POSTMENOPAUSAL HYPERANDROGENEMIA (ANDROID OBESITY, INSULIN RESISTANCE, DIABETES MELLITUS) AND THERAPEUTIC CONSEQUENCES

D. FOTH, TH. RÖMER

POSTMENOPAUSAL HYPERANDROGENEMIA

The clinically relevant androgens in women are androstendione, DHEA, DHEAS and testosterone. Testosterone is a fairly strong androgen and is the precursor of dihydrotestosterone. During reproductive age, 25% of the testosterone each are produced by the ovary and adrenal cortex, and 50% are the result of peripheral conversion. Testosterone production by the ovary and adrenal cortex and peripheral conversion can be detected up to a very high age. In the postmenopause, the ovary is the most important source of androgen production. Testosterone becomes the physiologically predominant androgen in the postmenopause. It was already shown many years ago that bilateral oophorectomy in postmenopausal women causes a decrease in androgen serum levels, so that the postmenopausal ovary secretes androgens [1, 2]. In the female, testosterone is important for the female sexual function, general well-being and performance.

Androgen synthesis in the ovary is stimulated by LH. High postmenopausal LH levels stimulate androgen production in the hilum and luteinized stroma cells of the ovary. This may be the mechanism by which the postmenopausal ovary secretes more testosterone than the premenopausal ovary [3]. The presence of thecal cells in the ovaries varies individually, however, so that postmenopausal women may develop hyperandrogenemia on the one hand, but also hypoandrogenemia on the other hand. Normally, the testosterone levels are not significantly reduced in the early postmenopause compared with the premenopause.

Estrogen deficiency leads to reduced SHBG production in the liver. Testosterone has a high affinity for SHBG. With decreasing SHBG concentration, less testosterone is bound to SHBG and the free testosterone in the blood increases, resulting in a relative hyperandrogenemia. This mechanism may be the cause of the androgenization signs

Table 1. Androgens in the reproductive phase and in the postmenopause

	Mean concentration (ng/ml)	Mean production rate (mg/d)
Testosterone		
Reproductive phase	0.4	0.3
Postmenopause	0.19	0.21
Androstendione		
Reproductive phase	1.4	2.8
Postmenopause	0.8	1.4
DHEA		
Reproductive phase	4.2	6.7
Postmenopause	2	3.1

observed in the postmenopause, e. g. in the form of facial hirsutism. On the other hand, the lower SHBG concentration results in a higher testosterone clearance rate. Androstendione, DHEA and DHEAS decrease in the postmenopause.

Endocrinologically, both hypo- and hyperandrogenemias are possible in the postmenopause.

Hyperandrogenemia – Insulin Resistance – Hyperinsulinemia

Increasing age is associated with a deterioration of glucose tolerance and an increased risk of manifest diabetes. A disturbed glucose tolerance or diabetes mellitus can be found in about 20 % of women aged 55 to 65 [4].

Insulin resistance and reactive hyperinsulinemia are typical of non-insulin-dependent diabetes mellitus (type II). The physiological insulin concentrations are not sufficient to obtain an adequate response from the target cell; to compensate for this, more insulin is produced. Hyperinsulinemia is an important risk factor for disorders of the lipid metabolism and cardiovascular diseases such as arteriosclerosis, myocardial infarction and apoplexia. There is a correlation between the incidence of endometrial carcinoma and the development of diabetes type II.

Possible causes for the development of insulin resistance are:

- obesity,
- chronic stress, and
- hyperandrogenemia.

What is the connection between insulin resistance and hyperandrogenemia?

The ovary has receptors for insulin and the insulin-like growth factors (IGF-1). With developing insulin resistance in the other organs, the sensitivity of the ovary for insulin is maintained. In the ovary, insulin enhances the LH effect and stimulates pituitary LH secretion. High LH levels lead to stimulation of androgen synthesis in the ovary [5]. The consequences of chronic hyperinsulinemia are also manifest in other organs:

- Skin and appendages: Stimulation of 5alpha-reductase activity (responsible for the conversion of testosterone into 5alpha-dihydrotestosterone)
- Liver: Disorders of the lipid metabolism; increased levels of triglycerides, VLDL and LDL cholesterol, and reduced levels of HDL cholesterol; inhibition of SHBG synthesis
- Adrenal gland: Stimulation of adrenal testosterone and androstendione synthesis; suppression of adrenal DHEA and DHEAS secretion (overview in Leidenberger [6]; Fig. 1)

The causes of insulin resistance are not fully known yet. Genetic causes may play a role, and chronic stress with the release of endogenous opiates promotes insulin resistance [7].

Hyperandrogenemia and insulin resistance are mutually dependent. As described above, insulin resistance may also cause hyperandrogenemia, which has itself a negative effect on insulin resistance.

