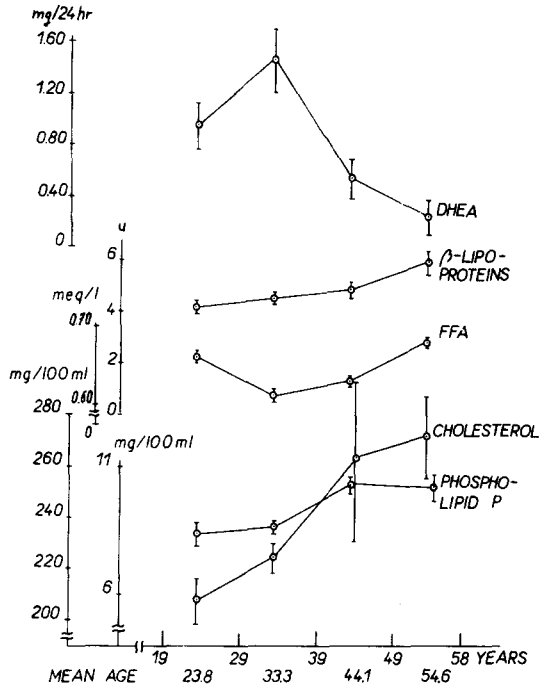

FIG. 1. DHEA excretion and serum levels of cholesterol, phospholipid P, β-lipoproteins, and FFA in relation to age. The pattern of DHEA excretion is different from that for serum lipids, which have a tendency to rise with age. Vertical bars, SD (n = 94); u, turbidity units.

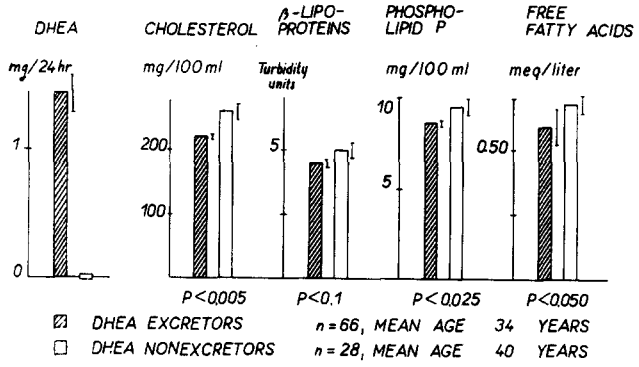

FIG. 2. Serum lipids in DHEA excretors and "nonexcretors." Blood donors excreting very low amounts (<0.08 mg/24 hr) of DHEA have somewhat higher levels of serum lipids than the group of blood donors who have a detectable amount of DHEA in their urine.

DISCUSSION

The metabolic role of the pentose cycle lies in the extramitochondrial production of NADPH which is a coenzyme in the synthesis of fatty acids, cholesterol, cortisol, aldosterone, and phospholipids (e.g. thromboplastin). NADPH is furthermore indispensable for the reduction of folate to tetrahydrofolate, a coenzyme in purine biosynthesis. Also of some importance is the role of NADPH in the reduction of disulfide bonds, which leads to a reversible inactivation of many proteins; most studies of this effect have been performed on insulin. Many factors, such as insulin (overeating), ACTH, some glucocorticoids, prolactin, and 3′,5′-AMP stimulate the dehydrogenase of glucose 6-phosphate, which is the rate-limiting enzyme of the pentose cycle (17). On the other hand, an inhibitory effect is exerted by DHEA, which is a very weak androgen and a probable precursor of testosterone and estrogens. It was suggested that lack of DHEA might contribute to enhanced reductive syntheses, especially in patients in whom other relevant factors are obviously absent (e.g. overeating, some other hormonal imbalance). The lack of DHEA, often encountered at the age of 40–50 yr, may be temporary or long-lasting. In some persons even an infusion of ACTH does not increase its excretion (18).

The most important objection to the supposed metabolic role of DHEA is the fact that DHEA circulates in blood as a sulfate, which is a very weak inhibitor of the dehydrogenase of glucose 6-phosphate in comparison with the free steroid. This may be counteracted (*a*) by the role of steroid sulfatases, which are present in all tissues so far studied, and (*b*) by the effect of DHEA on the dehydrogenase of glucose 6-phosphate in adrenal cortex and not in peripheral tissues. An enhanced production of cortisol, facilitated by an overproduction of NADPH, would directly influence lipid metabolism.

Although the past and present results confirm a certain correlation of DHEA with lipid synthesis, the matter is left open for further studies.

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