

# **REPLACEMENT OF STEROIDS: CARDIOVASCULAR EFFECTS AND INFLUENCE ON CARDIOVASCULAR RISK**

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## **1. INTRODUCTION**

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In the industrialized nations, coronary heart disease (CHD) is the most frequent cause of death in women. Before the age of 55, the incidence of coronary events in women is only about one third of that in men. After that, it rises steeply, in women aged 75 it reaches the same rate as in men and is even higher in older age [1]. The 10 years difference between men and women in the clinical manifestation of arteriosclerosis as well as the increasing incidence of cardiovascular events in women after the age of 55 is often explained by the anti-atherogenic effect of estrogens. However, little is known about the contribution of androgens to the sex-difference in atherosclerosis. Moreover, it is not clear, whether the increase of CHD-incidence in women after the age of 55 is an effect of age or menopause. In disagreement with the role of menopause as an independent cardiovascular risk factor, the incidence of cardiovascular events rises with the same degree after menopause as before menopause. In contrast, the rate of breast cancer disproportionately increases in postmenopausal women. From this observation, some authors concluded, that menopause is an age-independent risk factor for breast cancer, but not for CHD [2]. Nevertheless,

multiple potentially anti-atherogenic properties of estrogens (see below), which are lost upon menopause, result in a more disadvantageous cardiovascular risk factor profile with a higher body mass index, hypertension, total- and LDL-cholesterol, triglycerides, glucose and fibrinogen (table 1).

Also the increased incidence of coronary events after surgical bilateral ovariectomy, if not substituted with estrogens, argues for the causal relevance of menopause as a cardiovascular risk factor.

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## **2. HORMONE REPLACEMENT THERAPY WITH ESTROGENS AND PROGESTINS**

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Postmenopausal hormone replacement therapy (HRT) with estrogens and progestins is used in different combinations and forms of application, which at least differ in their influence on cardiovascular risk factors. Today, monotherapy with estrogens is restricted to hysterectomized women because of the increased risk of endometrial cancer. Otherwise, women should be treated with a combination of estrogens with progestins. These combinations mainly differ in type and/or dosage of estrogens (polyvalent conjugated equine

Table 1. Cardiovascular risk factors in 45–55 years old men and women (PROCAM-study)

	Men (n = 6552)	Women	
		Premenopause (n = 1053)	Postmenopause (n = 1457)
Age (years)	50,1 ± 3,2	48,5 ± 2,9**	51,0 ± 3,0**,##
BMI (kg/m <sup>2</sup> )	26,7 ± 3,2	25,8 ± 4,5**	26,5 ± 4,5##
Cholesterol (mg/dl)	231 ± 43	222 ± 39**	239 ± 43**,##
Triglycerides (mg/dl) <sup>1)</sup>	126	86**	96**,##
LDL-cholesterol (mg/dl)	155 ± 37	143 ± 37**	158 ± 40##
HDL-cholesterol (mg/dl)	46 ± 12	59 ± 15**	59 ± 16**
Lp(a) (mg/dl) <sup>1)</sup>	6,0	5,0	5,0
Fibrinogen (mg/dl)	265 ± 56	263 ± 50	278 ± 56**,##
Factor VIIc (mg/dl)	109 ± 23	112 ± 24	122 ± 29**,##
PAI-1 (U/l) <sup>1)</sup>	3,25	2,11**	2,64**,##
Diabetes mellitus (%)	11,4	7,0**	7,8**
High blood pressure (%)	28,1	23,9*	30,1#

<sup>1)</sup>: Median, \*: P < 0,01, \*\*: P > 0,001 women versus men (t-test)

#: P < 0,01, ##: P < 0,001 Postmenopause versus Premenopause (t-test)

estrogens vs. monovalent 17 $\beta$ -estradiol vs. synthetic ethinylestradiol), progestins (17-hydroxyprogesterone- or 19-nortestosterone derivatives) and in the application of the estrogens (oral versus transdermal).

