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MINIREVIEW

This article is dedicated to Professor Vratislav Schreiber on the occasion of his 75th birthday

Do DHEA/DHEAS Play a Protective Role in Coronary Heart Disease?

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Summary

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEAS), the major androgens secreted by human adrenal glands, were suggested to play a protective role in the pathogenesis of atherosclerosis and coronary heart disease. On the basis of a critical review of all existing studies we concluded that 1) there is no evidence of a protective role of DHEA and DHEAS in women, and 2) men with low plasma DHEA and DHEAS levels can be considered as beings at risk of developing a fatal cardiovascular event. These androgens can interfere with atherogenic process by several mechanisms. They influence enzymes such as glucoso-6-phosphate dehydrogenase, which can modify the lipid spectrum. Furthermore, they can inhibit human platelet aggregation, enhance fibrinolysis, slow down cell proliferation and reduce plasma levels of plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen. We suggest that all these DHEA(S) actions are dependent on sex hormone metabolic pathways. There are still insufficient data to advise DHEA supplementation in elderly men, but this type of hormone replacement therapy merits further studies.

Key words
DHEA • DHEAS • Coronary heart disease

Introduction

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEAS) are, from the quantitative point of view, the major secretory products of the human adrenal glands (Migeon *et al.* 1957, Baulieu *et al.* 1965). Nevertheless, the biological role of these steroids is not yet clearly established. The fact that the concentration of DHEA(S) progressively declines with aging (Longcope 1995, Nestler 1995b) and that there are many pathological states the incidence of which increases with age, has lead to a number of hypotheses about the possible causal role of DHEA(S) in the pathophysiology of many diseases, especially coronary heart disease (for detailed citations see below), atherosclerosis (Kask 1959, Marmoston *et al.* 1975, Gordon *et al.* 1988, Kalimi and

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Regelson 1990, Khaw 1996), obesity (Yen *et al.* 1977, Nestler *et al.* 1988, Usiskin *et al.* 1990), diabetes mellitus (Coleman *et al.* 1982, Cleary and Zisk 1986, Haffner *et al.* 1994), cancer (Gordon *et al.* 1990, Helzlsouer *et al.* 1992, Schwartz and Pashko 1995) and immunological disorders (Spencer *et al.* 1995). DHEA and DHEAS were even proposed as the discriminators of life expectancy and aging (Barrett-Connor *et al.* 1986). Moreover, the hormone replacement therapy using DHEA and DHEAS in the elderly has been discussed (Morales *et al.* 1994, Yen *et al.* 1995, Weksler 1996, Shomali 1997).

Because of this hope put into DHEA and its sulfate, these hormones were propulsed, at the end of the eighties, to one of the heading positions of scientific interest. The force and the extent of investigations devoted to DHEA(S) is well documented by the enormous number of studies dedicated to this topic during the nineties: 455 papers were cited by the MEDLINE between 1990 and 1999. We critically examined all these studies and the aim of this review is to answer the question whether DHEA and DHEAS actually do play a protective role in coronary heart disease.

Table 1. Animal studies

REFERENCE	STUDY SIZE	PERIOD	RELATIONSHIP
Gordon et al. 1988	34	12 weeks	50% reduction in plaque size
Arad et al. 1989	15	8 weeks	40% reduction in fatty streak formation
Eich et al. 1993	48	5 weeks	retardation of arteriosclerosis progression

In all cases dehydroepiandrosterone was administered to male rabbits.

Short overview of existing studies

Animal studies

The very optimistic view on the efficacy of DHEA(S) to prevent atherosclerotic processes was supported by the results of three animal studies (Gordon *et al.* 1988, Arad *et al.* 1989, Eich *et al.* 1993) which are summarized in Table 1.

