

# Menopause and the metabolic syndrome

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## Abstract:

Menopause is the period in a woman's life when she is undergoing hormonal and metabolic changes. Metabolic syndrome or syndrome X comprises of a set of cardiovascular risk factors: obesity, elevated blood pressure, hyperglycemia or insulin resistance and dyslipidemia. Menopause is the point in the timeline of a woman where she is exposed to risk factors for cardiac ill health. The preferential central pattern of fat deposition in obese post-menopausal women is associated with a higher risk of diabetes, hypertriglyceridemia, hypertension and cardiac disease. Hormone therapy improves the altered lipid profile in women with metabolic syndrome and these effects are more pronounced in post-menopausal women. It is important to have more efforts for regular lipid screening and educational programs for a healthy life style for an obese post-menopausal woman.

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## Introduction

The role of menopause in the life of woman is an unquestionable reality. During this period in a woman's life, she undergoes numerous metabolic and hormonal changes. Metabolic syndrome or syndrome X has been studied since the early 80's and Syndrome X was initially coined by Gerald Reaven (1) in 1988. It is also known as the insulin resistance syndrome, the central obesity syndrome and the deadly quartet. It comprises of the following components and a set of cardiovascular risk factors: obesity, elevated blood pressure, hyperglycemia or insulin resistance and dyslipidemia. Of the above components, obesity is said to be the biggest contributor of cardiac dysfunction in postmenopausal women.

When the profile of cardiac health is studied, the pattern of cardiovascular diseases is different in men and women. Typically it is said, women develop cardiac dysfunction ten years after men(2). Although woman enjoy better cardiac health than men, due to cardio protective factors, the risk of coronary artery disease (CAD) that is caused by Metabolic syndrome seems to be particularly high among females.

The incidence of metabolic syndrome is 20-30% of the general middle aged population and the incidence varies from 8 to 24% in males and from 7 to 46% in females (2-3). When woman approaches her 50's, her cardio vascular profile begins to change. At the same time, she begins experiencing the changes of perimenopause and enters into the period of climacteric. This period of her life also gives way to obesity, hypertension, hyperglycemia or insulin resistance and dyslipidaemia. Hence menopause is the point in the timeline of a woman where she is exposed to risk factors for cardiac ill health.

According to NCEP-ATP III, Metabolic syndrome represents the combination of three of the following variables:

1. Abdominal obesity: Waist circumference  $\geq$  88 cm
2. Hypertriglyceridemia: Serum TG level  $\geq$  150 mg/dl
3. Serum HDL:  $<$  50 mg/dl
4. High blood pressure: SBP  $\geq$  130 mmHg and/or DBP  $\geq$  85 mmHg or on treatment for hypertension.
5. High fasting glucose: Serum glucose level  $>$  110 mg/dl or on treatment for diabetes

It is estimated that half of all cardiovascular events in women is related to metabolic syndrome (4). Latin American studies in menopausal women have shown that age, sedentary lifestyle, time of menopause, obesity and hypertension increase the risk of developing metabolic syndrome or syndrome X.

## Definitions

**Climacteric:** Period of the woman's life between the end of the reproductive phase and the onset of senescence (40- 65 years).

**Symptomatic menopause:** It is characterized by vasomotor instability, irregular menstrual bleeding, psychological symptoms and genitourinary atrophy.

**Menopause:** Last spontaneous menstruation.

**Perimenopause or menopausal transition:** Period that extends from two years before the last menstruation and until one year later.

**Post-menopause:** Period that starts one year after the last menstruation.

The following changes occur in a woman's metabolic system when she enters the period of perimenopause:

- An increase in central (intra-abdominal) body fat.
- A shift toward a more atherogenic lipid profile - increased low density lipoprotein and triglycerides levels, reduced high density lipoprotein, lipoprotein

(a) (Lp (a)) levels and small, dense low density lipoprotein particles.

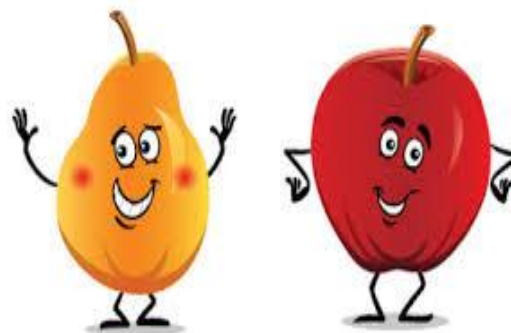
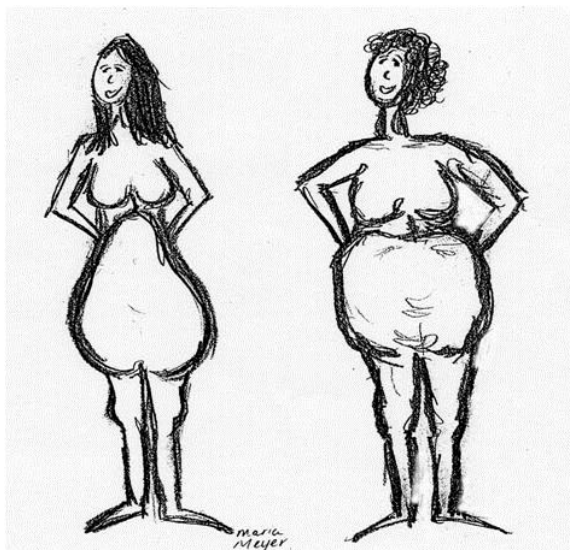
- An increase in blood glucose and insulin levels.