### 2.1. Epidemiological and clinical endpoint-studies

Most of the epidemiological population studies showed that postmenopausal women with HRT are suffering less frequently from myocardial infarction than women without HRT. In their meta-analyses of more than 30 studies Grady and colleagues calculated a 35–45 % reduced relative risk of cardiovascular events in estrogen-replaced postmenopausal women [3]. However, these uncontrolled and non-randomized examinations have substantial methodological problems. Women, who chose HRT, have a higher social and educational status as well as a stronger awareness of health issues and therefore important factors that have a

positive influence on cardiovascular risk [1]. Prospective, controlled and randomized intervention studies are therefore necessary to prove the significance of menopause as an independent cardiovascular risk factor and to confirm the importance of hormone replacement therapy for the prevention of cardiovascular events in women.

In the so far only published prospective, randomized and placebo-controlled intervention study (HERS-study) the effect of a combination of 0.625 mg conjugated equine estrogens with 2.5 mg medroxyprogesterone per day on the incidence of coronary events in 2762 women with existing coronary heart disease (thus secondary prevention) had been examined [4]. After an average follow-up time of 4.2 years, no significant difference in the rate of coronary incidences was found. After one year of treatment, women of the verum group even experienced significantly more CHD events than women of the placebo group. As of the third year of treatment, the rate for coronary

events tended to shift in favour of the HRT-group. However, in addition women treated with HRT suffered significantly more frequently from venous thromboembolic events and bile duct diseases. Thus, on a short-term basis HRT with CEE and medroxyprogesterone in women with pre-existing CHD is more likely to increase the risk of vascular events. The authors of the HERS-study therefore recommended that women with pre-existing CHD should not start HRT, whereas HRT-practising women can continue HRT [4].

Before advantages and disadvantages of HRT in primary and secondary prevention of CAD can be evaluated, results of further currently ongoing controlled studies have to be awaited.

## 2.2. Influence on cardiovascular risk factors

The progression of arteriosclerotic lesions as well as the clinical manifestation of CHD in form of myocardial infarction and acute cardiac death is mainly determined by risk factors. Classic independent risk factors of CHD are age, the presence of arteriosclerotic vascular diseases, a positive family history for myocardial infarction, diabetes mellitus, arterial hypertension as well as high serum levels of total- or low density lipoprotein- (LDL-) cholesterol and low serum levels of high density lipoprotein- (HDL-) cholesterol [5, 6]. Newer prospective population studies identified raised serum or plasma levels of triglycerides, lipoprotein(a) (Lp(a)), homocysteine, C-reactive protein, insulin, fibrinogen, coagulation factor VII and tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1) as further important risk factors [7]. The combined presence of several factors increases the risk of myocardial infarc-

tion exponentially [5, 6]. Controlled randomized studies proved that the elimination or correction of smoking, hypertension, hypercholesterolemia and the hypertriglyceridemia / low-HDL-syndrome reduces the risk for coronary events (fatal and non-fatal myocardial infarction, aortocoronary bypass or angioplasty) [5, 6].

Estrogens and progestins regulate multiple processes in lipid-, carbohydrate- and amino acid metabolism as well as coagulation and fibrinolysis, which can influence cardiovascular risk factors and therewith the development and progression of arteriosclerosis (table 2).

### *2.2.1. Lipid metabolism*

Oral monotherapy with estrogens (i.e. without progestins) positively influences the CHD risk by decreasing serum levels of LDL-cholesterol and Lp(a) as well as by increasing serum levels of HDL-cholesterol and negatively by raising triglyceride concentrations in serum [8–13].

Estrogens dose-dependently reduce serum levels of LDL-cholesterol by about 10–20% [13]. This effect is probably substantially due to the induction of the LDL-receptor gene expression and the thereby accelerated elimination of LDL. In addition to the quantity, the quality of LDL is changing under medication with estrogens. The size of LDL rises whereby the oxidizability and the atherogenicity is reduced [8–13].

