Unraveling the Link Between Sedentary Behavior and Metabolic Syndrome in Women Through Insulin Resistance

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Abstract. Metabolic syndrome (MetS) is a prevalent clinical and public health challenge among women globally, significantly elevating the risk of cardiovascular disease and type 2 diabetes. While current clinical guidelines emphasize pharmacological interventions and general exercise recommendations, they often fail to adequately address the specific contribution of prolonged sedentary time as a modifiable risk factor, especially among high-risk women. Clarifying the biological pathway from sedentariness to MetS can inform more effective behavioral interventions in clinical and public health practice. This study delineates a coherent pathophysiology linking sedentary behavior to Metabolic syndrome in women, mediated through lipid dysregulation, chronic inflammation, and subsequent insulin resistance. The synthesis demonstrates that women undergoing perimenopause, pregnancy, or with polycystic ovary syndrome (PCOS) exhibit heightened susceptibility to sedentariness-induced metabolic dysregulation. Each of these states magnifies the impact of sedentary behavior, resulting in more severe metabolic abnormalities. The evidence underscores the value of sex-specific preventive health recommendations. Key limitations include reliance on mechanistic insights from preclinical studies and variability in objective measures of sedentary patterns across human studies. This review aims to synthesize evidence on the biological mechanisms through which sedentary behavior contributes to Metabolic syndrome in women, and to explore the modifying effect of female-specific physiological conditions, thereby providing a mechanistic basis for tailored clinical and public health interventions.

Keywords: Metabolic syndrome, sedentary behavior, insulin resistance, prevention.

1. Introduction

MetS, characterized by obesity, dyslipidemia, hypertension, and hyperglycemia, is a clinical syndrome of metabolic disturbances that serves as a risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular diseases. Insulin resistance (IR), the core pathogenic mechanism of MetS, affects multiple metabolic components including hyperglycemia, dyslipidemia, and hypertension, making it the central driver of disease development [1]. Epidemiological data reveal a significant increase in the standardized prevalence of MetS to 31.1%, compared to 24.2% between 2010-2012, with women showing a higher prevalence at 32.3% versus 30.0% in men (p <0.001) [2]. As global MetS prevalence rises from 12.5% to 31.4%, this trend underscores its critical status as a major public health challenge worldwide [3].

It is noteworthy that women face a unique risk profile for developing MetS [4]. Multiple studies have indicated a higher susceptibility to MetS in women globally, supporting the observed higher prevalence in this population. This is attributed to factors such as female physiological structure and hormonal fluctuations, including changes in estrogen, metabolic disturbances in patients with PCOS, and the long-term metabolic consequences of gestational diabetes [4]. The confluence of these factors increases women's vulnerability to MetS. The severe subclinical pathological states induced by MetS have spurred significant attention towards its prevention and intervention.

In existing literature, sedentary behavior refers to waking activities undertaken in a sitting or reclining posture. A key criterion for this classification is an energy expenditure of 1.5 metabolic equivalents or lower [5]. Studies demonstrate that each additional hour of sedentary time is associated with a 39% increased risk of MetS ($p < 0.0001$) [6]. There is a parallel rise between sedentary behavior and the prevalence of various MetS-related chronic diseases, such as type 2 diabetes, cardiovascular

diseases, and obesity [7]. Furthermore, the association between sedentary behavior and MetS may be stronger in women, and MetS risk in women appears to be more significantly influenced by sedentary behavior [8].

Thus, the combination of women's unique physiology and sedentary behavior amplifies the impact on the core pathogenesis of MetS, leading to an increased incidence rate. Although numerous studies have explored the relationship between sedentary behavior and MetS, most current research focuses on the general population. Given the significant metabolic differences between men and women, the influence of sex-specific factors must not be overlooked in disease analysis and review. However, the current integration of research specifically addressing the core mechanisms linking sedentary behavior to MetS risk in women remains inadequately elucidated. Against this backdrop, this review aims to analyze the core mechanisms linking female physiological characteristics and sedentary behavior to MetS, with particular attention to life stages and conditions such as polycystic ovary syndrome and gestational diabetes that reshape metabolic processes, and to clarify how sedentary behavior interacts with the molecular mechanisms underlying MetS in women.