Gordon *et al.* (1988) studied the influence of DHEA oral supplementation on the atherosclerotic plaque formation in male hypercholesterolemic rabbits with provoked endothelial injury. These authors reported that DHEA administration reduced the plaque size by about 50 % in comparison with rabbits without DHEA treatment. They also noted a marked reduction in fatty infiltration of the heart and liver. The plaque size was inversely related to the serum level of DHEA attained. Arad *et al.* (1989) studied the effects of DHEA administration on aortic fatty streak formation in hypercholesterolemic male rabbits. They found 30-40 % reduction of aortic streak formation in the hypercholesterolemic rabbits fed a 0.5 % DHEA diet. Eich *et al.* (1993) reported that such chronic DHEA administration produced a 45 % reduction in the number of stenosed vessels in the transplanted hearts and a 62 % reduction in the non-transplanted hearts.

Epidemiological studies

In man, there are seven epidemiological and eight cross-sectional studies concerning DHEA(S) action on coronary artery disease. This is a relatively small fraction of the total number of papers on DHEA(S). The conceptions and the results of the epidemiological studies are summarized in Tables 2 and 3.

Of the seven epidemiological studies, five were performed in men (Table 2) and only two in women (Table 3). All epidemiological studies used the measurement of endogenous DHEAS (and never DHEA) concentrations. The choice of DHEAS measurement is understandable due to the fact that during the day the DHEAS levels are more stable than those of DHEA.

Dehydroepiandrosterone presents diurnal variations comparable with diurnal fluctuations of cortisol (Rosenfeld *et al.* 1971, Nieschlag *et al.* 1973). The metabolic clearance rate of DHEAS is lower than that of DHEA (5 to 20 liters per day for DHEAS and 2000 liters per day for DHEA) (Baulieu 1996). Thus, the half-time of DHEAS is much longer (7 to 10 h) than DHEA half-time (15 to 30 min) (Baulieu 1996, Khorram 1996). Nevertheless, all the above studies used a single measurement of endogenous DHEAS levels so that the problem of the reliability of the values determined, as well as of interassay variations, could have negatively influenced the relationships presumed by the studies.

Table 2. Prospective epidemiological studies in men

REFERENCE	STUDY PERIOD	STUDY SIZE	NUMBER OF CASES	END-POINT	LIPID PARAMETERS	CIGARETTE SMOKING	FASTING PLASMA GLUCOSE	PHHD	RELATIONSHIP DHEAS vs END-POINT
Barret-Connor et al. 1986	12 years	242	31	Fatal CVD	+	+	+	–	INVERSE
Contoreggi et al. 1990	9.5 years	170	46	Fatal and non-fatal CAD	+	–	–	–	NONE
Lacroix et al. 1992	18 years	714	238	Fatal and non-fatal CAD	+	+	+	–	NONE
		714	82	Fatal CAD	+	+	+	–	INVERSE
Newcomer et al. 1994	28 months	338	169	Non-fatal MI	–	+	+	+	NONE
Barret-Connor and Goodman-Gruen 1995b	19 years	1029	254	Fatal CVD	+	+	+	+	INVERSE #
		1029	157	Fatal IHD	+	+	+	+	INVERSE #

In all studies plasma DHEAS, blood pressure and body mass index were investigated. Unconjugated plasma DHEA was not determined in any study. CAD - coronary artery disease, CVD - cardiovascular disease, IHD - ischemic heart disease, MI - myocardial infarction, DHEA - dehydroepiandrosterone, DHEAS - dehydroepiandrosterone sulfate, PHHD - personal history of heart disease, # versus survivors (but NONE versus whole group, if fatalities from other causes were added to the comparison group). + investigated parameter, – non-investigated parameter.

Table 3. Prospective epidemiological studies in women

REFERENCE	STUDY PERIOD	STUDY SIZE	NUMBER OF CASES	END-POINT	RELATIONSHIP DHEAS vs END-POINT
Barret-Connor and Khaw 1987	12 years	289	87	Fatal CVD	DIRECT
Barret-Connor and Goodman-Gruen 1995a,b	19 years	942	199	Fatal CVD	NONE
		942	102	Fatal IHD	NONE

In all studies DHEAS, blood pressure, lipid parameters, cigarette smoking, body mass index, fasting plasma glucose and personal history of heart disease were investigated. CVD - cardiovascular disease, IHD - ischemic heart disease, DHEAS - dehydroepiandrosterone sulfate.