The concentration of lipoprotein(a) decreases during therapy with estrogens by up to 20% [8–13]. Like LDL, this lipoprotein includes one molecule apolipoprotein (apo) B and a cholesterol ester-rich core. In addition, it carries one molecule apo(a), which is structurally homologous to plasminogen [14]. Lp(a) has atherogenic and

Table 2. Effects of various hormone substitution regimes on cardiovascular risk factors

Risk factors	Estrogen (CEE, 17 $\beta$ -Estradiol)	Hydroxyprogesterone (MPA)	Estrogen Plus 9-Nortestosterone (Levonorgestrel)	Tibolon	SERMs (tamoxifene, raloxifene)
LDL-cholesterol	–	–	–	± 0	–
HDL-cholesterol	+	+	–	–	+
Triglycerides	+	+	± 0	± 0	± 0
Lp(a)	–	–	–	–	± 0
Fibrinogen	–	±	0	–	–
PAI-1	(–)	–	–	–	± 0
Glucose tolerance	+	+	(+)	+	?
Insulin resistance	+	+	(+)	+	?
Endothelial function	(+)	± 0	?	+	?

+ = Increasing effect on the respective parameter; - = decreasing effect on the respective parameter;  
( ) = parameters in parenthesis have weak or inconsistent relationships.

thrombogenic features. Its concentration in serum is mainly determined by the variation of the apo(a) gene. An Lp(a) level > 30 mg/dl is considered as a risk factor for myocardial infarction and stroke. Sex hormones are some of the few factors which influence Lp(a) concentration [14, 15].

The concentration of HDL-cholesterol increases by about 10–15% during substitution of estrogens [8–13]. Discussed mechanisms are the inhibition of the gene expression of hepatic lipase and the scavenger receptor B1 (SR-B1) [16, 17]. Both proteins mediate the catabolism of HDL; the hepatic lipase via hydrolysis of HDL-phospholipids, the HDL-receptor SR-B1 via selective uptake of cholesterol ester from HDL into hepatocytes or cells of steroid producing tissues [18, 19].

As an unwanted side effect, substitution of estrogens results in an increase of triglyceride levels by about 20–25 %. In some genetic conditions (e.g. lipoprotein lipase-deficiency), hypertriglyceridemia can exacerbate during therapy with estrogens and result in

acute pancreatitis. Furthermore, hypertriglyceridemia supports, for example through induction of factor VII, a thrombophilic state and thereby possibly contributes to the thromboembolic complications of hormone substitution therapy. The underlying mechanism of estrogen-induced hypertriglyceridemia is the enhanced synthesis of very low density lipoproteins (VLDL) in the liver [8–13].

The combination with progestins interacts with some estrogen effects on lipoprotein metabolism. The HDL-cholesterol rising effect of estrogens is moderated by 17-hydroxyprogesterone derivatives and even abolished or overcompensated by the androgenic effect of 19-nortestosterone derivatives [8–13]. The hypertriglyceridemic effect of estrogens is suspended by 19-nortestosterone-derivatives, but not or only to a minor degree by 17-hydroxyprogesterone derivatives [8–13]. The conventional dosages of progestins do not affect LDL-cholesterol. The Lp(a) lowering effect of estrogens is amplified by 19-nortestosterone derivatives [8–13].

If transdermally applied, the effects of hormone substitution therapy on both, the desired effect on LDL-cholesterol, HDL-cholesterol and Lp(a) and the unwanted hypertriglyceridemia are much less pronounced as compared with oral application. The reason is the missing first pass-effect in the liver [8–13].

### 2.2.2. Haemostasis

Hormonal contraceptives as well as HRT increase the risk of venous thromboembolic incidences. In so far, negative effects of HRT on haemostatic CAD-risk factors are expected. Contrary to this, plasma concentrations resp. activities of fibrinogen, factor VII and of the anti-fibrinolytic acting plasminogen activator inhibitor type 1 (PAI-1) increase. Oral estrogen monotherapy reduces plasma levels of fibrinogen and PAI-1 and increases levels of factor VII. Transdermal application of estrogen does not influence these parameters [12]. Progestins inhibit the effects of estrogens on fibrinogen, PAI-1 and factor VII. However, data about the degree of the inhibitory effects are contradictory. In a previous study we found no statistically relevant effects of a HRT with 1.25 mg or 0.6 mg CEE and 5 mg medroxyprogesterone on fibrinogen, but an 15–20% increase of factor VII and a 0–45% decrease of PAI-1 [13].