Obesity – Hyperandrogenemia – Insulin Resistance

In obesity, a distinction is made between android (abdominal) and gynecoid (ubiquitary, non-central) fat distribution. The definition is based on the

quotient of waist and hip circumference. If it is > 0.8, we speak of an abdominal type. The abdominal form of obesity reflects an increased visceral deposition of fat. In postmenopausal women, a shift in fat distribution towards the abdominal type is frequently observed. Temporally, these redistribution processes are more likely to be associated with the time since the menopause than with the biological age [8].

Android obesity is frequently associated with insulin resistance and its consequences, such as disorders of lipid metabolism, cardiovascular diseases (arteriosclerosis, myocardial infarction, hypertension, apoplexia), and hyperandrogenemia. For women with a female fat distribution, the risk of these disorders is lower. Obesity and hyperandrogenemia are two predisposing factors for insulin resistance.

Sexual hormones generally have an influence on body weight. Abdominal and gluteal fat are influenced by hormones in different ways. Chronic hyperandrogenemia leads to an abdominal form of fat deposition. Androgens have a lipogenic effect due to an increase in insulin resistance. On the other hand, androgen deficiency causes a reduced lipolysis in the same region of the body, and thus also leads to an increase in abdominal fat.

Overweight is also directly associated with the secretion of androgens by the adrenal cortex. At the same time, reduced SHBG levels lead to a higher level of free androgens, and the clearance rate is higher. If the metabolization rate does not increase parallel to the secretion rate, the androgen serum levels increase. The ratio between secretion and elimination determines the serum androgen levels, which need not necessarily be increased in obesity.

Android obesity, insulin resistance and hyperinsulinemia as well as hyperandrogenemia represent a complex of

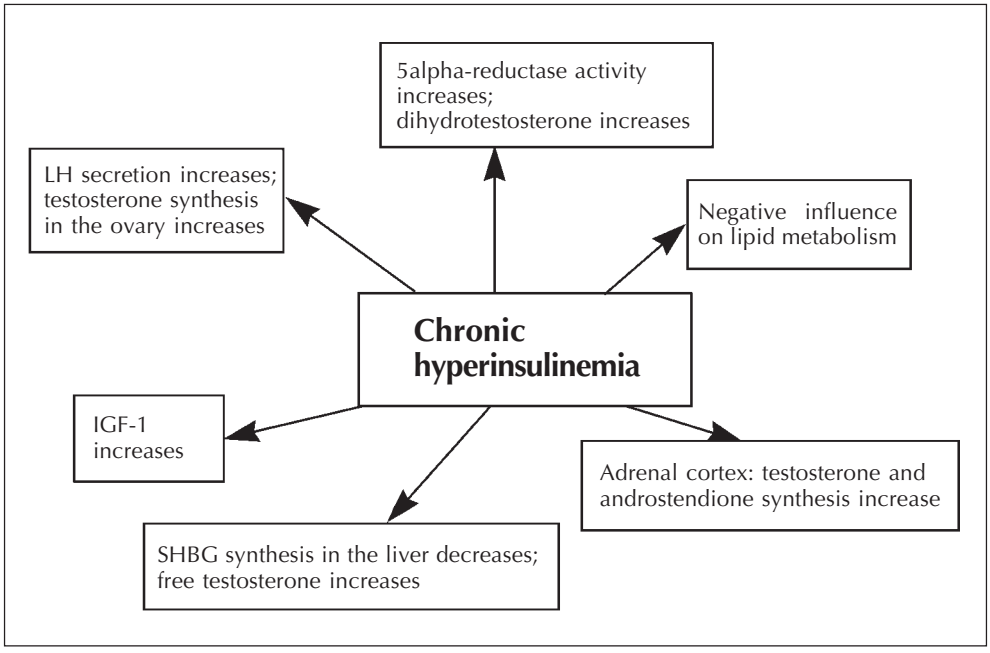

Figure 1. Consequences of chronic hyperinsulinemia

symptoms that are mutually dependent and maintain (Fig. 2).

The serious consequences and health risks are important: disorders of the lipid metabolism, cardiovascular diseases such as arteriosclerosis, myocardial infarction, hypertension, apoplexia and diabetes mellitus. Therefore, it is important for the gynecologist to diagnose and treat these diseases in order to prevent the long-term consequences.

Therapy

In obesity, the primary therapeutic goal is weight reduction. Thereby, a sustained, continuous weight reduction with a change in eating habits and physical activity is important. Systematic weight reduction is important for normalization of the androgen levels, the insulin sensitivity increases, and the insulin concentrations drop. Abdominal lipopexia is subject primarily to the intake of food, whilst lipolysis is testosterone-dependent [9]. A postmenopausal shift in fat distribution from gynecoid to android can be minimized by hormone replacement therapy, e.g. with conjugated estrogens and medroxyprogesterone acetate [10].

Androgenization signs in the postmenopause can be influenced positively by long-term hormone replacement with estrogen-gestagen combinations. Thereby, gestagens with partial antiandrogen effect, such as e.g. cyproterone acetate, dienogest and chloromadinone acetate should be used. Gestagens with residual androgen effect are not recommended for this indication due to possible negative effects on the lipid metabolism.

