METABOLIC SYNDROME AFTER MENOPAUSE AND THE ROLE OF HORMONES

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Abstract

Objectives
The purpose of this review is to focus on the importance of Metabolic Syndrome (MBS) and its increased prevalence in postmenopausal (PM) women) Also the role of hormonal therapy in PM women with MBS will be discussed.

Methods
Review of the relevant literature and results from recent clinical trials

Results
MBS may occur in 40% of PM women and is largely determined by overweight status and obesity. Weight gain, particularly an increase in central fat mass increases in PM women, beginning a few years prior to menopause. Hormonal Therapy (HT) in normal PM women, generally decreases abdominal fat, but the effect of transdermal estrogen is preferable to oral therapy in this regard. In women with MBS, oral therapy was found to increase leptin and the leptin/adiponectin ratio, while transdermal therapy showed no changes. HT has been found to improve insulin resistance in PM women, although the data are mixed. In women with MBS, oral therapy was found to worsen parameters of insulin resistance, while transdermal therapy had minimal effects overall. Women with MBS have elevations in several inflammation and coagulation factors. Both oral and transdermal HT reduce inflammation markers except for levels of CRP and MMP-9, which increase with oral therapy, but are unaffected by the transdermal route. Oral estrogen has a small pro-coagulant effect, not observed with transdermal therapy, in both normal PM women and those with MBS. The beneficial effects of HT on lipids occur in PM women with and without MBS, although the changes in the latter are minimal. Blood pressure was not affected by HT in women with MBS.

Conclusions
Weight gain and obesity largely drives the increased prevalence of MBS in PM women. Use of HT is beneficial overall for reducing many of the parameters of MBS. Our own data would suggest that in MBS, transdermal therapy may be preferable to oral therapy, at least in standard doses.

Key words: Metabolic Syndrome, estrogen, oral, transdermal, obesity, insulin, lipids, inflammation, coagulation.

Rates of obesity have been increasing in many parts of the world to near epidemic proportions. In the United States and Europe, obesity defined as a BMI> 30 occurs in

approximately one-third of the total population [1]. Obesity leads to a number of co-morbid conditions, and appears to be a major contributing factor to metabolic syndrome (MBS).

MBS, while considered a distinct disorder, is made up of a number of components. These include an increased central distribution of body fat, insulin resistance (IR), dyslipidemia (elevated triglycerides, small dense LDC particles and reduced HDL-C), elevated blood pressure (BP), and an increased hypercoagulable and proinflammatory state in blood [2]. The presence of three or more risk factors (Table 1) qualifies for the diagnosis of MBS. Depicted in Table 1 are the criteria for the diagnosis of MBS in the United States using ATP-3 criteria, as well as that used by WHO which divides risk factors into major and minor abnormalities. The importance of diagnosing MBS is heralded by data showing that over time, having MBS increases coronary heart disease (CHD) and cardiovascular disease (CVD) mortality by RRs of 3.77 (1.74-8.17) and 3.55 (1.18 – 8.43) respectively [3].

The overall prevalence of MBS in the United States is 22.6% in women [4], and increases with age [5]; being between 40 – 50% in postmenopausal (PM) women [5]. In postmenopausal women, many components of MBS are driven by weight gain, if not the development of obesity in a large proportion of the PM population.

Weight gain is a substantial finding in women after menopause. Longitudinal data from PM women in the United States show a substantial increase in waist circumference and fat mass, which begins a few years before the final menstrual period [6] (Fig. 1), with essentially no change occurring in skeletal muscle mass. These findings can be shown to correlate with the monophasic increase in FSH [6].

The deposition of fat mass, and particularly central fat mass, is also responsible for an increase in circulating adipocytokines, which have implications for IR and CVD. In obese PM women with MBS, we have found significant increases in leptin and resistin, and reductions in adiponectin [7] (Fig. 2). In these women, leptin was highly positively correlated with markers of

IR, but adiponectin was statistically negatively correlated [7]. The decrease in adiponectin is of greater concern given its protective effect for CHD [8,9].

In postmenopausal women, the role of hormones on various components of the MBS has been controversial, but it is of substantial importance, given the associations with CV and metabolic diseases. The data presented below will summarize what is currently known.

Weight Gain and Fat Mass

Although it is common for women to think that hormonal therapy (HT) causes weight gain after menopause, in general the reverse is true. Using a meta-analytic technique, HT has been shown to significantly decrease abdominal fat by -6.8 % (- 11.8 to -1.9%), but not to change waist circumference [10] (Fig. 3). Interpretation of some of these data may be hampered by the fact that various studies have utilized different HT preparations, and lengths of treatment have varied. There does, however, appear to be a difference between oral and transdermal therapy in this regard. Oral therapy, but not transdermal, decreases IGF-1 and stimulates GH [11 – 13]; it has also been shown that oral estrogen suppresses lipid oxidation [11-13]. The net effect for oral estrogen is to increase fat mass (through suppression of lipid oxidation) and to decrease lean body mass (suppression of 16F-1). In another study the increase in fat mass observed to occur in untreated PMI women was correlated with increases in serum leptin; while women treated with transdermal estrogen had no changes in body mass or leptin [14].These data are consistent with our own data where obese PM women with MBS were randomized to receive oral or transdermal E_2. With oral E_2, leptin increased resulting in an increased L/A ratio [15] (Table 2). Transdermal E_2 therapy on the other hand did not affect leptin but increased adiponectin significantly [15].