The sulphur containing amino acid homocysteine is an intermediate product of the methionine/cysteine metabolism and one further important risk factor for arteriosclerosis and thrombosis. The most important determinants for homocysteine levels in the populations are the dietary uptake of folic acid, vitamin B6 and vitamin B12. Until menopause, women have lower homocysteine levels than men. HRT practising postmenopausal women have lower homo-

cysteine levels than women without HRT.

### 2.2.3. Obesity and insulin resistance

Visceral or central obesity and insulin resistance are important aetiological factors of the metabolic syndrome. This is characterised by the coincidence of several cardiovascular risk factors, namely glucose intolerance or overt diabetes mellitus, hyperinsulinemia, decreased HDL-cholesterol, hypertriglyceridemia, small dense LDL, arterial hypertension, a pro-coagulatory state with increased plasma levels of PAI-1 and factor VII as well as hyperandrogenemia. Cross-sectional studies showed an increase of visceral obesity and insulin resistance (increased fasting-insulin-levels) after menopause. Retrospective case-control-studies have shown contradictory results on the effects of HRT on insulin-resistance and visceral obesity. Estrogen substituting women tended to have lower insulin levels than postmenopausal women without HRT. Addition of progestins neutralised these minimal effects. Actually, placebo-controlled studies about the effects of HRT on insulin-resistance and visceral obesity are missing [11, 12, 20].

In postmenopausal women with diabetes mellitus type 2 HRT with estrogens results in decreases of serum resp. blood levels of glucose, glycated haemoglobin, C-peptide, sex-hormone-binding globulin (SHBG) and free testosterone and, therefore, seems to have an positive effect on insulin sensitivity [20].

### 2.3. Vascular effects

*In vitro*-examinations, animal experiments and clinical examinations about endothelial function have shown that estrogens have direct anti-atherogenic effects on the arterial wall [9–11, 21].

### 2.3.1. *In vitro-examinations*

Estradiol regulates the functions of the arterial endothelium and muscle cells by genomic mechanisms via binding to nuclear estrogen receptors as well as by non-genomic mechanisms e.g. via modulation of ion channels in the plasma membrane. In endothelial and smooth muscle cells, estradiol stimulates (by genomic and non-genomic mechanisms) the production and release of nitric oxide (NO). By activation of guanylate cyclase, NO exerts numerous vasoprotective effects. For example, NO stimulates the relaxation of smooth muscle cells and thus causes vasodilatation, inhibits platelet aggregation and adhesion of leukocytes to the endothelium and thereby their invasion into the arterial wall. Non-genomic effects of estradiol on calcium flow and sodium channels in smooth muscle cells most possibly mediate vasodilative effects of estradiol on smooth muscle cells, too. In addition, estradiol inhibits the proliferation of smooth muscle cells and promotes angiogenesis [21]. Moreover, estradiol inhibits the accumulation of lipids in macrophages and therewith formation of foam cells, which besides endothelial dysfunction is considered as an important initial step in the pathogenesis of arteriosclerosis [9–11, 21].

### 2.3.2. *Clinical studies*

The effects of estradiol on endothelial NO-production explains the endothelial dysfunction in many postmenopausal women, which at least for a short period is improved after uptake of estradiol. Different authors found an enhanced, acetylcholine-induced dilatation of coronary arteries or an enhanced, flow-induced dilatation of brachial arteries after acute uptake of

estradiol (sublingual, intraarterial, intravenous). Nevertheless, it is not clear whether these effects on endothelium-dependent dilatation stay for a long term or are weakened by progestins [9–11, 21].

As a further indication for the improvement of endothelial function by estrogen, a reduced serum concentration of soluble adhesion molecules was found in women with HRT. Angioplasty studies demonstrated the clinical relevance of the reduced proliferation of smooth muscle cells mediated by estrogens: In estradiol-substituted women, re-stenosis and cardiovascular incidences were less frequent than in untreated controls. However, no controlled study-experiences exist on the effects of combined substitution of estrogens and progestins [10, 11].

