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GUEST EDITORIAL

Emergence of Metabolic Syndrome Out of Menopausal Box!!!

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ABSTRACT

Metabolic syndrome is the constellation of risk factors that predisposes to increased risk of cardiovascular diseases (CVD) and type 2 diabetes mellitus that is increasingly coming to light in menopausal females, thereby raising the morbidity and mortality. Declining estrogen levels along with genetic susceptibility and central obesity adversely affect the lipid metabolism, making postmenopausal females vulnerable to metabolic syndrome. Early identification of the various risk factors and appropriate preventive strategies (lifestyle modification and use of statins in selective cases) may decrease the emergence of metabolic syndrome in such females, thereby improving the longevity.

Screening of risk factors for metabolic syndrome in postmenopausal females should be routinely done and therefore incorporated and inculcated in every postmenopausal clinic so that suitable candidates can be referred to cardiologists for expert advice and proper intervention if required.

Keywords: Cardiovascular disease, Menopause, Metabolic syndrome, Prevention, Risk factors.

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INTRODUCTION

Menopause is just puberty's evil older sister and estrogen is topped-up hormone of puberty, while it starts emptying up with the onset of menopause. Estrogen is a vengeful hormone affecting woman's fertility, moods, sleep patterns, and appetite; therefore, we can say that "Estrogen is the household heating oil of womanhood." Shrinking estrogen level can have multiple enigmas for a woman during her menopause from which she can attract several chronic health problems.

Constant hormonal change makes the woman leap several phases during her lifetime. After crossing her reproductive phase, comes the climacteric phase, which is defined as the aging of the woman, marking the transition from reproductive phase to the nonreproductive state known as menopausal transition. It is the time where the female experiences irregular cycles and may or may not be accompanied with vasomotor symptoms lasting up to approximately for 4 to 5 years.

Menopause follows the climacteric phase, which is a normal, natural event accompanying amenorrhea of 12 months consecutively and results in permanent cessation of the menstrual period and marks the end of reproductive life. The age of menopause ranges from 45 to 55 years and varies in different regions of the world. According to the American Congress of Obstetricians and Gynecologists, the average age of menopause is 51 years, but Indian women's average age of menopause is around 47 years.[1] The major factors behind this early menopause in India are educational attainment, standard of living, number of children, age at first and last birth, use of contraception, body mass index (BMI) and anemia, lifestyle, and socioeconomic status.[1]

The menopausal transition marks a period of physiological changes as women approach reproductive senescence. The Stages of Reproductive Aging Workshop (STRAW) defined seven stages ranging from the onset of menstrual cycles at menarche and the reproductive age to the peri-menopausal and post-menopausal phases. Principal (menstrual cycle), supportive (biochemical and imaging), and descriptive criteria (symptoms) are used to characterize the phases. The STRAW has made substantial contribution for women's health by providing definitive classification of menopausal status and serves as a clinical application for women and the health care providers to guide the assessment of fertility, contraceptive needs, and health care decision-making (Flow Chart 1).[2,3]

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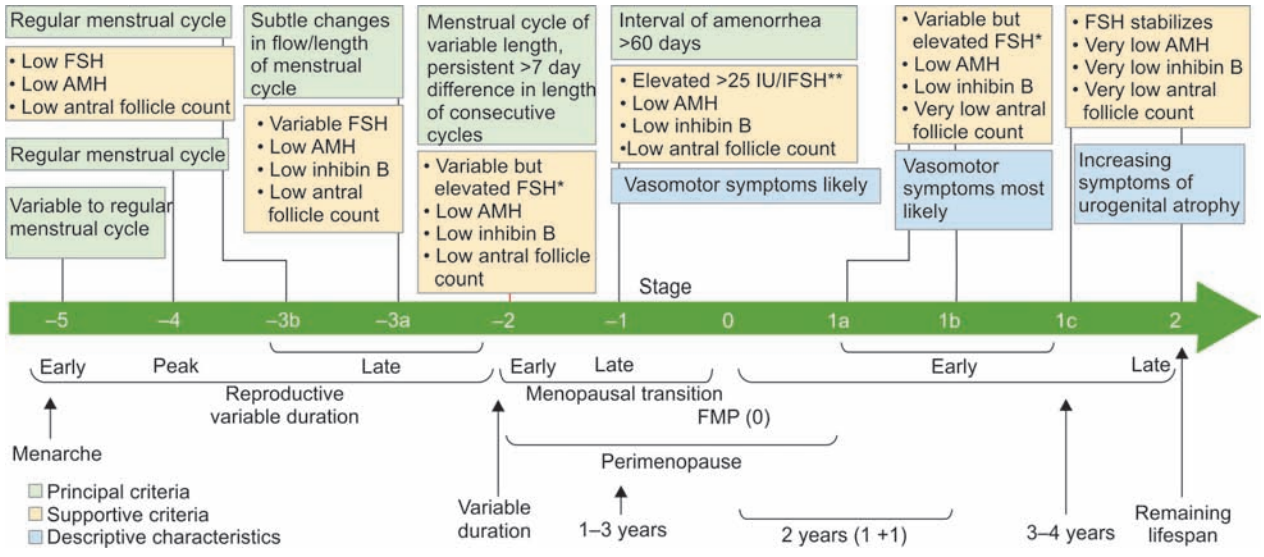
Flow Chart 1: The STRAW classification.[4,5] *Blood drawn on cycle days 2 to 5; **Approximate expected level based on assays using current international pituitary standard



