



Sex hormones and the development of type 2 diabetes in women

Renato Pasquali

University Alma Mater Studiorum of Bologna, Bologna, Italy

Correspondence to: Renato Pasquali. University Alma Mater Studiorum of Bologna, Via Santo Stefano 38, 40125 Bologna, Italy.

Email: renato.pasquali@unibo.it.

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In the last two decades several cross-sectional or prospective studies demonstrated that increased testosterone blood levels and reduced sex-hormone binding globulin (SHBG) concentrations may significantly predict the development of type 2 diabetes (T2D) in women (1-3). In addition, those studies including a male cohort demonstrated that the best predictive factors of the development of T2D were lowered SHBG but also low testosterone blood levels (2). Based on these studies it is clear that the role of sex steroids in predicting susceptibility to T2D is dichotomous. The role of excess androgens and low circulating levels of SHBG as potential factors in the development of T2D has been clearly demonstrated in women with polycystic ovary syndrome (PCOS), who are characterized not only by hyperandrogenism, either clinical (hirsutism) and/or biochemical (elevated testosterone), and ovarian dysfunction (oligo-amenorrhea and oligo-anovulation), according to the available guidelines (4,5), but also by intrinsic insulin resistance and compensatory hyperinsulinemia and a very high prevalence of obesity and abdomino-visceral fat expansion (6). Although association does not imply causality, these findings strongly support the concept that an altered and specific sex hormone imbalance may represent key factors in determining the development of T2D in middle-aged and elderly men and in adult women, particularly during postmenopausal years.

The study by Muka and co-workers (7) published in this issue adds a new piece of work on the complex topic related to the potential responsibility of altered sex hormone balance in women on the development of T2D. They prospectively analysed a large cohort of women participating in the Rotterdam study (8) to investigate

whether endogenous sex hormones and SHBG blood levels were associated with the risk of incident T2D and found that low SHBG and total estradiol blood levels, but not total and bioavailable testosterone, were significantly associated with a significant increased risk to develop T2D. Moreover, these findings were confirmed in a meta-analysis of population-based prospective studies. Interestingly, they also demonstrated by multiple statistical analyses that the association of low SHBG and T2D was not changed by menopausal status, whereas that between estradiol and T2D was significant only in postmenopausal women. These findings merit specific and appropriate comments.

The impact of androgens on the risk and development of T2D

Recent studies have clearly demonstrated that an androgen profile is better than testosterone in evaluating androgen balance in pre- and postmenopausal women, provided that androgens are measured by appropriate new methodologies such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), which combines high sensitivity and specificity (9). In fact, available immunoassays for testosterone measurement are decidedly unsatisfactory (9). In addition, several recent studies have clearly demonstrated that not only testosterone (total and free), but particularly $\Delta 4$ -androstenedione and dihydrotestosterone (DHT), are significantly associated with parameters of the metabolic syndrome and indices of insulin resistance (10-13), at least in women with PCOS. A recent study also found that 11-oxygenated androgens (measured by LC-MS/MS) which are mostly of adrenal origin, represent a large proportion

of circulating androgens in women with PCOS, with a close correlation to markers of metabolic dysfunction and insulin resistance (14). This further emphasizes the need to expand the androgen pool investigation in these women (and possibly even in non-PCOS women), that should not be limited to testosterone (total or free), in order to discover their potential link with metabolic derangements and, ultimately, with the risk of developing T2D. Obviously, this should be done separately in pre- and postmenopausal women, with careful investigation of the impact of excess weight and obesity, due to the fact that excess body weight, particularly if associated with enlarged visceral fat, has a close bidirectional interaction with sex hormones, specifically androgens (3).

These considerations are particularly important as in the study by Muka *et al.* (7) it is relatively unclear how many women had a hyperandrogenic state, such as PCOS. Certainly, in their meta-analysis they also included a study including only women with PCOS (15) and at least two additional studies in which the inclusion of women with PCOS was likely (2,16). Another aspect that should be discussed is related to the fact that in the Rotterdam study, 5.3% of women were taking hormone replacement therapy, which obviously interferes with the balance of androgens and estrogens, even this was considered in the statistical model including different covariates. In spite of these aspects, that can be justified in very large prospective studies, the finding that lowered SHBG and increased total estradiol may predict the development of T2D merits consideration.

The impact of SHBG on the risk and development of T2D

In women, reduced SHBG concentrations are frequently associated with metabolic issues, defined by the cluster of the metabolic syndrome (3). Visceral fat expansion and insulin resistance are key factors responsible for this. In fact, it is well known that hyperinsulinemia secondary to insulin resistance leads to a decreased synthesis of SHBG in the liver, therefore explaining its lowered circulating blood concentrations (3). On the other hand, in their study Muka and co-workers (7) found that, after adjusting for BMI, insulin and glucose, the association between SHBG blood levels and T2D was still significant. This obviously implies that further mechanisms are involved. First, this may lead to an increased availability of estradiol precursors, chiefly $\Delta 4$ androstenedione and testosterone, although their

different binding activity is much higher for testosterone than estradiol (3). Notably, however, the association between circulating levels of SHBG with T2D remains significant after adjusting for total and free testosterone, which suggests that, in women, SHBG predicted T2D independently of androgen levels.