### 2.3.3. *Animal experiments*

Arteriosclerosis is inhibited or prevented by substitution of estradiol in mice, rabbits or monkeys after ovariectomy. These anti-atherogenic effects in part were independent of changes of lipid metabolism and went along with an improved endothelial function resp. a reduced proliferation of smooth muscle cells. The addition of progesterone erased the anti-atherogenic effect of estradiol in monkeys and rabbits [9–11].

## 3. ALTERNATIVE FORMS OF MENOPAUSAL HORMONE REPLACEMENT THERAPY

Because estrogen substitution is bearing risks with regard to endometrial and breast cancer as well as to venous thromboembolism, alternative forms of

hormone replacement therapies are looked for, which solely exert the positive effects of estrogens on bone, the cardiovascular system and lipid metabolism. Clinical experiences have been obtained from studies with Tibolone, selective estrogen receptor modulators (SERMs) and phytoestrogens.

### 3.1. Tibolone

Tibolone is a synthetic tissue-specific steroid, which is utilised by postmenopausal women for the prevention of osteoporosis and the treatment of climacteric complaints [22]. Because of the missing bleeding, the compliance of the herewith-treated women is better than the compliance of women with conventional HRT. Tibolone is metabolised into three important metabolites, which have estrogenic, progestinic, and androgenic features. The treatment decreased serum or plasma concentrations of triglycerides, Lp(a), glucose, insulin, fibrinogen, PAI-1 and t-PA as well as increased plasma concentrations of plasminogen [22, 23] (table 2). The effects on blood pressure, LDL-cholesterol and apoB are neutral. However, treatment with Tibolone notably decreases serum levels of HDL-cholesterol about 20%. The important question is whether the HDL-decreasing effect is eliminating the positive effects of Tibolone on triglycerides, Lp(a), of insulin and haemostatic factors and whether the treatment with Tibolone thereby affects the occurrence of cardiovascular events. Tibolone improves the endothelial dysfunction, too [22].

### 3.2. Selective estrogen receptor modulators

The selective estrogen receptor modulators (SERM) tamoxifene and raloxi-

fene were originally developed for the therapy of breast cancer. Both drugs decrease the concentration of LDL-cholesterol by about 10% and thereby are similarly effective as the combined replacement therapy with ethinyl-estradiol and medroxyprogesterone (table 2). Treatment with raloxifene decreases the concentration of Lp(a) but to a smaller extent than combined HRT. Raloxifene decreases the plasma concentration of fibrinogen, but has no significant effects on HDL-cholesterol, triglycerides and PAI-1. From the effects on lipid metabolism and haemostasis no conclusion can be drawn on whether treatment with SERM is superior to conventional HRT [8] (table 2).

Animal experiments provided contradictory results on the anti-atherogenic effects of raloxifene. In rabbits, treatment with raloxifene decreased aortic arteriosclerosis but to a lesser degree than treatment with estradiol. In ovariectomized monkeys, raloxifene had no effect on coronary arteriosclerosis [8].

In the Breast Cancer Prevention Trial, treatment of more than 13,000 women for more than 5 years with tamoxifene or placebo did not decrease the rate of CHD events, but similar to conventional HRT [24] increased the rate of thromboembolic events.

### 3.3. Phytoestrogens

Numerous plants contain components with biological activities similar to estrogen. Major classes of these phytoestrogens are isoflavones, coumestanes and lignanes [25, 26]. Legumes are rich in the isoflavones genistein and daidzein. The high consumption of soy bean products in Asia has often been interpreted to be the reason for the lower cardiovascular mortality and

morbidity in these countries. However, effects of isoflavones on cardiovascular risk factors vary interindividually and have not been proven by every investigator. In a meta-analysis of 38 studies, a daily uptake of 47 g soy-protein per day was calculated to cause mean decreases of total and LDL-cholesterol and triglycerides by about 10%. Uptake of 40 mg isoflavone resulted in a 20% increase of HDL-cholesterol but did not exert any effect on other parameters of lipid metabolism [25].

In animal experiments, uptake of soy-phytoestrogen by cholesterol-fed *Cynomolgus*-monkeys decreased the development of arteriosclerosis in all arterial vascular beds. This anti-atherogenic effect was independent of changes in lipid metabolism and is most likely due to direct effects of phytoestrogens on cells of the arterial wall [25].