METABOLIC SYNDROME

The name metabolic syndrome is given to the aggregate of clinical conditions comprising central or abdominal obesity, systemic hypertension, insulin resistance, and atherogenic dyslipidemia associated with unhealthy eating habits, poor dietary choices (junk food) coupled with sedentary lifestyle; there are multiple proposed definitions, but the two most widely accepted definitions are those of the National Cholesterol Education Program; Adult Treatment Panel III (NCEP: ATP III) and IDF (International Diabetes Federation), focusing specifically on waist circumference, which is a surrogate measure of central obesity[6] and it is the most clinically applicable measure, as the criteria are all measurements that are easily accessible to clinicians.

In contrast, the American Association of Clinical Endocrinologists, World Health Organization, and the European Group of Insulin Resistance definitions are all largely focused on insulin resistance (Table 1).

According to the various above-mentioned criteria, the metabolic syndrome can be stated as constellation of these abnormalities or a state of pre-disease where type II diabetes and CVD may manifest in the future.

RISK FACTORS FOR METABOLIC SYNDROME

Several risk factors are associated with metabolic syndrome, but the most important is "hypertriglyceridemic waist" that is increasingly being recognized as a significant cardiovascular risk factor. Metabolic risks, such as elevated plasma glucose, high blood pressure (BP), and dyslipidemia contribute to atherosclerosis as well as to prothrombotic and proinflammatory state characterized by increased inflammatory cytokine activity. Compared with females who do not have metabolic syndrome, those with metabolic syndrome are twice as likely to develop coronary heart disease and 5 times more likely to develop diabetes mellitus (DM);[7-9] 41% of males and 37% of females aged 40 to 59 years, and 52% of males and 54% of females older than 60 years meet diagnostic criteria for metabolic syndrome (Flow Chart 2).[10]

PATHOPHYSIOLOGY OF METABOLIC SYNDROME

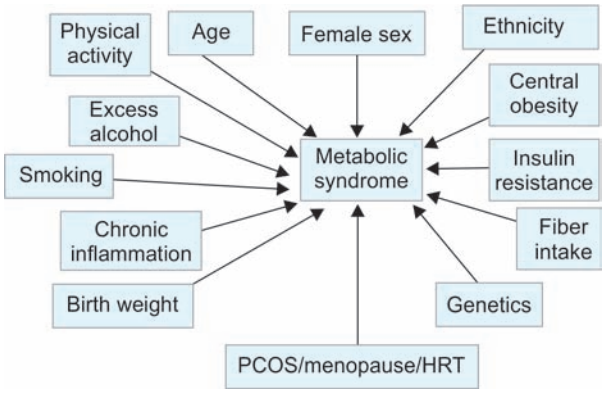
Metabolic syndrome or the "deadly quartet" has complex etiopathogenesis involving both genetic and acquired factors. Of all the proposed mechanisms, insulin resistance, neurohormonal activation, and chronic inflammation

Table 1: Currently used criteria for metabolic syndrome

Risk factors for metabolic syndrome	*NCEP:ATPIII criteria 2001**	*IDF criteria 2005***
Waist circumference (central obesity)	≥80 cm	Not used
Triglycerides	≥150 mg/dL	Triglycerides ≥150 mg/dL
High-density lipoprotein cholesterol	<50 mg/dL	<40 mg/dL in men and <50 mg/dL in women
Blood pressure (BP): systolic BP	>130 mm Hg	≥130 mm Hg
Diastolic BP	>85 mm Hg	≥85 mm Hg
Fasting blood glucose	≥100 mg/dL	≥100 mg/dL

*In 2003, the American Diabetes Association changed the criteria for IFG tolerance from 110 to 100 mg/dL; **Central obesity (defined as waist circumference, but can be assumed if BMI > 30 kg/m^2) with ethnicity-specific values; *plus two of the above

Flow Chart 2: Risk factors of metabolic syndrome. PCOS: Polycystic ovary syndrome



appear to be the main players in the initiation, progression, and transition of metabolic syndrome to CVD.