2. Diagnosis and Pathogenesis of MetS

Currently, diagnostic criteria for MetS are not fully standardized across different regions. According to the World Health Organization criteria, the diagnosis of MetS is based on a set of core indicators and their respective thresholds. As shown in Table 1, these include fasting plasma glucose of at least 110 mg/dL or documented insulin resistance requiring treatment, a body mass index of 30 kg/m² or higher or a waist-to-hip ratio greater than 0.90 in men and 0.85 in women, triglyceride levels of 150 mg/dL or higher together with reduced high-density lipoprotein cholesterol (HDL-C) below 35 mg/dL in men and 39 mg/dL in women, elevated blood pressure of 140/90 mmHg or higher or current use of antihypertensive medication, and abnormal renal indices reflected by a urinary albumin excretion rate of 20 μg/min or more or an albumin-to-creatinine ratio of at least 30 mg/g. A diagnosis of MetS requires the presence of insulin resistance or diabetes together with at least two of these abnormalities.

Table 1. Core Diagnostic Criteria for MetS

Core Diagnostic Domain	Specific Thresholds
Dysglycemia	Fasting plasma glucose ≥ 110 mg/dL, or confirmed diabetes, or insulin treatment required
Central Obesity	Male: Waist-to-hip ratio > 0.90, or BMI ≥ 30 kg/m² Female: Waist-to-hip ratio > 0.85, or BMI ≥ 30 kg/m²
Dyslipidemia	Triglyceride ≥ 150 mg/dL HDL-C: Male< 35 mg/dL; Female < 39 mg/dL
Hypertension	Blood pressure ≥ 140/90 mmHg
Renal Indicator	Urinary albumin excretion rate ≥ 20 μg/min, or albumin-to-creatinine ratio ≥ 30 mg/g

At the pathophysiological level, insulin resistance is the central mechanism underlying the development and progression of MetS, characterized by diminished tissue responsiveness to insulin [9]. The reduced sensitivity of tissue cells to insulin signaling leads to decreased glucose utilization efficiency and sustained elevation of blood glucose levels. Concurrently, insulin resistance exacerbates dyslipidemia, manifesting as elevated plasma free fatty acids and an abnormal lipoprotein profile. It also promotes increased blood pressure via aberrant activation of the sympathetic nervous system and the renin-angiotensin system. Furthermore, a bidirectional relationship exists between insulin resistance and central obesity, wherein adipose tissue inflammation and secretory dysfunction further impair insulin's metabolic regulatory effects, creating a vicious cycle. This multidimensional pathogenic network, with insulin resistance at its core, explains why MetS spans diverse clinical

phenotypes and exhibits systemic detrimental effects. A deep understanding of these mechanisms is crucial for elucidating the relationship between sedentary behavior and MetS, as well as for deciphering the metabolic susceptibility of women during specific physiological stages.

3. Core Mechanism Linking Sedentary Behavior, Insulin Resistance, and MetS

3.1. Pathways Through Which Sedentary Behavior Induces Insulin Resistance

Sedentary behavior is closely associated with the development of Insulin Resistance (IR). It leads to a reduction in skeletal muscle contractions. As the primary site for glucose consumption in the body, sustained muscle activity is crucial for improving glucose regulation . This indirectly indicates that decreased skeletal muscle activity due to sedentary behavior can result in abnormal glucose metabolism. Reduced glucose uptake and utilization by muscles lead to hyperglycemia. Excess glucose supply further impedes the activation of AMPK, indirectly suppressing certain glucose transporter type 4 (GLUT4) translocation pathways [10]. This causes a significant decrease in GLUT4 transport capacity, prompting the pancreas to compensatorily secrete more insulin, thereby increasing its burden. Chronic hyperinsulinemia can develop, reducing the sensitivity of muscle cells to insulin and ultimately leading to IR [11, 12].