## 4. TESTOSTERONE

Considering both, the 20–30% prevalence of hypoandrogenism in men aged 65 and older and the 2–20% prevalence of hyperandrogenism in premenopausal women, the question on the influence of testosterone and its metabolites on atherogenesis is an important clinical issue. Furthermore, testosterone is increasingly used for the treatment of male hypogonadism, for hormone replacement therapy in ageing men as well as for contraception in men [27].

### 4.1. Epidemiological and clinical experiences

In eight prospective studies, no association was found between serum concen-

trations of testosterone and coronary events in men [27, 28]. 18 cross-sectional-studies in men found significantly lower serum levels of testosterone or dehydroepiandrosterone sulfate (DHEAS) in CHD-patients compared to controls. 11 studies could not show any difference. In contrast to this neutral or positive role of testosterone in men, few studies in women found evidence for negative effects of testosterone on CHD. In angiographic studies, the concentration of free testosterone correlated positively and independently of other risk factors with the degree of CHD. Other studies found clinical signs of hyperandrogenemia (hirsutism, polycystic ovaries) at higher prevalence in female CHD-patients as compared to control-patients [27].

There are only few data available from intervention studies on the role of androgens in arteriosclerosis. Moreover, symptoms of myocardial ischemia rather than clinical coronary endpoints were investigated. In all cases, treatment of male patients with testosterone resulted in a decrease of the amount and the degree of angina pectoris attacks [27–29]. These positive effects of testosterone are in contrast to case reports of young athletes, who suffered from early myocardial infarction after intake of anabolic androgens [27, 28].

### 4.2. Effects of androgens on cardiovascular risk factors

#### *4.2.1. Lipid metabolism*

Testosterone influences the serum concentrations of HDL-cholesterol and lipoprotein(a) (Lp(a)), but not those of LDL-cholesterol and triglycerides [29] (table 3). In clinical studies, a positive correlation between serum levels of testosterone and HDL-cholesterol was

found. In contrast, several studies revealed that hyperandrogenemic women with polycystic ovaries have significantly lower levels of HDL-C than healthy women of the same age group [29]. In most studies, application of testosterone to hypogonadal men resulted in a decrease of HDL-cholesterol [29]. Application of supra-physiological dosages of non-aromatizable androgens or testosterone to hypergonadal men decreased HDL-cholesterol [29]. In healthy probands, suppression of testosterone serum levels e.g. by short time application of gonadotropin releasing hormone (GnRH) antagonists or analogues resulted in a dosage- and time-dependent increase of HDL-cholesterol concentrations [29]. The mechanisms by which testosterone lowers the concentration of HDL-cholesterol include the enhancement of hepatic lipase activity [30].

Testosterone reduces the concentrations of Lp(a), too. Orchidectomy in patients with prostate cancer causes a significant increase of Lp(a) serum concentrations. The application of testosterone to orchidectomized patients with prostate cancer or of supraphysiological dosages of testosterone-enanthate in healthy men was associated with a significant decrease of Lp(a) serum concentrations by about 25–60 %. By contrast, suppression of endogenous testosterone by treatment with the GnRH-antagonist Cetrorelix resulted in a 40–60 % increase of Lp(a) concentration [27]. Presumably, testosterone regulates the concentration of apo(a) on the transcriptional level [27].

#### 4.2.2. Relationship between androgens, adipose tissue, and insulin resistance

Multiple findings point to the importance of testosterone for the distribution of adipose tissue, which again is

considered as an important determinant of insulin sensitivity and HDL-cholesterol levels (table 3). In men, overweight and insulin resistance are often associated with testosterone deficiency. On the other hand, overweight is often found in hypogonadal men [27]. The serum concentrations of insulin and leptin are increased in hypogonadal men and decrease after testosterone substitution. Suppression of testosterone by GnRH-antagonists increased serum levels of insulin and leptin [31]. These findings underline, that testosterone in men keeps the amount of adipose tissue low and (thereby?) improves insulin sensitivity. However, supraphysiological dosages of testosterone-enanthate result in weight gain [27].

