Gynecological Endocrinology, January 2010; 26(1): 1–3

informa
healthcare

EDITORIAL

Metabolic syndrome and cardiovascular risk factors in the menopausal transition

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Alterations of the hormonal profile begin in the early 40s, before the complete cessation of menses, consequently changes in risk factors for cardiovascular disease (CVD), such as lipids and anthropometric characteristics could also be observed in this period. It has been necessary to investigate the behavior of these factors during the transition to menopause and still it is not clear when metabolic alterations occur. Some authors have found that perimenopausal women did not show more adverse alterations in lipids than premenopausal ones [1]. On the other hand, others have described an increase in atherogenic lipoproteins [2], although not always associated with hormonal status [3].

By other side, postmenopausal status is associated with an increased risk of metabolic syndrome, even after adjusting for confounding variables, such as age, body mass index, or physical inactivity [4]. Moreover, the risk of CVD attributed to the metabolic syndrome appears to be especially high in women; it is estimated that half of all cardiovascular events in women are related to this syndrome. The etiology of the metabolic syndrome is unknown, but it is thought to be a cluster of factors and its underlying pathophysiology is related to increased visceral obesity and insulin resistance. There are a few studies nowadays that investigate the behavior of the metabolic syndrome during the transition to the menopause and it is not clear when metabolic alterations begin.

With regard to the standard methods of evaluating insulin resistance, such as the hyperinsulinemic euglycemic clamp technique and the intravenous glucose tolerance test, they are considered to be impractical in clinical practice and difficult to perform in population-based research studies. More simple but indirect methods have been suggested for quantification of insulin resistance, such as the homeostasis model assessment, the quantitative insulin sensitivity check index (QUICKI) and, more recently, the triglyceride/HDL-cholesterol index [5]. Some authors suggest that the latter offers a good surrogate method in the identification of insulin-resistant subjects, given the well-standardized methods for the evaluation of triglycerides and HDL-cholesterol, and the good correlation found with the gold standard method.

On the other hand, changes in androgen levels during the menopausal transition are controversial. Although it is generally accepted that testosterone levels do not change significantly in this period of life, some authors have found a decrease in testosterone, androstenedione, and sex hormone binding globulin (SHBG) 2 years around menopause [6]. Meanwhile, other authors consider that this is a period of relative hyperandrogenism as a consequence of the greater decrease in estrogens in comparison with the decrease in androgens [7]. However, the androgenic profile in the menopausal transition has been scarcely studied.

Our aim was to assess if there is a relationship between the main components of the metabolic syndrome, insulin resistance, and androgens with the menopausal status across the menopausal transition from pre- to postmenopausal state, including the earlier and later phases of perimenopause.

In our studies, we evaluated four groups of women: premenopausal, menopausal transition women with menstrual bleeding, menopausal transition women with 3–6 months amenorrhea, and postmenopausal women.

The incidence of metabolic syndrome, increased across the menopausal transition [8]. None of the

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ISSN 0951-3590 print/ISSN 1473-0766 online
DOI: 10.3109/09513590903080969

premenopausal women studied presented three or more of the characteristics that define the metabolic syndrome, but, from the first stage of the menopausal transition, the appearance of these features increased up to the postmenopause. In the women in menopausal transition, as well as in the postmenopausal group, we found that the metabolic syndrome affects 20–22% of women, without differences among them. The most common alterations observed were the increase in waist circumference and blood pressure, and the decrease in HDL-cholesterol. Regarding insulin resistance surrogate markers, triglyceride/HDL-cholesterol index was the only one which increased across the menopausal transition towards menopause.

From these studies, we can observe that the prevalence of the metabolic syndrome significantly rises from the earlier stages of the menopausal transition, in comparison to premenopausal women. However, when applying multivariate analysis adjusting by age, this variable accounted for most of the variation in the metabolic syndrome development.

Our studies also showed that, as the menopausal transition goes ahead, androgenic status increases in association with abdominal fat deposition [9]. It should be remarked that waist circumference is an interesting surrogate marker of abdominal obesity, and we observed that abdominal obesity, more than menopausal status, is the main determinant of the differences found in androgenic profile. An increment in the androgenic milieu that correlates with abdominal fat, insulin resistance, and atherogenic lipoproteins becomes evident after the menopausal transition and suggests that evaluation of cardiovascular disease risk in these women should include androgens, considering that abdominal obesity is one of the main determinants of the relationship between androgenic parameters and cardiovascular risk factors.

Multiple environmental and genetic factors are thought to influence the manifestation of abdominal obesity [10]. Intra-abdominal fat increases with age in both overweight and normal weight individuals, independently of changes in total body fat. Sex steroid hormones also contribute to body fat distribution; we have recently shown that the increase in abdominal obesity shows a trend to inversely correlate with estradiol levels across the menopausal transition [2].

By other side, we must remark that it is very difficult to establish if natural menopause is an independent risk factor, as it is not easy to design studies that could separate the effects of the natural aging process from menopause.

Our results suggest that the evaluation of the risk of cardiovascular disease in women should begin since early menopausal transition and should include abdominal obesity, metabolic syndrome and androgenic parameters, such as SHBG levels and the free androgen index.

Three questions interview

1. What would be the most important determinations to assess these risk factors for CVD in patients?
   It would be important to evaluate blood pressure, waist circumference, lipid profile through triglycerides, total-cholesterol, HDL-cholesterol, LDL-cholesterol, glucose, insulin and calculated HOMA and triglycerides/HDL-cholesterol indices.
2. What do you consider the main variables that lead to increased risk of cardiovascular disease?
   It is not a single variable, but all the same, so you should do a holistic approach to women in this stage of his life.
3. What conduct should be taken to reverse the risk of cardiovascular disease?
   Major changes in habits and HRT.

Acknowledgement

The authors thank Prof. V. Mesch and Prof. H. Benencia for their contribution to this article.

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