The results of the epidemiological studies are controversial and a detailed analysis of these studies shows that there are dramatic differences according to sex and according to the end-point chosen by the authors.

It can be seen in Table 2 that there is a profound difference depending on whether the pathological state was or was not fatal. Thus, all studies comparing survivors with men who died due to coronary artery disease (Lacroix *et al.* 1992), cardiovascular events (Barrett-Connor *et al.* 1986, Barrett-Connorr and Goodman-Gruen 1995b) or ischemic heart disease (Barrett-Connorr and Goodman-Gruen 1995b) disclosed an inverse relationship between the baseline DHEAS levels and cardiac end-point. On the contrary, the studies comparing baseline DHEAS levels between controls and men suffering non-fatal myocardial infarction (Newcomer *et al.* 1994), or between the whole groups of men with fatal and non-fatal coronary artery disease or between non-fatal myocardial infarction and controls (Contoreggi *et al.* 1990, Lacroix *et al.* 1992) found no significant relationship.

The only two epidemiological studies in women did not find an inverse relationship between the baseline plasma DHEA levels and cardiovascular events even if they were fatal. Barrett-Connor and Khaw (1987) described even the reverse relationship – cardiovascular disease incidence was higher in women with the highest levels of DHEAS. Barrett-Connor and Goodman-Gruen (1995a) found no significant relationships between plasma baseline DHEAS levels and either cardiovascular or coronary heart disease mortality.

Cross-sectional studies

There are eight cross-sectional studies which examined the relationship between plasma DHEA(S) levels and the incidence of cardiovascular events, seven of which being performed in men (Table 4) and only one in women (Table 5). The results of these studies were not uniform.

Four of the male studies demonstrated the protective role of DHEAS, because the plasma DHEA and/or DHEAS levels were significantly lower in men with cardiovascular pathology. Slowinska-Srzednicka *et al.* (1989), Gray *et al.* (1991) and Mitchell *et al.* (1994) carried out comparable cross-sectional studies in which they compared the plasma DHEAS levels in men with previous coronary events with those in controls (men without coronary pathology). These three studies revealed significantly decreased DHEAS levels in men with prior myocardial infarction or coronary heart disease. Recently published paper of Feldman *et al.* (1998), which was based on the data from the Massachusetts Male Aging Study, confirmed the results of Gray *et al.* (1991). The study of Herrington *et al.* (1990) also indicated the positive role of plasma DHEAS, which was lower in men with pathological coronary arteriography than in men without any coronary stenosis.

Nevertheless, the results in three other male studies did not confirm such a positive role of DHEA(S). Hauner *et al.* (1991) performed a study comparable with the angiographical study by Herrington *et al.* (1990), but they did not find any significant relationship between DHEAS levels and angiographically confirmed coronary artery disease. Zumoff *et al.* (1982) and Hautanen *et al.*

Table 4. Cross-sectional case-control studies in men

REFERENCE	STUDY SIZE	SUBGROUPS	PLASMA DHEA	LIPID PARAMETERS	FASTING PLASMA GLUCOSE	PHHD	RELATIONSHIP(S)
Zumoff et al. 1982	117	13 - prior MI 35 - controls 44 - survival coronary arteriogram 25 - severe CAD by arteriogram, but no MI	+	–	–	–	DHEA and DHEAS elevated in MI men versus controls
Slowinska-Srzednicka et al. 1989	108	32 - prior MI 76 - controls	–	+	–	+	DHEAS decreased in MI men versus controls
Herrington et al. 1990 (#)	103	All had undergone coronary angiography	+	–	–	–	DHEAS lower in men with at least one stenosis versus men without any stenosis DHEAS inversely related to the number of diseased coronary vessels DHEAS inversely related to the extent of coronary atherosclerosis.
Gray et al. 1991(*) (#) *Feldman et al. 1998*	1709	1294 (§) 475 - controls	+	+	+	+	DHEAS is lower in men with a history of CHD
Hauner et al. 1991	274	All had undergone coronary angiography	–	+	–	–	No significant relationship between DHEAS and angiographically confirmed CAD
Hautanen et al. 1994	159	62 - non fatal MI or cardiac death 97 - controls	–	+	–	–	High DHEAS levels are associated with the CHD risk among dyslipidemic middle-age men
Mitchel et al. 1994	98	48 - survivors of premature MI 48 - controls	–	+	–	–	DHEAS levels were significantly lower in men with MI versus controls.