Postmenopausal women have higher total cholesterol, LDL cholesterol, triglycerides (TG), and lipoprotein (a) (Lp (a)) levels and lower HDL cholesterol levels than premenopausal women.

#### Hormonal milieu:

What causes the metabolic syndrome to emerge in a woman's life, particularly when she enters menopause: Studies suggest the changing hormonal milieu could be the reason. Decreasing oestrogen, relative rise in oestrone and an alteration of the oestrogen testosterone ratio has been implicated in the changing hormonal environment of menopause. Menopausal hormonal changes as well as an age related deteriorating metabolic profile ultimately lead to a clustering of the risk factors for the syndrome X.

The preferential central pattern of fat deposition in obese post-menopausal women is associated with a higher risk of diabetes, hypertriglyceridemia, hypertension and cardiac disease. Metabolic syndrome occurs in 40 percent of postmenopausal women and is characterised by extreme obesity in most. Oestrogen promotes the accumulation of gluteo-femoral fat. At the onset of menopause the declining levels of oestrogen cause fat to distribute more in the centre of the body. This classical pattern of central fat distribution predisposes women to be at a higher risk of cardiovascular disease and more so the post-menopausal woman. Contrary to popular belief, the weight gain in women begins few years prior to the actual onset of menopause i.e. during the climacteric.



The distribution of fat is primarily central in location and this android or central fat mass, is also responsible for an increase in circulating adipocytokines. Adipocytokines have a direct plausible relationship with an increase in Insulin resistance and CVD (5).

Studies have shown that in obese postmenopausal women, there are increases in leptin and resistin, and reductions in adiponectin, if they have the metabolic syndrome. The decrease in adiponectin is of great importance, as adiponectin is considered protective of cardiac dysfunction.

Jose Neto et al (6) concluded in his study that metabolic syndrome was more prevalent among postmenopausal women than among premenopausal women by both criteria. The study also said that menopause is not an independent risk factor for metabolic syndrome.

#### Hormone therapy:

When post-menopausal hormone therapy is studied, it is seen that Hormonal Therapy (HT) in postmenopausal women, generally decreases abdominal fat distribution. When the different modes of hormone therapy are compared, it is seen that transdermal oestrogen therapy reduces the central fat deposition as compared to oral therapy. Weight gain has largely been attributed to menopause in the minds of postmenopausal women. This however is far from reality. In women with metabolic syndrome, oral hormone therapy increases leptin and the leptin/adiponectin ratio (5). Oral therapy, but not transdermal, decreases IGF-1 and stimulates Growth hormone. It has also been shown that oral oestrogen suppresses lipid oxidation. The net effect for oral oestrogen is to increase fat mass (through suppression of lipid oxidation) and to decrease lean body mass (suppression of 16F-1).

Hormone therapy improves the altered lipid profile in women with metabolic syndrome and these effects are more pronounced in postmenopausal women. However in postmenopausal women who already have Metabolic syndrome it has been observed that with oral oestrogen, there may be a worsening of Insulin resistance, an unfavourable alteration in adipocytokines (elevated leptin/adiponectin ratio) and an increase in the ratio of MMP-9/tissue inhibitor (TIMP) (7-8). All these factors

form cluster of high risk scenarios for the development of cardiovascular disease in postmenopausal women.

### Managing metabolic syndrome in the postmenopausal:

Weight loss and physical exercise are both mainstays of therapy. This two pronged method targets the insulin resistance and extreme obesity that is the hallmark of the metabolic syndrome. Aerobic exercises that target the central fat are usually preferred. A reality check should be ensured and idealistic goals should be set. Regular prolonged low intensity exercise (i.e. brisk walking) to reduce visceral adipose tissue is preferred. Setting unobtainable weight loss goals should be discouraged.

Lifestyle changes though desired, may prove be insufficient to treat the deranged lipid profile associated with the metabolic syndrome (increased TG, reduced HDL, and small dense LDL particles). The primary target for lipid lowering agents is LDL cholesterol and triglycerides are the preferred secondary. Nicotinic acid and fibric acid derivatives both act to reduce triglycerides and increase HDL cholesterol.

### Conclusion

Studies have shown a high prevalence of metabolic syndrome exists among postmenopausal women referred to menopause clinic. Abdominal obesity and hypertension are the most prevalent components of metabolic syndrome among the post-menopausal. These components can lead to an increase in cardiovascular diseases.

Interventions are needed to modify these risk factors such as abdominal obesity, dyslipidemia, hypertension, and insulin resistance leading to glucose intolerance. This in turn will decrease the risk of cardiovascular ill health. Therefore, it is important to have more efforts for regular lipid screening and educational programs for a healthy life style for an obese post-menopausal woman.

Hormone therapy for symptoms of menopause can help improve many of the components of Metabolic syndrome (fat mass lipids), and in so doing may contribute to the reduction in cardiac disease and mortality, especially in younger postmenopausal women.

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