In women, inverse observations were made. Testosterone and BMI correlate positively. Increased androgen levels are a marker for truncal obesity. Hyperinsulinemia and insulin resistance come along with lower serum concentrations of SHBG, an indirect measure of hyperandrogenism in women. Women with the polycystic ovary syndrome often suffer from visceral obesity and have increased serum levels of leptin and insulin (basal and after glucose stress). A prospective study showed that 20 % of women with SHBG-levels below the fifth percentile develop diabetes mellitus within 12 years [27]. However, from the above-mentioned clinical studies in women it remains unclear, whether obesity precedes hyperandrogenism or vice versa. Results from clinical studies in transsexual women and from animal examinations indicate that hyperandrogenism goes ahead of and most possibly determines obesity and thereby insulin resistance. However, recent findings have shown as well that insulin stimulates androgen production in the ovary and thus make

a positive feedback between insulin and testosterone possible (table 3) [27].

#### 4.2.3. Haemostasis

Testosterone is having prothrombotic as well as antithrombotic effects on the haemostatic system (table 3). Serum levels of testosterone inversely correlate with plasma levels of fibrinogen and PAI-1. Hypogonadal men show a reduced fibrinolytic plasma activity, possibly due to increased PAI-1-levels. Supraphysiological testosterone levels significantly reduce plasma levels of fibrinogen, PAI-1, Protein C and Protein S. In vitro, testosterone inhibits the secretion of PAI-1 from endothelial cells. However, testosterone promotes platelet aggregation by the inhibition of cyclooxygenase activity [27].

#### 4.3. Vascular effects

There exist only a few and contradictory data from clinical studies on the effects of testosterone on vascular reactivity in human. The results of most in vitro examinations and animal experiments showed that testosterone improves vascular reactivity [27–29]. In isolated vessel rings of the aorta or of coronary arteries, application of testosterone improved endothelium-dependent and endothelium-independent vasodilatation. Infusion of testosterone improved the endothelium-dependent and endothelium-independent vasodilatation in monkeys and dogs, too. These effects are at least in part mediated by non-genomic effects. In addition, they are independent of estradiol, into which testosterone

Table 3. Results from clinical and epidemiological studies on the relationships between testosterone and different metabolic parameters

		Men	Women
Association of endogenous testosterone levels with metabolic parameters	Lipoproteins Glucose metabolism Lipid tissue Haemostasis	HDL + (LDL –, Trigl. –) Glucose +, insulin – Body fat +, leptin – Fibrinogen –, PAI-1 –	HDL –, LDL +, Trigl. + Glucose –, insulin – Body fat +, leptin + Fibrinogen +, PAI-1 +
Effects of testosterone substitution in hypogonadism	Lipoproteins Glucose metabolism Lipid tissue Haemostasis	Lp(a) – Insulin – Leptin – Fibrinogen –	
Effects of supraphysiological testosterone dosages	Lipoproteins Glucose metabolism Lipid tissue Haemostasis	HDL –, Lp(a) – Fibrinogen –, PAI-1 –	HDL –* Fibrinogen –*, PAI-1 –*
Effects of suppression of endogenous testosterone	Lipoproteins Glucose metabolism Lipid tissue Haemostasis	HDL +, Lp(a) + Insulin + Leptin +	

+ = Positive correlation of testosterone with or increasing effect of testosterone on the respective parameter; – = Negative correlation of testosterone with or decreasing effect of testosterone on the respective parameter; () parameter in parenthesis = weak or inconsistent relationship; HDL-C = HDL-cholesterol, LDL-C = LDL-cholesterol, PAI-1 = plasminogen activator inhibitor type 1; \*= effect of androgenic anabolics, e.g. Danazol.

one can be metabolised by endothelial aromatase [27].