Plasma DHEAS was determined in all studies. (*) These authors also investigated blood pressure and body mass index. (#) These authors examined cigarette smoking. (§) One or more of next conditions: CHD, hypertension, diabetes, ulcer, cancer, obesity, alcoholism, prostate problems, all prescription medication. CAD - coronary artery disease, CHD - coronary heart disease, DHEA - dehydroepiandrosterone, DHEAS -dehydroepiandrosterone sulfate, MI - myocardial infarction, PHHD - personal history of heart disease, + investigated parameter, – non-investigated parameter.

(1994) described even higher DHEA(S) levels in men with prior myocardial infarction compared to controls (men without infarction).

The only existing cross-sectional women's study performed by Herrington *et al.* (1990) found no association between DHEA(S) and angiographical signs of coronary atherosclerosis (Table 5). It should be mentioned that a similar study of these authors carried out in the group of 103 men indicated that the plasma DHEAS levels in men were inversely related to the number of afflicted coronary vessels and to the extent of atherosclerosis (Herrington *et al.* 1990).

Table 5. Cross-sectional case-control studies in women

REFERENCE	STUDY SIZE	SUBGROUPS	PLASMA DHEA	PLASMA DHEAS	CIGARETTE SMOKING	RELATIONSHIP(S)
Herrington et al. 1990	103	103 - all had undergone coronary angiography	+	+	+	No association between DHEA or DHEAS and CD

In this study blood pressure, body mass index, lipid parameters, fasting plasma glucose and personal history of heart disease were not investigated. CD - coronary disease, DHEA - dehydroepiandrosterone, DHEAS –dehydroepiandrosterone sulfate. + investigated parameter.

Dehydroepiandrosterone administration in humans

There are only four studies (Mattson *et al.* 1980, Nestler *et al.* 1988, Mortola and Yen 1990, Morales *et al.* 1994) which tested the effect of DHEA administration in man. The precise characteristics of these studies (subjects, extent of the studied group, dose of DHEA, route of DHEA administration and final results) are reviewed in Table 6. The methodological heterogeneity of these studies makes difficult to draw any conclusions of their results. Nevertheless, it seems that DHEA supplementation in women lowers their HDL-cholesterol values.

Possible sources of controversial results

It has already been noted above that there are several important contradictions in the conclusions of various DHEA studies. What is the reason for this? It concerns three basal questions.

1. Why are not the results of the three optimistic animal studies confirmed by the results in man ?
2. Why is there apparent contradiction in the DHEA(S) effects between males and females ?
3. Why did not the methodologically comparable male studies give uniform results ?

First, as far as the animal studies are concerned, there are two aspects which should be considered. Rodents are not the optimal laboratory experimental animals for these studies because their DHEA(S) levels are extremely low (Nestler 1995a). Plasma DHEA levels in rabbits are about ten times lower than those in man, whereas plasma DHEAS levels are almost undetectable.

Furthermore, all three studies in rabbits used very high doses of DHEA given as 0.5 % DHEA diet (Gordon *et al.* 1988, Arad *et al.* 1989, Eich *et al.* 1993). Plasma DHEA rose from 2.0 nmol/l before the study to 12.1 nmol/l after 12 weeks; the plasma DHEAS was undetectable before the study and attained 220 nmol/l after DHEA application (Gordon *et al.* 1988). Thus, the feeding of 0.5 % DHEA diet represents an extremely high intake of this androgen in rabbits. This is in contrast with the idea that only replacement doses could be sufficient for the prevention of atherosclerotic lesion development. As the replacement dose of DHEA, we consider such a dose which induces an increase of low DHEA levels in the elderly (about 17 nmol/l in women and about 7 nmol/l in men; DHEAS levels about 2.5 μmol/l in women and 4 μmol/l in men) to the levels found in normal young adults (about 35 nmol/l in women and about 30 nmol/l in men for DHEA and about 8 μmol/l in women and up to 12 μmol/l in men for DHEAS) (Orentreich *et al.* 1984, Parker 1991, Baulieu 1996, Šulcová *et al.* 1997).

