Editorial

What drives metabolic syndrome after menopause, and can we do anything about it?

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Metabolic syndrome (MetS) is considered to be an important parameter of cardio-metabolic health and has been correlated with the risks of diabetes mellitus (DM), cardiovascular disease (CVD), mortality and cancer risk, and a poorer cancer risk prognosis. Because it is comprised of a number of factors, requiring only three out of five criteria to make the diagnosis, it has been argued that this risk factor clustering makes MetS not a real syndrome, and may not be clinically useful, although this is still debated. Nevertheless, MetS has been used widely, and for many is still considered to be a valid measure of health status.

One of the major drivers of MetS is weight gain and the evolution of insulin resistance. Indeed, MetS may be a better predictor of DM than of CVD. Even younger women, who are obese and have insulin resistance are at a greater risk of MetS as is noted in women with polycystic ovary syndrome. However weight gain and insulin resistance emerge with aging, and the decrease in insulin sensitivity with aging is thought to be largely explained by an increase in adiposity, although aging also results in a decrease in muscle mitochondrial function. Because adiposity is such an important factor in determining MetS, it has been suggested that lower levels of adiponectin may serve as a good biomarker of MetS in older women. Also, because adipose tissue secretes leptin, the leptin/adiponectin ratio has been considered to be of value in predicting MetS, and its components; particularly correlating with DM and CVD. Another intriguing recent observation is that serum follicle stimulating hormone (FSH) after menopause correlates with weight gain, presumably through an induction of pro-adipogenic gene expression. Paradoxically, however, there are data suggesting that an inverse relationship exists between MetS and its components, and FSH; with lower FSH levels being associated with a higher rate of MetS among postmenopausal women.

The association between menopause and MetS has been studied for some time, and in different populations, mainly in cross-sectional studies. A prospective study in the United States showed a statistical association, and in concert with other studies suggested that this association was independent of age. However, not all studies have shown this effect when adjusting for the effect of age. To further clarify whether menopause is an independent risk factor for MetS, Christakis et al. in this issue of Menopause have examined data from a large Canadian cohort of women, aged 45-85. In this observational cohort of 30,097 women, a multivariable model was used to adjust for co-variates, the most important being that of age. Different from other studies, while a consensus definition of MetS was used, two definitions of MetS were employed based on either a waist circumference of ≥88 cm (35 inches) or ≥80 cm (32 inches). When using the unified criteria, and the higher waist circumference cutoff, the occurrence of menopause was not statistically associated with MetS: adjusted relative risk (aRR) 1.09 (0.99-1.19). However, when the lower waist circumference was used, the association was significant aRR 1.10 (1.01-1.19); and these data were independent of age. Also showing significant associations were impaired glucose tolerance, elevated blood pressure, and elevated triglycerides. Thus, it appears that while the association is not strong, it is a significant association and appears to be independent of age as has been shown in other studies.

In this cohort, 38.7% of the women were using some form of menopausal hormone therapy (MHT). While the authors did not find a difference in the risk of MetS in women receiving or not receiving MHT, they did find that MHT was associated with a significantly lower risk of impaired glucose tolerance aRR 0.90 (0.85-0.96). These data are consistent with an abundant literature showing that MHT decreases the risk of developing DM after menopause.

So, why is menopause associated with MetS? It would seem logical that women at menopause and beyond are older, and age would seemingly be a major determinant. As noted above, adiposity and insulin resistance increase with age. Yet the data from the Canadian study in this issue of Menopause, and others, show no age effect on the development of MetS. Not studied here and a plausible hypothesis is that a decreased estrogen status contributes to the risk of MetS. Endogenous estrogen has many beneficial arterial effects influencing vascular tone and also improves insulin sensitivity before menopause. Although aging itself increases various risks such as an increase in adiposity and the risk of hypertension and insulin resistance, menopause with its associated relative hypoestrogenism may...
also contribute to this occurrence. Data also suggest that surgical menopause, with its greater hypoestrogenic effect, increases the risk of MetS 1.5 fold over that of women undergoing natural menopause.\(^7\) As potentially the major driver of MetS, insulin action is enhanced by several mechanisms of action of estrogen. Most recently, estradiol was shown to enhance glucagon–like peptide-1 secretion through ER\(_\beta\) binding.\(^8\)

What does this knowledge suggest to us? Menopause heralds an opportunity for preventative strategies for improved health and longevity\(^9\) in women. Screening for many risks assumes a much greater importance after the onset of menopause, thus preventing or attenuating diseases that increase within the first 10 years of menopause.\(^10\) Because of the significant adverse consequences of MetS, at the onset of menopause, providers of health to women should aggressively pursue risk factors for cardio-metabolic health and institute prescriptions for lifestyle management, with weight control being of paramount importance. Because MHT improves many of the components of MetS, as well as preventing DM, some consideration should also be given to including MHT as part of this overall prevention strategy.\(^20\)

**REFERENCES**