Insulin Resistance

It increases the circulation of free fatty acids (FFAs) by impairing insulin-mediated inhibition of lipolysis and further inhibiting the antilipolytic effect of insulin.[11] The FFAs are also lipotoxic to beta cells of the pancreas causing decreased insulin secretion.[12]

Neurohormonal Activation

Leptin is an adipokine that controls energy homeostasis mediated by the hypothalamus and is known to stimulate the immune cells activating the Th1 pathway.[13] Adiponectin is an anti-inflammatory and antiatherogenic adipokine and its effects counter those of leptin. Therefore, it has been considered a protective factor against the development of diabetes, hypertension, and acute myocardial infarction.[14-16] An increase in adipose tissue mass correlates with reduced adiponectin and higher leptin levels, which eventually enhance the CVD risk. Activation of the renin-angiotensin system also serves as an important neurohumoral pathway contributing to the development of metabolic syndrome (Flow Chart 3).[11]

PREVALENCE

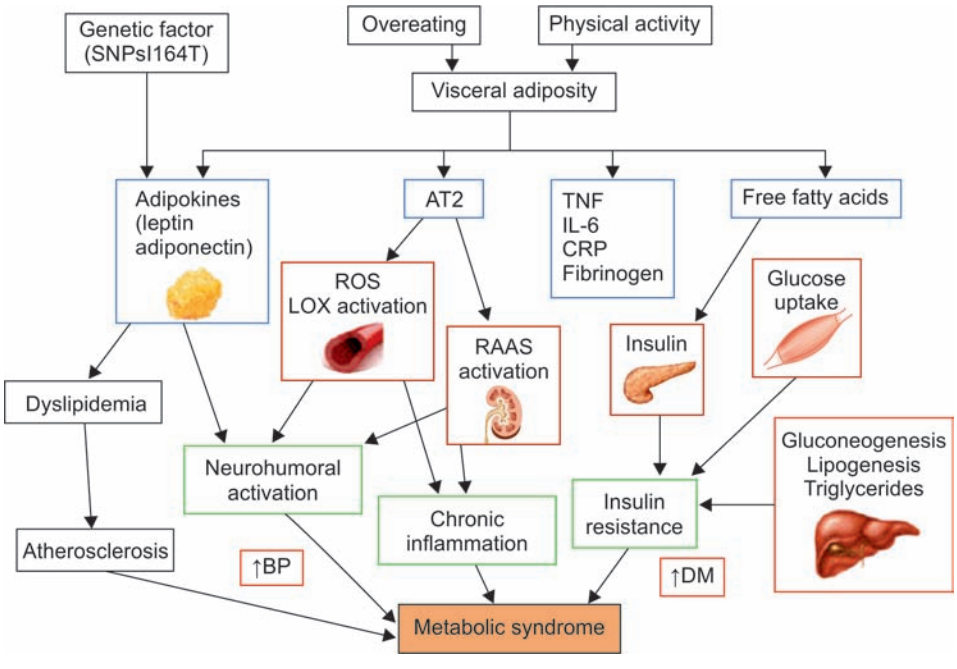
Prevalence of metabolic syndrome among women has ranged from 13.8% in pre-menopausal to more than 60% in post-menopausal women in different populations based on the differences probably related to ethnicity, sample size, criteria used for definition, socioenvironmental and genetic factors, lifestyle, and type of menopause (natural/surgical).[7,17-27]

The metabolic syndrome is also known as insulin resistance syndrome/syndrome X/Reaven syndrome with an average of 40% prevalence in Indian women. The prevalence reported among peri-menopausal women in India is 22.2% rising to 32.2 to 48% in the post-menopusal females.[28,29] It is 1.5 to 2 times more common in women than in men.

