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Relationships between age, dehydro-epiandrosterone sulphate and plasma glucose in healthy men

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Abstract

Background: dehydro-epiandrosterone sulphate (DHEAS) has been reported to ameliorate diabetes mellitus in rats.
Aim: we investigated the relationships between plasma glucose, age, serum DHEAS and weight in healthy men.
Methods: we measured the serum DHEAS, fasting plasma glucose, plasma cortisol and body mass index in 169 subjects (mean age 46.5 years).
Results: there was a significant decline in serum DHEAS with age ($P < 0.0001$). Multiple linear regression showed significant relationships with plasma glucose for all measured variables. Age was not a significant determinant of plasma glucose after adjusting for log serum DHEAS, body mass index and log serum cortisol.
Conclusions: a lowered serum DHEAS is paralleled by an elevated plasma glucose within the normal reference interval, and this may contribute to the rise in fasting plasma glucose which occurs with ageing.

Keywords: *ageing, dehydro-epiandrosterone sulphate, plasma glucose*

Introduction

Reduced serum concentrations of dehydro-epiandrosterone (DHEA) and dehydro-epiandrosterone sulphate (DHEAS) have been associated with ageing in men [1]. Low DHEAS levels have also been implicated as a cardiovascular risk factor in men [2]. Lack of DHEA may stimulate NADPH-dependent lipogenesis [3]. DHEA may also inhibit age-related mutagenesis [4]. The reported association between diabetes mellitus and serum DHEAS is also of interest [5, 6]. Hyperglycaemia is a natural consequence of obesity, with a high body mass index [BMI; weight in kg divided by (height in m)^2] being associated with increased plasma glucose [7].

DHEA is an adrenal androgen. It is produced in much smaller quantities in the ovaries and the testis [1]. The sulphated form is more easily measurable in serum. Its reproducibility on re-testing over a prolonged period of time is excellent [8]. Its role as a potential anabolic hormone, the lack of which may increase age-related degenerative processes, has been speculated on for over a decade (particularly in relation to ischaemic heart disease [2]).

More recently, low levels have been associated with impairment of the activities of daily living in elderly people [9]. An age-related decrease has been documented in men not only in serum but also in cerebrospinal fluid [10]. A therapeutic benefit of DHEA preparations in ameliorating streptozotocin-induced diabetes mellitus has been clearly demonstrated in laboratory animals [11]. DHEAS causes an increase in insulin levels and granulated β-cells in murine pancreas. Ando and co-workers have shown an inverse correlation between blood glucose and serum testosterone concentrations in diabetic patients [5], but did not measure DHEAS. However, an inverse relationship between DHEAS and blood glucose has been demonstrated in elderly men with non-insulin-dependent diabetes mellitus [6].

We describe an inverse correlation between DHEAS levels and plasma glucose in healthy men, which appears to be independent of age.

Subjects and methods

One hundred and sixty-nine healthy men were recruited from hospital staff, their relatives and healthy husbands of female patients, some of whom were part

of a previous study [12]. All were free of major disease as determined by clinical history, examination and comprehensive biochemical testing. Fourteen were smokers, 130 drank alcohol (none more than 50 g per day) and none was on any drugs known to influence carbohydrate metabolism. This study was approved by the research ethics committee of the Royal Adelaide Hospital.

After an overnight fast, samples of blood were collected for plasma glucose, sex hormone binding globulin, serum testosterone, serum cortisol and serum DHEAS assays. Plasma glucose was measured by the glucose oxidase method, serum creatinine by the alkaline picrate Jaffe technique (Technicon Dax), sex hormone binding globulin by an immuno-radiometric assay (Orion Diagnostica, Espoo, Finland, CV = 7.4% at 22 nmol/l), serum testosterone (Diagnostic Systems Laboratories Inc., Webster, TX, USA, CV = 7.7% at 23.6nmol/l) and DHEAS by an in-house radioimmunoassay (CV = 7.6% at 14.1 μmol/l).

Variables which were not normally distributed were log-transformed before analysis. Relations between variables were analysed by simple linear regression. Plasma glucose was related to serum DHEAS, age, BMI and serum cortisol by multiple linear regression, using Minitab for Windows.