Beyond impaired glucose metabolism, sedentary behavior also reduces overall energy expenditure. The rate of calorie burning drops, and enzymes responsible for breaking down lipids and triglycerides decrease by up to 90%, leading to increased fat deposition, particularly the accumulation of visceral and hepatic fat [13]. Visceral adipose tissue functions not only as an energy depot but also as an endocrine organ. With excessive hypertrophy, it releases chemotactic signals such as monocyte chemoattractant protein-1 that recruit immune cells into adipose depots and promote macrophage accumulation. A principal consequence of this dysfunction is increased secretion of pro-inflammatory cytokines into the circulation, establishing a systemic, low-grade, chronic inflammatory state [14]. This inflammation directly disrupts insulin signaling pathways, accelerating the development of IR [15]. Hypertrophied visceral adipocytes trigger enhanced lipolysis. This process results in a substantial flux of Free Fatty Acids (FFAs) into the portal circulation, flooding both the liver and the systemic bloodstream [16]. The deposition of high concentrations of FFAs in non-adipose tissues (primarily skeletal muscle and liver) interferes with insulin signaling, ultimately causing IR . As described above, sedentary behavior can induce IR by disrupting insulin signaling pathways through mechanisms including reduced muscle activity, glucose metabolism dysfunction, lipid metabolism disorders, and inflammatory responses.

3.2. The Pivotal Role of IR in the Core Phenotypes of MetS

Insulin resistance shapes the major clinical features of metabolic syndrome through distinct but interconnected pathological pathways. In the liver, the inability to suppress key gluconeogenic enzymes such as pyruvate carboxylase and glucose-6-phosphatase enhances hepatic glucose production, driving a persistent release of glucose into the circulation and contributing to both fasting and postprandial hyperglycemia. In skeletal muscle and adipose tissue, impaired insulin signaling disrupts the translocation of glucose transporter type 4 (GLUT4) from the cytoplasm to the cell membrane. This defect reduces cellular glucose uptake and further aggravates systemic hyperglycemia [17].

Regarding lipid metabolism, IR decreases lipoprotein lipase (LPL) activity, affecting lipoprotein metabolism. Studies show significantly reduced LPL activity under IR conditions, leading to a decreased LPL/Hepatic Lipase (HL) ratio [18]. Reduced LPL activity also diminishes the hepatic uptake of very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL), prolonging their circulation time in the blood and causing abnormal lipoprotein metabolism, which ultimately worsens dyslipidemia. Furthermore, IR increases the hepatic secretion and synthesis of VLDL, leading to hypertriglyceridemia. Decreased LPL activity

and increased VLDL synthesis due to IR manifest as dyslipidemia, characterized by elevated triglyceride and low HDL levels

Hypertension is also closely linked to IR. The hyperinsulinemia present in IR states can affect renal insulin signaling, upregulating the expression of sodium-glucose cotransporter 2 (SGLT2) in renal tubules and promoting increased sodium reabsorption [19]. This leads to water and sodium retention and blood volume expansion, ultimately raising blood pressure. Concurrently, hyperinsulinemia can activate the sympathetic nervous system (SNS), increasing cardiac output and peripheral vascular resistance, which also contributes to hypertension [20].

IR decreases the sensitivity of adipose tissue to insulin, impairing adipocytes' ability to effectively uptake glucose. This process results in adipocyte hypertrophy and excessive deposition of fatty acids, a state of lipotoxicity that drives visceral fat expansion and contributes to central obesity [21]. The subsequent release of large amounts of FFAs from these hypertrophied fat cells, in turn, exacerbates IR, creating a vicious cycle [16, 17]. Thus, insulin resistance, by disrupting glucose regulation, blood pressure homeostasis, lipid turnover, and adipose tissue distribution, gives rise to hyperglycemia, hypertension, dyslipidemia, and central obesity, encompassing the defining components of metabolic syndrome.