Recent studies have clearly shown that specific polymorphisms of SHBG may play a specific role in favouring the development of T2D or protecting against it. Using a Mendelian randomization principle in a large population of subjects of both sexes with T2D or non-diabetic controls derived from 15 studies, Perry and co-workers (17) found that a common single nucleotide polymorphism (SNP) near the SHBG gene, rs1799941, is an important risk factor for the development of T2D in women [odds ratio (OR) 0.93; 95% CI: 0.89, 0.98; $P=0.003$], with the SHBG raising allele being associated with a reduced risk of T2D. It is worth mentioning that there is evidence that alterations in SHBG levels precede the development of alterations in glucose homeostasis, which implies the early identification of subjects at risk for T2D (3). Additional still poorly defined mechanisms by which SHBG may disrupt glucose homeostasis may involve its structure and function at the intracellular level and, potentially, the transcriptional regulation of the *SHBG* gene (3).

The impact of estrogens on the development of T2D

The most important finding of the study by Muka *et al.* (7) is that estradiol blood levels and the risk for T2D were positively associated, regardless of BMI or years since menopause. In some way, this belies what has been known for a long time about the relationship between estrogens and T2D. This requires a brief review on the metabolic effects of estrogens and their potential impact in altering the glucose-insulin system. Animal studies provide some interesting aspects on the role of estrogens on metabolic issues. For example, estrogen deficiency in the female aromatase knockout (ArKO) mice favours the development of the metabolic syndrome and leads to glucose intolerance and insulin resistance. Conversely, estrogen replacement in the female wild type and ArKO mice leads to both insulin sensitizing and resistance effects, depending on age and dosage (18). There is experimental evidence from *in vitro* studies that estrogens may activate glucose-stimulated insulin biosynthesis and promote β -cell survival, via activation of estrogen receptors alpha ($ER\alpha$) and beta

(ER β) (19). On the other hand, it has been shown that overstimulation of ER α by estrogen excess will produce excessive insulin signaling, leading in turn to systemic insulin resistance (20). In addition, estrogens play a central role in the control of energy homeostasis, even at central brain levels (21). In rodents, changes in the adipose tissue can be reversed by estrogen replacement (3). There are several studies confirming that estrogen replacement may inhibit adipose tissue deposition by decreasing the expression involved in the lipogenic pathways (22). At variance, other studies reported that estradiol increased the proliferative capacity of subcutaneous preadipocytes in rats (23) as well as in human preadipocytes. In postmenopausal women, the hypoestrogenic environment has been found to favour an increase of visceral fat, with increased adipocytes size and number (22). Nonetheless, the role of estrogen replacement in postmenopausal women in modulating adiposity is still controversial (22). Taken together, the full activity of estrogens on adipose tissue in women remains partly unclear and requires more intensive and focused basic investigation and well conducted clinical research trials in homogeneous populations and for a long period of time.

Estrogen deficiency has also been suggested to play a role in favouring the development of the metabolic syndrome after menopause, whereas estrogen replacement has been found to improve insulin sensitivity and the risk for diabetes in rat models (24). In addition, as the main production of estradiol in postmenopausal women comes from the adipose tissue, it has been suggested that it may act as a messenger between adipocytes and β -cells in obesity (20). A relatively large amount of data also supports the concept that estrogen may contribute to the prevention of the metabolic syndrome and adipose tissue inflammation through the regulation of the production and activity of key adipocytokines involved in the control of energy homeostasis and insulin resistance (25).

Although for many years the clinical administration of estrogens, particularly in postmenopausal women, had a poor reputation with regard to glucose metabolism, the Estrogen Progestin Replacement Study and the Women Health Initiative study found that treatment with estrogen significantly reduced the incidence of T2D (26). These findings have been confirmed by additional prospective studies published later in time (26). In addition, these studies provided some evidence that this effect was partly related to the simultaneous reduction of fat tissue, although modest. Although these clinical studies support the concept that estrogens might benefit insulin

secretion and action, there are data both for and against this hypothesis (25). Many concerns regarding this issue have not yet been answered, even if it is clear that, based on animal studies and prospective clinical trials in women, especially after menopause, that excess estrogen and estrogen replacement, both in the short and long term, may result in relatively divergent effects on the glucose-insulin system. Consequently, we still need additional clinical trials, pursuing replacement therapy on individual-based rather than on population-based trials. Whatever the case, these trials should also consider the impact of excess body weight and fat distribution. The findings of the positive relationship of estradiol blood levels with incident T2D reported in the study by Muka and co-workers (7) suggests the need to go in this direction. Another aspect of great interest is represented by the fact that low levels of SHBG may coexist with relatively normal or elevated estradiol blood concentrations. Therefore, future studies should more properly investigate the potential involvement of unbalanced sex hormones in women, extended to androgens and intermediate metabolites, in determining major changes in circulating levels of SHBG and in modulating its activity at the cellular levels. This could impressively help in explaining the development of T2D, particularly in the menopausal years.

Conclusions

In conclusion, the history of the causal relationship between sex hormones and the risk of metabolic diseases, especially T2D, is still far from being adequately explained. A better understanding of the molecular mechanisms and related genetic aspects of androgens and estrogens and, above all, of SHBG, on the regulation of the glucose-insulin system may suggest new approaches for the prevention of T2D in women, especially after the menopause. Future studies in women will necessarily have to distinguish specific subgroups, particularly those with PCOS, who seem to have a specific susceptibility to T2D. In addition, particular attention must be given to the opportunity to modulate hormone replacement therapy after menopause on the basis of individual metabolic characteristics of patients, according to the concept of personalized medicine.

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