The second surprising conclusion of our analysis concerning the role of DHEA(S) in human atherosclerosis is the obvious contrast between the possible protective role of these steroids in men but no or even negative DHEA(S) effect in women.

Table 6. Studies concerning dehydroepiandrosterone administration

REFERENCE	SUBJECTS	STUDY SIZE	DOSE OF DHEA	ADMINISTRATION	END-POINT(S)
Mattson et al. 1980	Young ovariectomized women	8	200 mg of DHEA enanthate	Intramuscular	Decrease in total cholesterol. Decrease in HDL-cholesterol.
Nestler et al. 1988	22- to 25-year old men	5	1600 mg/day for 28 days	Oral	Decrease in total cholesterol. Decrease in LDL - cholesterol. No changes in HDL-cholesterol, tissue sensitivity to insulin, total testosterone, free testosterone, SHBG, estradiol, estrone. Increase in androstendione
		5	controls		
Mortola et al. 1990	Postmenopausal women	6	1600 mg/day for 28 days	Oral	Decrease in total and HDL cholesterol. Increase in estrone and estradiol. Increase in androstendione, testosterone and dihydrostestosterone. No changes in LH, FSH, body weight, or percent body fat. Decrease in SHBG and TGB. Increase in peak insulin levels during the 3-hours glucose tolerance test.
Morales et al. 1994	41- to 70-years old men	13	50 mg/day for 3 months	Oral	Increase in androstendione No changes in testosterone, dihydrotestosterone
	41- to 70-years old women	17	50 mg/day for 3 months	Oral	Increase in androstendione, testosterone, dihydrotestosterone. Decrease in HDL-cholesterol.
	41- to 70-years both sexes	30	50 mg/day for 3 months	Oral	No changes except HDL-cholesterol in women in lipid spectrum. No changes in SHBG, estrone, estradiol, insulin sensitivity, percent body fats, GH, IGFBP-3 levels. Increase in IGF-I levels. Decrease in IGFBP-1 levels. Increase in perceived physical and psychological well-being.

FSH - follicle stimulating hormone, GH - growth hormone, LDL - low density lipoprotein, HDL - high density lipoprotein, IGF-I - insulin like growth factor I, IGFBP-1 - insulin like growth factor- binding protein 1, IGFBP-3- insulin like growth factor- biding protein 3, LH - luteinizing hormone, SHBG - sex hormone-binding globulin, TGB - thyreoglobulin.

It is known that there are similarities but also differences in the levels of these steroids depending on the sex. Both hormones, which are low during childhood, reach peak levels in adolescence and decline with age. However, there is a second additional peak of DHEA in women, which reaches the values of about 30 nmol/l at the age of around 40 years; this second peak is absent in men (Šulcová *et al.* 1997).

Furthermore, it is evident that the DHEA levels in women are higher than those in men (Zumoff *et al.* 1980, Šulcová *et al.* 1997). This is explained 1) by the considerably higher DHEAS-DHEA cleavage in women than in men (Zumoff and Bradlow 1980) and 2) by the ovarian involvement in the regulation of DHEA metabolism (Šulcová *et al.* 1997). The ovary is also one of the DHEA sources in women, but it seems that only less than 10 % of DHEA in women is secreted by the ovaries (Migeon *et al.* 1957, Khorram 1996).

However, neither the sexual differences in DHEA(S) levels nor the analysis of different metabolic pathways in both sexes could explain the contradictory role of DHEA(S) in women (Tables 3 and 5).

Given the evident impasse in the DHEA(S) action in women, Ebeling and Koivisto (1994) proposed an elegant hypothesis that DHEA can have a dual action according to the hormonal milieu. They presumed that in an androgenic milieu in men, DHEA acts as an estrogen and protects against cardiovascular diseases. On the other hand, in postmenopausal women, it is metabolized into testosterone and increases the risk of cardiovascular disease. No further studies have confirmed or denied this theory.