4. Interactive Effects of Sedentary Behavior and Insulin Resistance in Women

4.1. Menopause and Estrogen Withdrawal

A large-scale cross-sectional analysis based on NHANES data revealed a stronger association between sedentary time and the risk of developing MetS in women compared to men, with a hazard ratio of 2.47 for women versus 1.85 for men, indicating a higher susceptibility to the metabolic hazards of sedentariness in women [22]. Notably, this risk is not constant throughout a woman's life cycle. Research focusing on menopause as a key milestone indicates that the risk of MetS associated with sedentary behavior increases in postmenopausal women compared to premenopausal women, rising from 27.4% to 48.6% [23].

The core reason for this significant difference lies in the gradual loss of the metabolic protective effects of estrogen. Estrogen itself enhances insulin sensitivity and inhibits visceral fat accumulation. Menopause, the permanent cessation of menstruation resulting from estrogen deficiency, leads to a decline in estrogen levels [24]. This decline weakens the body's natural protective barrier against IR and central obesity [25]. Consequently, the IR-inducing effects of sedentary behavior become more pronounced and severe during this period. Thus, the withdrawal of estrogen during menopause exacerbates sedentary-induced IR, significantly increasing the risk of developing MetS.

4.2. Pregnancy, Postpartum, and Physiological Insulin Resistance

During pregnancy, to prioritize nutrient allocation for the developing fetus, maternal metabolism undergoes significant adaptation, including a physiological reduction in insulin sensitivity of 50%-60%. This resistance increases maternal blood glucose levels, facilitating glucose transfer to the fetus to support its growth [26]. While this adaptation is physiologically purposeful, it also places the mother in a state of potential metabolic vulnerability.

In this context, sedentary behavior does not merely cause IR but rather superimposes upon and worsens the pre-existing physiological IR. Hyperglycemia, as a consequence of pronounced insulin resistance, is a key driver in the significantly increased risk of developing Gestational Diabetes Mellitus (GDM). Importantly, the impact of GDM extends beyond pregnancy itself. Women with a history of GDM were found to have a significantly higher risk of progressing to T2DM, by nearly a factor of ten, than their counterparts with normoglycemic pregnancies, according to a meta-analysis ($p < 0.001$) [27]. Therefore, pregnancy and the postpartum period constitute a phase of increased metabolic vulnerability in which the adverse effects of sedentary behavior are intensified. The superimposition of physiological insulin resistance and unfavorable lifestyle patterns amplifies metabolic disruption and establishes a foundation for the later development of MetS.

4.3. Polycystic Ovary Syndrome and Sedentariness

Polycystic Ovary Syndrome (PCOS) is a prevalent condition affecting reproductive-aged women, marked by a combination of clinical and biochemical hyperandrogenism, chronic anovulation, and the morphological appearance of polycystic ovaries [28]. Women with PCOS typically exhibit inherent, significant IR, which is a core pathological feature of the condition. This IR affects reproductive function by promoting androgen production, suppressing Sex Hormone-Binding Globulin (SHBG), and disrupting insulin signaling.

In this context, sedentary behavior exhibits a strong amplifying effect. The pre-existing inherent IR is further exacerbated by factors such as lack of muscle activity, dyslipidemia, and chronic inflammation associated with sedentariness. In turn, aggravated insulin resistance enhances ovarian and adrenal androgen production, intensifying clinical features of PCOS such as anovulation and hirsutism, and reinforcing the pathological loop. This mechanism highlights that women with PCOS are trapped in a difficult-to-break pathological cycle. IR is both a cause and a consequence of PCOS, and sedentary behavior further elevates the risk of developing MetS.