Results

Mean values of the measured variables are given in Table 1. The mean age of the subjects was 47 years (range: 20–83 years) and BMI 25 (range 19–31). Serum DHEAS and cortisol were not normally distributed but their log values were, so these were used in the statistical analysis. There were significant positive correlations between age and BMI ($P < 0.001$) and age and plasma glucose ($P < 0.001$; Table 2). There were significant inverse correlations between log serum DHEAS and age ($P < 0.0001$), log serum DHEAS and plasma glucose ($P < 0.001$), and log serum DHEAS and BMI ($P = 0.005$).

Table 1. Mean (and SD) demographic and biochemical variables in 169 normal men

Variable	Mean value (SD)	Reference ranges
Age (years)	46.5 (15.7)	–
Weight (kg)	76.9 (9.3)	–
Body mass index (kg/m^2)	24.5 (2.8)	–
Plasma glucose (mmol/l)	5.05 (0.56)	–
Serum testosterone (nmol/l)	17.5 (4.9)	8–30
DHEAS (μmol/l)	7.42 (4.15)	2.5–13
SHBG (nmol/l)	31.1 (13.1)	15–45
Cortisol (nmol/l)	419 (135)	250–750

DHEAS, dehydro-epiandrosterone sulphate; SHBG, sex hormone binding globulin.

Table 2. Correlation matrix for age, body mass index (BMI), plasma cortisol, serum dehydro-epiandrosterone sulphate (DHEAS) and plasma glucose in 169 normal men

	Age	BMI	Log serum cortisol	Log serum DHEAS
BMI	0.299[a]			
Log serum cortisol	0.171[b]	−0.120		
Log serum DHEAS	−0.610[a]	−0.215[c]	−0.091	
Plasma glucose	0.306[a]	0.266[a]	0.173[d]	−0.332[a]

Significance of correlation coefficients: [a]$P < 0.001$; [b]$P = 0.027$; [c]$P = 0.005$; [d]$P = 0.025$.

No significant correlations were found between log serum DHEAS and log serum cortisol, log serum cortisol and BMI (Table 2), log serum DHEAS and serum testosterone and serum testosterone and plasma glucose (data not shown).

Figure 1 demonstrates the inverse relationship between age and serum DHEAS and Figure 2 the inverse relationship between plasma glucose and serum DHEAS.

Multiple linear regression of plasma glucose on age, BMI, log serum cortisol and log serum DHEAS showed significant correlations of plasma glucose with BMI (regression coefficient +0.04; $P = 0.007$), log serum cortisol (regression coefficient +0.299; $P = 0.026$) and log serum DHEAS (regression coefficient –0.203; $P = 0.013$; Table 3).

Taking the regression coefficients for plasma glucose on BMI, log serum cortisol and log serum DHEAS (0.04, 0.299, –0.203 respectively), multiplying each by the range for each of the variables (12 kg/m^2, 1.8 nmol/l and 2.9 μmol/l respectively), we obtained values of 0.45, 0.54 and 0.59 mmol/l for their theoretical maximum influence on glucose in this set.

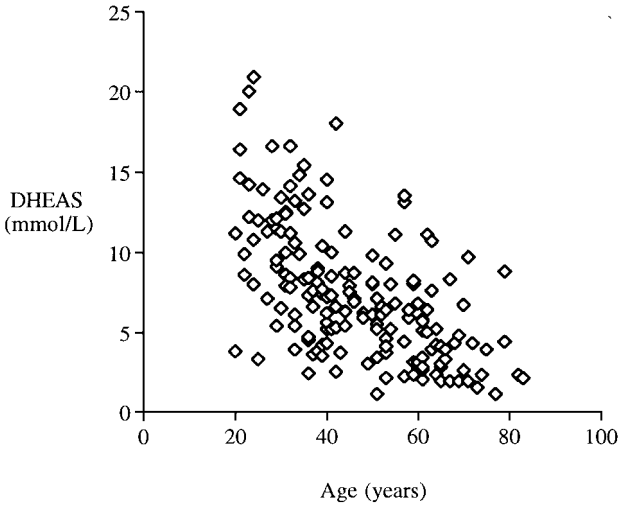

Figure 1. Plot of serum dehydro-epiandrosterone sulphate (DHEAS) *versus* age in 169 subjects.