In several studies, the effects of testosterone on arteriosclerosis of castrated male e.g. ovariectomized female animals were examined. In comparison to control-animals, male rabbits, which were treated with testosterone, developed less arteriosclerotic lesions after feeding of cholesterol or balloon-injuries of the aorta [27, 28, 32]. In cocks, the application of testosterone dosage-dependently favoured the development of arteriosclerosis [27, 28]. Application of testosterone to female, cholesterol-fed *Cynomolgus*-monkeys or rabbits doubled the extent of arteriosclerosis as compared to non-treated and ovariectomized control-animals. The atherogenic effects of testosterone occurred independently of lipoprotein parameters and other coronary risk factors [27, 28]. The contradictory results are most likely due to sex specific effects of testosterone, which in male animals appear to be anti-atherogenic or neutral but rather pro-atherogenic in female animals [27, 28].

gen- and estrogen-like effects. Although DHEA(S) is generally considered as a "fountain of youth" and is marketed as such in the USA, clinical and experimental evidence for the postulated anti-atherogenic effects is poor [34].

In two of four prospective population studies, inverse associations between serum concentration of DHEAS and the risk of myocardial infarction were found in men. In several clinical case-control studies or angiographic studies the relationship between the presence or the degree of coronary arteriosclerosis and DHEA(S) serum concentration in men was inverse, too. In contrast, women with high DHEAS concentrations were found to have an elevated risk of myocardial infarction. Like testosterone, DHEA and DHEAS have sex-specific effects on cardiovascular risk factors. Several components of the metabolic syndrome are inversely associated with DHEAS levels in men but positively in women.

In analogy to testosterone, no conclusions can be drawn from association studies, on whether there exists a causal relationship between DHEA(S) and arteriosclerosis or on whether it only is a surrogate marker for the existence of an atherogenic situation of metabolism [27, 28].

In castrated male rabbits, uptake of DHEA(S) delayed the progression of arteriosclerotic lesions [27, 28, 32]. This anti-atherogenic effect was less pronounced than that of testosterone [32].

There exist only a few controlled studies with sufficient long period of treatment to evaluate the effect of DHEA(S) on cardiovascular risk factors. The effects appear to be marginal. In postmenopausal women, application of DHEA results in a slight reduction of HDL cholesterol [34]. In vitro, DHEA inhibits the migration and proliferation of smooth muscle cells and the accu-

## 5. DEHYDROEPIANDROSTERONE (-SULFATE)

In addition to menopause in women and andropause in some men, the endocrinology of ageing is characterised by increasing insulin-resistance and decreasing beta-cell-function, by a reduced function of the thyroid gland, by somatopause as well as by adrenopause with decreasing serum-levels of dehydroepiandrosterone (sulfate) (DHEA(S)) [33]. The physiological functions of DHEA and DHEAS are unknown. In vitro, DHEA and DHEAS exert andro-

mulation of cholesterol in macrophages [27, 28]. Clinical examinations on the effects of DHEA(S) on vessel function have not been published.

## 6. SUMMARY AND CONCLUSIONS

After menopause, cardiovascular diseases substantially contribute to cardiovascular morbidity and mortality of women. Although estrogens exert several positive effects on the cardiovascular system and risk factors, controlled intervention studies have shown that HRT with estrogens in secondary prevention raises the risk of venous thromboembolic events and does not prevent myocardial infarction. Data of controlled studies for primary prevention are missing. Insofar, today no common recommendations can be given on the suitability of hormone replacement therapy for the prevention of cardiovascular diseases. Markers are necessary, which identify those women, who benefit from HRT, without taking the hazard of a higher-than-average risk for thrombosis or breast cancer. Evidence is also missing, that postmenopausal treatment with Tibolone, Raloxifen or similar substitutive steroids shows a more favourable risk-benefit relationship than conventional HRT with estrogens and medroxyprogesterone. Thus, postmenopausal women with elevated CHD-risk should preferentially be treated with those drugs, which in controlled studies have been proven to be safe and to prevent cardiovascular events, namely statins, beta blockers and acetylsalicylic acid [5, 6]. Certain risk factors can serve as an argument to start (e.g. increased Lp(a)) or to omit HRT (e.g. the oral therapy with estrogens in hypertriglyceridemia or thrombophilia).

In view of the controversial results from population studies, animal experiments and clinical studies and especially due to the lack of controlled intervention studies, the significance of testosterone and DHEA(S) for arteriosclerosis is uncertain.

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