The third question posed concerns the discrepancies in male DHEA(S) studies. We made a detailed analysis of all reports and we have concluded that there are several facts which can, at least partially, explain the differences found.

Firstly, we suppose that some discrepancies in the epidemiological male studies can be explained by vaguely defined cardiac end-points by some authors. The fact that all studies comparing men with fatal cardiovascular events versus controls found significantly lower baseline DHEAS levels in men who died, while this relationship was not present if the non-fatal cases were added to the "case" group. This brought us to look for a precise definition of such non-fatal cardiovascular cases. We have found that actually it is not possible to exclude that there are some open and debatable questions in the definitions of cardiac end-point in some studies. For example, Contoreggi *et al.* (1990) proposed a "scoring system for cardiac disease classification" which consists in adding points according to several personal history data and ECG signs at rest and during exercise. The fact that some "probable" criteria were included in this "scoring system" put men with a definite history of myocardial infarction to the same group as men with "probable angina pectoris" and "probable history of myocardial infarction". However, the precise explanation of these "probable events" was never given. This can be a source of error, when all these subjects are considered as "cases" belonging to the same group.

Furthermore, we do not expect that telephone calls could provide totally trustworthy data, although those who were questioned were doctors of medicine (Newcomer *et al.* 1994). This can be one reason why their epidemiological study found no relationship between the baseline DHEAS levels in men with non-fatal myocardial infarction compared to the controls (Table 2).

In the male cross-sectional control studies the results of which did not support the protective role of DHEA (Zumoff *et al.* 1982, Hauner *et al.* 1991, Hautanen *et al.* 1994), we have found a small subgroup of men with prior myocardial infarction, i.e. 13 cases in the study of Zumoff *et al.* (1982). This can explain why these authors did not find decreased DHEAS levels in men with prior myocardial infarction, as did three comparable studies (Slowinska-Srzednicka *et al.* 1989, Gray *et al.* 1991, Mitchel *et al.* 1994) where "case" subgroups were larger (Table 2).

The second controversial study (Hautanen *et al.* 1994) has to be judged separately, because these authors selected only men with hyperlipoproteinemia, another well-known risk factor in coronary heart disease, but we are lacking a precise information on the type of lipid disturbances present. This can be decisive because the degree of atherogenicity differs in various types of hyperlipoproteinemia. Moreover, no data are available about hyperhomocysteinemia, another cardiovascular risk factor, which is often ignored in dyslipidemic coronary patients.

The third (and last) male cross-sectional case-control study, which failed to confirm the positive role of DHEA, was reported by Hauner *et al.* (1991). This angiographical study used a methodology comparable with that employed by Herrington *et al.* (1990). All men in both studies had undergone coronary angiography, but Hauner *et al.* (1991) did not find the significant

relationship described by Herrington *et al.* (1990) (for more details see Table 4). Unfortunately, we have no explanation for this discrepancy.

Possible mechanisms of DHEA(S) action on cardiovascular events

The exact mechanism of DHEA(S) action is far from being elucidated, although there are numerous studies trying to explain the DHEA(S) action by the influence on known cardiovascular risk factors. On the other hand, a lot of partial but interesting facts were described in the past few years.

As far as the cardiovascular risk factors are concerned, the role of DHEA(S) in lipid metabolism remains unclear and the results of various studies are contradictory. They range from studies suggesting favorable effects of DHEA(S) on lipid parameters (Nestler *et al.* 1988, Kurzman *et al.* 1990, Haffner and Valdez 1995) to those indicating no effect (Gordon *et al.* 1988, Arad *et al.* 1989, Eich *et al.* 1993) or even negative action of DHEAS (Mattson *et al.* 1980, Mortola and Yen 1990, Morales *et al.* 1994, Bednarek-Tupikowska *et al.* 1995). The majority of these differences seems to be sex-dependent.