The preventive effect of hormone replacement therapy in the postmenopause on cardio- and cerebrovascular disorders must be regarded as confirmed. It has a beneficial effect on lipid metabolism. Women with insulin resistance, obesity and hyperandrogenemia have a higher risk of lipid metabolism disorders and cardiovascular diseases, and should receive hormone replacement therapy.

Patients with non-insulin-dependent diabetes mellitus also benefit from hormone replacement: the androgen levels normalize, and the glucose metabolism is influenced positively [11, 12]. The extent of insulin resistance can also be influenced positively by hormone replacement with estrogens in the postmenopause [4, 13]. In short-term therapy, low-dose estrogen-gestagen combinations do not have any effect on insulin sensitivity [14].

IUDs with levonorgestrel can abolish the improvement of insulin sensitivity achieved with transdermal estrogen replacement [15]. However, there is not much data available. In total, gestagens with partial androgen effect seem to have a more negative influence on the estrogen effect than progesterone derivatives [4]. In insulin resistance and hyperinsulinemia, the best results can be expected from low-dose estrogen monotherapy.

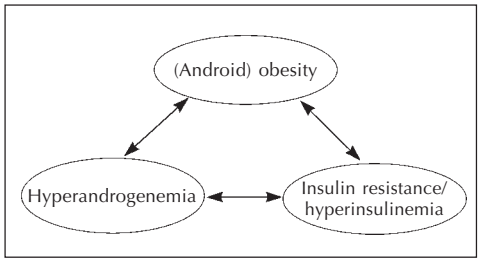

Figure 2. Connection between obesity, hyperandrogenemia and insulin resistance/ hyperinsulinemia

BIBLIOGRAPHY

1. Adashi EY. The climacteric ovary as a functional gonadotropin-driven androgen-producing gland. Fertil Steril 1994; 62: 20.
2. Judd HI, Korenman SG. Aging and reproductive function in women. In: Korenman SG (ed). Endocrine aspects of aging. Elsevier Biomedical, New York 1982; 169.
3. Sluijmer AV, Heineman MJ, De-Jong FH, Evers JL. Endocrine activity of the postmenopausal ovary: the effects of pituitary downregulation and oophorectomy. J Clin Endocrinol Metab 1995; 80: 2163–7.
4. Gaspard UJ, Gottal JM, van den Brule FA. Postmenopausal changes of lipid and glucose metabolism: a review of their main aspects. Maturitas 1995; 21: 171–8.
5. Haffner SM. Sex hormone-binding protein, hyperinsulinemia, insulin resistance and noninsulin-dependent diabetes. Horm Res 1996; 45: 233–7.
6. Leidenberger FA. Klinische Endokrinologie für Frauenärzte. Springer-Verlag, Berlin; Heidelberg; New York 1997; 320.
7. Schoemaker J. Neuroendocrine control in polycystic ovary-like syndrome. Gynecol Endocrinol 1991; 5: 277.
8. Tremollieres FA, Pouilles JM, Ribot CA. Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. Am J Obstet Gynecol 1996; 175: 1594–600.
9. Azziz R, Downing Potter H, Bradley E, Boots L. Androstene-3-beta, 17-beta-diol in healthy eumenorrheic women: relationship to body mass and hormonal profile. Fertil Steril 1994; 62: 2.
10. Reubinoff BE, Wurtmann J, Rojansky N, Adler D, Stein P, Schenker JG, Brzezinski. Effects of hormone replacement therapy on weight, body composition, fat distribution, and food intake in early postmenopausal women: a prospective study. Fertil Steril 1995; 64: 963–8.
11. Andersson B, Mattsson LA, Hahn L, Marin P, Lapidus L, Holm G, Bengtsson BA, Bjorntorp P. Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1997; 82: 638–43.
12. Brussaard HE, Gevers Leuven JA, Frolich M, Kluft C, Krans HM. Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM. Diabetologia 1997; 40: 843–9.
13. Elkind-Hirsch KE, Sherman LD, Malinak R. Hormone replacement therapy alters insulin sensitivity in young women with premature ovarian failure. J Clin Endocrinol Metab 1993; 76: 472.
14. Kimmerle R, Heinemann L, Heise T, Bender R, Weyer C, Hirschberger S, Berger M. Influence of continuous combined estradiol-norethisterone acetat preparations on insulin sensitivity in postmenopausal nondiabetic women. Menopause 1999; 6: 36–42.
15. Raudaskoski T, Tomas C, Laatikainen T. Insulin sensitivity during postmenopausal hormone replacement with transdermal estradiol and intrauterine levonorgestrel. Acta Obstet Gynecol Scand 1999; 78: 540–5.

Editor:
Franz H. Fischl

MENOPAUSE
ANDROPAUSE

Hormone replacement therapy through the ages
New cognition and therapy concepts

http://www.kup.at/cd-buch/8-inhalt.html

Krause & Pachernegg GmbH
VERLAG für MEDIZIN und WIRTSCHAFT