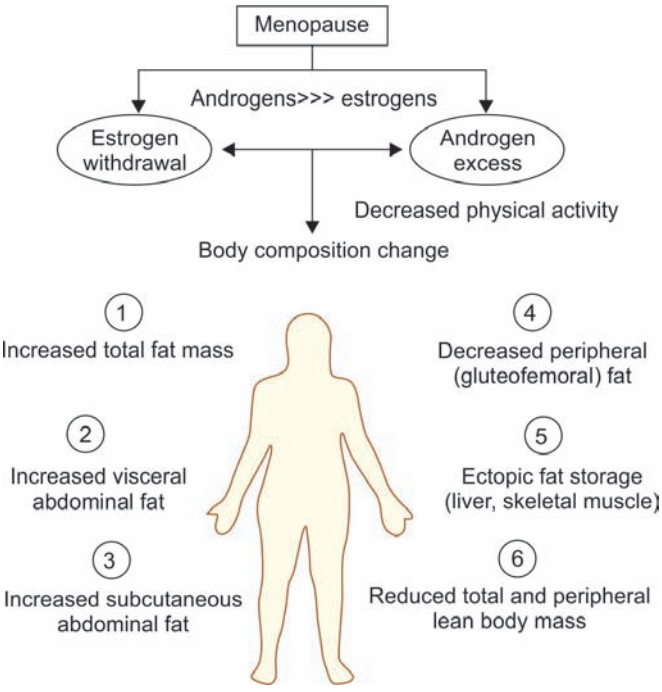
CHANGE IN BODY COMPOSITION

Due to declining estrogen in the body, a woman experiences a lot of physical changes in various organ systems like (Flow Chart 4).

Flow Chart 3: Pathophysiological mechanisms in metabolic syndrome. AT2: angiotensin II type II receptor; CRP: C-reactive protein; IL-6: interleukin 6; LOX: lectin-like oxidized low-density lipoprotein; RAAS: renin-angiotensin-aldosterone system; ROS: reactive oxygen species; TNF: tumor necrosis factor



Flow Chart 4: Major body composition changes induced by menopause



- Skin (thinning of the skin and increased wrinkling),
- Hair (hirsutism, alopecia),
- Mouth (dry mouth and gingivitis),
- Brain (mood swings, anxiety depression),
- Decreased reproductive ability (dyspareunia, vulval dryness),
- Osteopenia or osteoporosis, osteoarthritis,
- Urogenital symptoms (urinary frequency, cystitis, and incontinence).

Above menopausal symptoms can be effectively treated with hormonal replacement therapy (HRT).

With all the above-mentioned alterations in the body, menopause can also lead to a major clinical challenge, i.e., metabolic syndrome emerging as a new menace in this subpopulation group, which may be a direct result of ovarian failure or alternatively, an indirect result of metabolic consequences of central fat redistribution with estrogen deficiency.

CARDIOVASCULAR RISK AFTER MENOPAUSE

Since menopause is characterized by increased intraabdominal fat deposition with little change in muscle mass and these visceral fat cells gain direct access to liver via portal circulation which are significant source of multiple inflammatory proteins responsible for CVD, resulting from natural decline of ovarian estradiol, a hormone that in the pre-menopausal period provides anti-inflammatory protection. Framingham investigators have found a fourfold increase in CVD within 10 years following natural menopause, premature or surgically induced, with significant associations of menopause and cardiovascular risk.[30] This increased risk of CVD might be due to changing lipid metabolism with estrogen deficiency directly affecting central obesity, insulin action, the arterial wall, and fibrinolysis.

Weight

Between ages 45 and 55, women gain on an average half a kilo a year and start getting obese after menopause due to high fat deposition, lack of exercise, and sedentary lifestyle.[31]

Intraabdominal fat (android or apple-shaped) and fat in gluteofemoral (gynoid or pear-shaped) region are the two patterns of body fat distribution. Loss of estrogen promotes the accumulation of central fat (intraabdominal) which has emerged as a cardiovascular risk factor independent of overall obesity[32] along with increased risk of diabetes, hypertriglyceridemia, and hypertension. Visceral fat has a direct effect to increase the appetite and reduce energy expenditure. In pre-menopausal females, appetite is controlled by increased adiponectin and ghrelin and decreased resistin and leptin, whereas it is *vice versa* in post-menopausal obese individuals.