Hypertension and obesity, the states characterized by high insulin levels and insulin resistance, are accompanied by decreased DHEAS levels (Nestler *et al.* 1989, Beer *et al.* 1994, Ebeling and Koivisto 1994, Slowinska-Srzednicka *et al.* 1995). In animal studies, DHEA administration inhibited adipocyte differentiation (Schantz *et al.* 1989), reduced fat cell size (Cleary *et al.* 1982) and increased protein content of body mass (Tagliaferro *et al.* 1986). Nevertheless, human studies disclosed different relations between DHEA(S) and body fat or lipids parameters in men and women as well as in obese and non-obese young men, probably due to hypoandro-genemia known to be present in obese men (Evans *et al.* 1983, Wild *et al.* 1983, Nestler *et al.* 1988, 1995, Mortola and Yen 1990, De Pergola *et al.* 1991, 1996).

On the contrary, the studies concerning DHEA(S) and smoking are unambiguous. The DHEA(S) are higher in smokers and lower in those who had never smoked. Former smokers have DHEA(S) levels between these two groups (Khaw *et al.* 1988, Salvini *et al.* 1992). No explanation for this surprising finding has been found. It is possible that the elevation of DHEA(S) is a reaction, tending to counterbalance the negative consequences of cigarette smoking ? Perhaps the low DHEAS levels found in men who had died from coronary heart disease are due to exhaustion of this protective mechanism. In this context, it is interesting to mention that Japanese men have the lowest DHEAS levels and Caucasian white men the highest ones (Wang *et al.* 1968, 1976). The data regarding the genetic basis of DHEAS levels have recently been published (Jaquish *et al.* 1996a,b).

To our knowledge, no studies assessing the relationship between physical activity and DHEA(S) levels have been hitherto performed.

On the other hand, several papers have dealt with different partial effects of DHEA(S). Yoneyama *et al.* (1997) reported that DHEA(S) attenuated the *in vitro* proliferation of vascular intimal cells. These antiproliferative effects, proved in tissue cultures and animal studies, could prevent atherosclerotic plaque formation and inhibit atherosclerosis (Herrington 1995). Another *in vitro* study found that DHEA pretreatment significantly improved muscle flap microcirculation and protected against ischemic injury (Lohman *et al.* 1997). Since vascular contractility *in vitro* is influenced by DHEAS, Barbagallo *et al.* (1995) suggested that DHEAS serves to buffer vascular responsiveness to a wide variety of depolarizing and constrictor hormonal stimuli. Jesse *et al.* (1995) published an interesting paper about the capacity of DHEA to inhibit human platelet aggregation *in vitro* and *in vivo*. Beer *et al.* (1996) demonstrated that oral DHEA administration reduced plasma levels of plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen in men.

It is known that DHEA(S) influences several key enzymes, such as glucoso-6-phosphate dehydrogenase or glycerol-3-phosphate dehydrogenase. It was found that DHEA inhibits the enzymatic activity of glucoso-6-phosphate dehydrogenase in the pentose phosphate cycle which reduces NADP (Lopez and Krehl 1967a,b). NADPH is involved in a number of metabolic pathways such as fatty acid synthesis or phospholipid, cholesterol and steroid production. As a result of reduced NADPH production, fatty acid synthesis is diminished and thus the production of very low density lipoproteins is lowered. If the levels of LDL are decreased, less LDL can be oxidized and fewer atheromas would be formed (Watson *et al.* 1996).

When thinking about the mechanism of DHEA action in target tissues, we should consider the possibility that its action is mediated by some of its metabolites. Such mediators could include metabolic products of DHEA oxidation at the position C7, namely

7-hydroxydehydroepiandrosterone and 7-oxo-dehydro-epiandrosterone (Hampl *et al.* 1997).

More studies are needed for understanding these different mechanisms in relation to the hormonal milieu.

Conclusions

We thus conclude that DHEA and DHEAS may interfere with the atherosclerotic process by several independent mechanisms, all related to sexual hormone metabolic pathways. We had accepted that we are still far from being able to envision the DHEA replacement therapy comparable with the present well-known hormonal replacement treatment for menopause. However, we must also realize that this estrogen-progestin replacement was not acceptable 40 years ago. We are convinced that DHEA is a good candidate for the male hormone replacement in the future and that the strategy of this treatment merits to be studied.

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