Insulin Resistance

Although the data on the effect of HT on IR are extremely mixed, in aggregate the evidence would suggest that HT (primarily estrogen) has a beneficial effect on IR by improving insulin sensitivity. Controversy in this area relates to the study of different populations and ages of women, different types of HT, various lengths of therapy and different techniques used to assess IR. Using a meta analytical technique, yet not including every study available, it was found that IR was reduced by -12.9% (-17.1 to -8.6%) with HT (10) (Fig. 4). A summary of a number of studies would suggest that in general the addition of a progestogen , unless in low dose, blunts the beneficial effect of estrogen on IR (16-18). Further, while both oral and transdermal estrogen, when used alone, improves IR, there is a biomodal effect of oral estrogen, where larger doses of CEE (1.25 mg) were found to increase IR while the dose of CEE 0.625 mg improved IR (Fig. 5, A/B). With more standard doses of estrogen there was a general improvement in IR in normal younger PM women. The meta-analysis cited above [10] found a slightly better effect with oral than transdermal E_2 or IR using HOMA-IR as the measure. It appears that an important variable here is the type of patient studied and the length of treatment. While the data cited above pertain to "normal" healthy postmenopausal women, in women with MBS, our recent study showed a worsening of IR with oral E_2 (1 mg) compared to transdermal therapy 0.05mg) [15]. Here several markers of IR were worsened over 3 months with oral E_2 (Fig. 6), while there were no appreciable changes with transdermal E_2 [15].

The overall improvement in IR parameters with HT is in keeping with data on diabetes in PM. Several prospective studies now point to a reduction in new onset diabetes in women receiving HT [19, 20]. While there are several possible mechanisms for this effect, improvement in HOMA-IR after one year of therapy has been documented [20]. Further, there are several studies pointing to an improvement in glycemic control in women with diabetes while receiving HT [21,22].

Coagulation and Thrombosis

Although there are no specific diagnostic criteria for MBS which involve coagulation and inflammation markers, MBS is thought to be a state where there is heightened CVD which is at least In part related to abnormalities in these parameters. Indeed, we have observed that PM women with MBS have higher levels of CRP, PAI-1 and fibrinogen compared to normal postmenopausal women [23].

In normal PM women, oral and transdermal estrogen have somewhat different effects on inflammation and coagulation markers. In common are reductions in certain inflammation markers (ICAM-1, VCAM-1, MCP-1, E-selection, as well as homocystene) and with divergent effects on CRP and MMP-9. Both of these (CRP and MMP-9) increase with oral therapy but not with transdermal therapy [10, 24, 25, 26, 27].

Among coagulation markers, both oral and transdermal therapy exhibit beneficial changes in decreasing fibrinogen and PAI-1. However, oral therapy generally worsens pro-coagulation factors, specifically lowering anti-thrombin III and protein-S and increasing factor VII and prothrombin fragment F1+2 [10,28,29.]. These changes with oral HT are dose dependent. Although these findings cannot be correlated to adverse events, there are data suggesting that transdermal therapy, which generally does not affect procoagulant factors, may not result in an increase in venous thrombosis which occurs with oral therapy (30, 31). Our data on PM women with MBS [23] are essentially confirmatory of the above findings, except that certain markers such as CRP and fibrinogen were higher before treatment in the women with MBS as noted above.

Lipids and BP

Lipid profiles are generally improved with HT and have been the subject of many reviews in the past. It should be noted, however, that the major differences between oral and transdermal therapies is an increase in HDL-C and triglycerides with oral therapy which does

not occur with transdermal therapy [10] LDL-C and Lp(a) are decreased with both routes of administration. While the increase in HDL-C with oral estrogen is desired, the concern is often that of hypertriglyceridemia in women with MBS. We have observed that while all the above trends are similar in normal PM women and those with MBS, the majority of changes in MBS were quite small in our study, and generally not statistically significant [15].

BP, another component of MBS, is largely unaffected by HT, with some studies showing a small increase or decrease in BP, and others showing no change. In the recent meta-analysis [10], there was a small but significant reduction in mean BP with HT. In our study of MBS, no changes in BP were observed with oral or transdermal HT [23].

Conclusion

It is clear that weight gain and obesity after menopause drives the increased prevalence of MBS in PM women. Because of the associated sequelae of CHD, CVD, and diabetes, life style management should be of paramount importance in helping to control this disorder. It is clear that a prescription of diet, exercise, and a generally healthy life style should begin early in life and certainly before the onset of menopause [6]. HT for symptoms of menopause can help improve many of the components of MBS (fat mass, IR , inflammation markers, lipids), and in so doing may contribute to the reduction in CHD and mortality observed in younger PM women [32]. However, in PM women who already have MBS we have observed that with oral estrogen, there may be a worsening of IR, an unfavorable alteration in adipocytokines (elevated leptin/adiponectin ratio) and an increase in the ratio of MMP-9/tissue inhibitor(TIMP). The latter change is of concern for CHD in women with significant atherosclerosis because it may promote plaque instability and rupture [33]. These inflammation related findings were not observed with transdermal E_2 therapy in women with MBS. Therefore it is suggested, based on our own preliminary data, that transdermal E_2 may be more preferable to prescribe in higher risk women, including those with MBS. Nevertheless, on balance, it appears that HT should

be beneficial for PM women with MBS and should be considered as a treatment for

symptomatic women, along with aggressive life style measures.

Table 1.

Criteria for the diagnosis of Metabolic Syndrome

ATP-3 criteria requires 3 or more of the following: waist circumference >88cm; HDL-C<50

mg/dl; Triglycerides >150 mg/dl; BP>130/>85 mm Hg; Fasting blood sugar ≥110 mg/dl

WHO criteria requires one major finding (Diabetes, insulin resistance or abnormal glucose

tolerance) and two minor findings (BMI>30, elevated BP, elevated triglycerides with/without

changes in HDL-C and micoalbuminuria.)

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