Changes in Lipid Profile

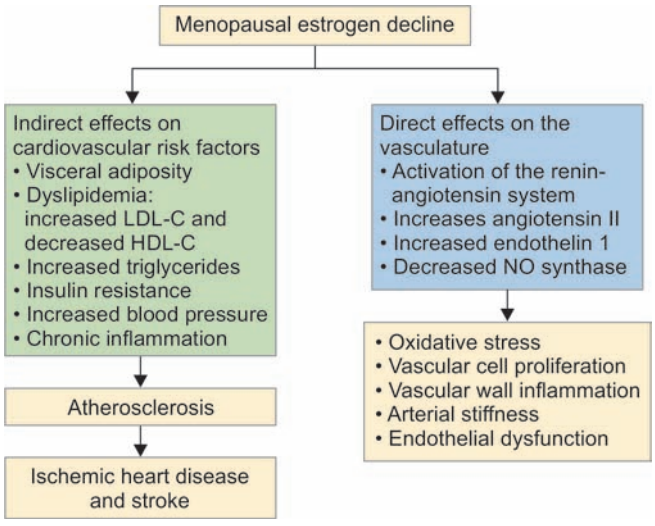
Menopause has a dramatic effect on lipid physiology, leading to increased free fatty acid levels, and decreased adiponectin (which helps in breakdown of fat). All these factors lead to increased secretion of apolipoprotein B-containing particles with increased hepatic lipase activity resulting in a predominance of small dense low-density lipoprotein (LDL) particles, triglycerides (TG), lipoprotein (a), and a reduction in large antiatherogenic high-density lipoprotein (HDL)2 particles, hence, increasing the risk of CVD significantly as compared with pre-menopausal females (Flow Chart 5).

HOW TO PREVENT METABOLIC SYNDROME?

As of studies, there is increased risk of post-menopausal female dying of metabolic syndrome and its complications, than with female genital tract cancer risk; so, if cancer screening is justified, screening and creating awareness of metabolic syndrome should be an integral part of every post-menopausal clinic which will help in reducing morbidity and mortality associated with CVD and ischemic heart disease because primary prevention is best prevention.

Hormone replacement therapy was an option for treatment of the menopausal metabolic syndrome before because it improved many of metabolic abnormalities.[33]

Flow Chart 5: Lipid profile changes during menopause



But now, estrogen–progestin arm of the Women's Health Initiative has been demonstrating increased CVD risk in HRT users and therefore it is no longer recommended for preventive therapy of CVD.[29]

- Prevention of metabolic syndrome includes a combination of lifestyle modification and drug therapy.

Lifestyle Modification

- Physical exercise along with dietary modification has promising effects on various health problems and thus leading a healthy life. Weight loss directly influences the underlying etiology of metabolic syndrome, i.e., to improve visceral adiposity and insulin resistance. Therefore, moderate regular intensity workout (at least 30 minutes for at least 3 times a week, optionally in combination with two exercise sessions with load or at least 150 min/week of walking) is advisable. Also, there is a preferential loss of abdominal fat with aerobic exercise (walking, running, and jogging), as visceral adipocytes appear to respond more quickly to exercise-induced weight loss than subcutaneous adipocytes.[34]
- Healthy diet: One should take a proper balanced diet with low salt intake (2.4 gm sodium) along with high-fiber diet (fruits and vegetables). Consumption of saturated fatty acid and low carbohydrates will help reduce the fat.
- Giving up smoking and alcohol
- Intellectual activity

The aim of lifestyle modification therapy is to bring BMI values below 25 kg/m^2.[35]

Lipid-lowering Treatment

Though lifestyle changes may improve the metabolic derangement of this syndrome, it may be inadequate to treat the dyslipidemia, thereby requirement of statins when LDL cholesterol is >100 mg/dL. Although LDL cholesterol has remained the primary target of lipid-lowering therapy, TG lowering is an important secondary target to reduce CVD risk.[36] Antihypertensive therapy should be initiated if BP ≥ 140/90 to avoid end organ damage.

Nicotinic acid and fibric acid derivative drugs both act to reduce TG and increase HDL cholesterol. They are frequently used with statins, but caution should be used in combining these drugs. Although niacin is an expensive monotherapeutic agent that corrects the combined dyslipidemia of the metabolic syndrome, it has the disadvantage of increasing glucose levels in some patients.

CONCLUSION

"Having a visionary approach for diagnosing the menopausal women with metabolic syndrome and treating them will definitely result in reclaiming the health."

The CVD is the leading cause of death of women in developed as well as developing countries, but very little is known about atherosclerotic disease progression in women. There has been recent emphasis on the metabolic syndrome as an atherosclerotic risk factor and its impact on CVD risk in women.[36] Many of the features of the metabolic syndrome (central obesity and dyslipidemia with elevated TG, reduced HDL, and small dense LDL particles) emerge with estrogen deficiency in postmenopausal women, which may explain the acceleration of CVD in women after menopause.

It is the need of the hour that gynecologists should be more vigilant about detecting all the risk factors for metabolic syndrome in menopausal females so that early referral to cardiologists for their proper evaluation and initiation of treatment can be done. The strategy of managing the menopausal women should primarily be focusing on preventive measures, not only pharmaceutical treatment.[35]

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