5. Discussion

This review systematically delineates the core pathway through which sedentary behavior impairs metabolic health in women, which can be summarized as a cascade reaction progressing from behavior to cells, then to organs, and finally to systems. Sedentary behavior initially induces dyslipidemia and chronic inflammation at the molecular and cellular levels. This subsequently leads to insulin resistance, a dysfunction at the organ functional level, ultimately manifesting as the systemic clinical phenotype of Metabolic Syndrome. The main contributions of this analysis can be summarized in two dimensions. First, earlier research on sedentary behavior has largely been fragmented into three separate domains: its associations with obesity, with inflammation, and with dysglycemia. By reintegrating the evidence around the central hub of insulin resistance, these findings are incorporated into a coherent pathological chain, more clearly revealing how the detrimental effects of sedentary behavior accumulate progressively at the molecular, organ, and system levels, finally presenting as MetS. Second, a gender dimension was introduced into the analytical framework. Most prior studies have used men as the reference, often treating female-specific factors like hormonal fluctuations, pregnancy, and menopause merely as ancillary variables. By considering these physiological stages as potential effect modifiers, we can more concretely explain the differential manifestation of sedentary hazards in women and identify the specific metabolic contexts in which risks are significantly amplified. This perspective reveals that women's metabolic risk is not fixed but dynamically adjusts according to life stage and hormonal environment, providing a clear direction for future precision metabolic interventions.

Current public health guidelines place primary emphasis on moderate-to-vigorous physical activity, while the independent risks of sedentary behavior are insufficiently addressed. The concept of exercise should therefore be redefined to include both the reduction of sedentary time and the promotion of moderate-to-vigorous activity. For women who lack the opportunity for regular exercise, particularly those in long-term office or home environments, breaking up sitting time by standing or walking for two to three minutes every twenty to thirty minutes is not only a practical and easily implementable measure but could also serve as a crucial preventive strategy against insulin resistance. At the clinical level, pregnant and postpartum women, individuals with PCOS, and perimenopausal women represent the highest priority for intervention due to their inherent metabolic vulnerabilities. Screening for and managing sedentary behavior in these populations could yield health benefits far exceeding those in the general female population. The mechanistic pathways summarized in this review suggest that sedentary reduction measures may be particularly effective in alleviating insulin resistance in these groups.

Future research faces several unresolved questions. Mechanistic studies should apply omics technologies such as metabolomics and proteomics to identify human biomarkers specific to

sedentary behavior. Mechanistic clinical trials are also required to investigate the specific signaling pathway changes through which interrupting sedentary periods improves insulin sensitivity. In population research, prospective cohorts employing objective tools such as accelerometers are required to compare the effects of different sedentary patterns, including prolonged and interrupted sitting, on women's metabolic health. In intervention studies, tailored strategies such as micro-interruption protocols for office workers or pregnant and postpartum women should be evaluated, with insulin resistance and related molecular markers as primary outcomes.

6. Conclusion

This study clarifies the pathological mechanism by which sedentary behavior contributes to MetS in women via the core pathway of insulin resistance. Compared to traditional recommendations focusing solely on increasing physical activity volume, this study emphasizes that reducing and interrupting sedentary time should be considered an independent and actionable intervention target. This is particularly relevant for metabolically vulnerable groups such as perimenopausal women, pregnant women, and individuals with PCOS, holding practical application value in primary care and public health management.

However, most current studies still analyze sedentary behavior as a monolithic indicator. Different sedentary patterns, such as occupational sitting, commuting-related sitting, and leisure screen time, may involve distinct psychosocial and behavioral patterns, and their impacts on metabolic health could differ. Existing research has yet to adequately dissect the specific effects of these sedentary behavior subtypes, which may lead to insufficiently precise intervention targets. The development of future research should utilize objective tools like accelerometers and behavioral epidemiology methods to deeply explore the differential effects of sedentary patterns across various domains on women's metabolic health and their specific underlying biological mechanisms. Secondly, efforts should be directed toward developing context-specific precision intervention strategies. For example, testing the relative effectiveness of micro-interruption activity protocols for office-based women compared to screen-time restriction programs for home-based populations in improving insulin sensitivity. Finally, future research could explore integrating digital health technologies, such as smartphone applications and wearable devices, to provide real-time, personalized sedentary behavior feedback and management solutions tailored to women with diverse lifestyles.

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