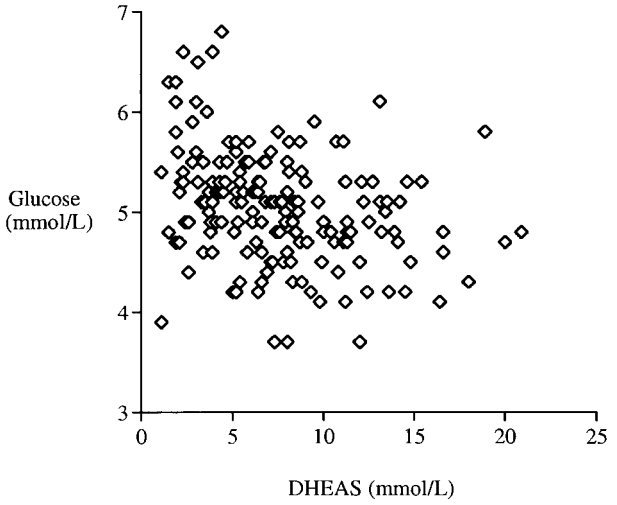

Figure 2. Plot of plasma glucose *versus* serum dehydroepiandrosterone sulphate (DHEAS) in 169 subjects.

Table 3. Multiple linear regression of plasma glucose on age, body mass index, log plasma cortisol, and log serum dehydro-epiandrosterone sulphate (DHEAS) in 169 subjects

Plasma glucose =	*P*
+0.003 × age	0.398
+0.04 × body mass index	0.007
+0.299 × log serum cortisol	0.026
−0.203 × log serum DHEAS + 2.5 mmol/l	0.013

$R = 0.43$, $P < 0.001$.

The sum of these effects is 1.58, which is 70% of the range of glucose values seen (2.29 mmol/l).

Discussion

We have described a negative correlation between fasting plasma glucose and log serum DHEAS. A similar inverse correlation is reported in adolescents with insulin-dependent diabetes mellitus and poorly controlled glycosylated haemoglobin levels [13]. We found fasting plasma glucose to be positively related to age (as expected), to plasma cortisol [14] and to BMI [7] (Table 2). However, when fasting plasma glucose was regressed simultaneously on all three independent variables, the effect of age became insignificant. Thus, the expected rise in plasma glucose with ageing may be secondary to these important factors. The rise of BMI with age is well known [15]. However, plasma cortisol does not normally rise with age [16]. It is unclear why it is associated with age in our subjects.

We have shown, as did Haffner *et al.* [17], that there is a significant negative correlation between fasting plasma glucose levels and serum DHEAS in euglycaemic men (without diabetes mellitus). The reason that our study shows this correlation so strongly is probably due to the large sample and wide range of DHEAS values studied (Figure 1). Our subjects were normal volunteers free from serious disease. It is not clear how DHEAS may lower plasma glucose concentrations. However, one study has revealed a progressive rise in levels of insulin-like growth factor I in patients who are on DHEAS [18].

This study clearly does not prove that serum DHEAS has an effect on the development of diabetes; these are only associations. Benbassat *et al.* [19] have reported no relationship between DHEAS and fasting plasma glucose. On the other hand, an inverse relationship was reported by Haffner *et al.* [17]. Insulin sensitivity may affect DHEAS levels—as suggested by Nestler *et al.* [20], who lowered serum insulin and raised serum DHEAS using benfluorex treatment.

Serum DHEAS may be only a marker that predicts the onset of diabetes. If there is a therapeutic role for DHEAS in the prevention of diabetes mellitus, this should be explored by prospective observational study or a blinded, randomized controlled study.

Key points

- Dehydro-epiandrosterone sulphate (DHEAS) is an adrenal hormone whose function is not fully known.
- DHEAS administration has been reported to prevent the development of diabetes mellitus in animals.
- In this study, fasting plasma glucose was positively related to age, log serum cortisol and body mass index, and inversely to log serum DHEAS.
- After correlation for serum DHEAS, serum cortisol and body mass index, fasting plasma glucose was no longer related to age.

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