Review

Metabolic Syndrome: Current State and Prospects

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Posted Date: 29 October 2024

doi: 10.20944/preprints202410.2224.v1

Keywords: Caveolae; Metabolic diseases; Lifestyle alteration; Personalized medicine

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Metabolic Syndrome: Current State and Prospects

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Abstract: Metabolic syndrome (MetS), first conceptualized in 1923, encompasses a cluster of metabolic abnormalities, including insulin resistance (IR), hyperglycemia, dyslipidemia, hypertension, and central obesity. This syndrome significantly increases the risk for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Its global prevalence has surged, largely attributed to lifestyle factors such as poor diet and physical inactivity. Recent research highlights the crucial role of caveolae, small cellular structures, in the pathophysiology of MetS, particularly in insulin signaling, lipid metabolism, and vascular function. Managing MetS effectively requires a comprehensive strategy focused on lifestyle modifications and pharmacological treatments. Dietary approaches, environmental factors, regular physical activity and behavioral changes have demonstrated positive impacts on metabolic health. Despite current pharmacological options to individual conditions of MetS, emerging therapies targeting caveolae offer promising new avenues for treatment. While, microbiome modulation and certain natural agents may assist in managing the syndrome. Public health initiatives, including educational campaigns and stress reduction programs, are essential for the prevention and management of MetS. A multifaceted approach combining lifestyle changes, pharmacotherapy, and personalized interventions is vital for effective management. Future strategies may benefit from precision medicine and the integration of emerging biomarkers for targeted therapies.

Keywords: caveolae; metabolic diseases; lifestyle alteration; personalized medicine

Introduction

The concept of metabolic syndrome (MetS) traces its origins to 1923, when Kylin first described a syndrome characterized by hypertension, hyperglycemia, and hyperuricemia (Kylin, 1923). In the 1940s, Vague further expanded on this by linking abdominal obesity and fat distribution with diabetes and other metabolic disorders (Vague, 1996). In 1965, Avogaro and Crepaldi presented findings at the European Association for the Study of Diabetes annual meeting, identifying a syndrome involving hypertension, hyperglycemia, and obesity (Avogaro et al., 1965). In 1988, Reaven proposed that insulin resistance (IR) is not only central to the pathogenesis of type 2 diabetes mellitus (T2DM) but also plays a significant role in cardiovascular disease (CVD) (Reaven, 1988). He referred to this cluster of abnormalities as syndrome X, and the term "metabolic" was later added to distinguish it from an unrelated cardiological syndrome X. MetS, therefore, represents a significant risk factor for CVD, independent of T2DM, and is characterized by IR, hyperinsulinemia, dysglycemia, dyslipidemia, and hypertension. The modern global definition of MetS was introduced by Alberti et al. in 2009, which specified that the presence of three abnormal findings would confirm a diagnosis (Alberti et al., 2009). The International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute identified core risk factors for MetS, including elevated blood pressure, dyslipidemia (characterized by elevated triglycerides and reduced high-density lipoprotein cholesterol), elevated fasting glucose, and central obesity (Alberti et al., 2009).

The diagnosis of MetS has evolved over time, with various organizations offering diagnostic criteria to improve consistency in identification. The International Diabetes Federation (IDF) provides a widely accepted framework for diagnosing MetS. According to IDF (Alberti et al., 2009), MetS is diagnosed when central obesity is present—defined as a waist circumference of ≥ 94 cm for men and ≥ 80 cm for women—along with any two of the following risk factors:

1. **Elevated triglycerides** (≥ 150 mg/dL)

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2. **Reduced high-density lipoprotein cholesterol (HDL-C)** (< 40 mg/dL for men and < 50 mg/dL for women)
3. **Hypertension** (≥ 130/85 mmHg)
4. **Elevated fasting glucose** (≥ 100 mg/dL)

These criteria highlight the interconnected nature of metabolic disturbances and their collective impact on cardiovascular health. By identifying individuals with multiple metabolic risk factors, clinicians can take early action to prevent or manage associated conditions such as cardiovascular disease and T2DM.

The prevalence of MetS has reached alarming levels worldwide. A 2015 global survey on obesity, covering 195 countries, revealed that 604 million adults and 108 million children were classified as obese (del Rio, 2019). Since 1980, the rates of obesity and MetS have doubled in 73 countries and increased in most others, with childhood MetS rising at an even more concerning rate (del Rio, 2019). Globally, the prevalence of MetS ranges from 12.5% (95% CI: 10.2-15.0) to 31.4% (29.8-33.0), while in the United States, the total prevalence significantly increased from 37.6% in 2011-12 to 41.8% in 2017-18 (p for trend = .028) (Xiaopeng et al., 2023), with higher rates observed in certain demographic groups (Ervin, 2009). In China, the prevalence of overweight and obesity rose from 14.6% to 21.8% between 1992 and 2002, based on WHO criteria, by 2010, the prevalence of MetS had reached 33.9% (31.0% in men and 36.8% in women). (Lu et al., 2017). Among Japanese patients with T2DM, the prevalence of MetS was found to be 43.0%, increasing alongside higher BMI (Ishigaki et al., 2024).

MetS has widespread implications, contributing to the rise of non-communicable diseases and straining healthcare systems. Its increasing prevalence is closely linked to lifestyle factors like poor diet, physical inactivity, and sedentary behaviors (Lima et al., 2024). This review aims to provide an update on the current state of MetS and its future prospects.

Pathophysiology and Mechanism of MetS Formation

The pathophysiology of MetS has been identified as complex and multifactorial. Central to its development is IR, which occurs when cells become less responsive to insulin, leading to elevated blood glucose levels. IR is often accompanied by dyslipidemia and hypertension, which together create a metabolic milieu conducive to cardiovascular diseases (Fahed et al., 2022; Hosseinpour-Niazi et al., 2024). It has been suggested that IR and elevated free fatty acids (FAs) contribute to increased low-density lipoprotein (LDL) and triglyceride levels, which in turn can induce hypertension and its associated metabolic abnormalities. The rise in inflammation further exacerbates the development of vascular plaques, IR, and hypertension, all of which contribute to the progression of cardiovascular diseases (Hosseinpour-Niazi et al., 2024). However, the precise mechanisms underlying the formation of MetS and its related components had remained unclear until recent studies.

Zhang has elucidated the association between the constellation of MetS and cellular membrane caveolae, demonstrating that MetS-associated active molecules are colocalized and interact within the caveolar domains of the cell membrane to perform specific biological functions (W. Zhang, 2014). This discovery provides insight into the cellular and molecular mechanisms that explain the concurrent manifestation of MetS components, offering a clearer understanding of its pathophysiology.

Caveolae are small, flask-shaped invaginations in the plasma membrane of various cell types, particularly in adipocytes, endothelial cells, and muscle cells. These structures are rich in lipids, and proteins especially signaling molecules, playing a critical role in cellular processes such as signaling, lipid metabolism, and endocytosis (Filippini & D'alessio, 2020). Caveolae are primarily formed by caveolin proteins, particularly caveolin-1, which is essential for both their structure and function, and vital for insulin signaling pathways. Insulin receptors and associated signaling molecules are localized within caveolae, enabling rapid and efficient signal transduction. Upon insulin bound to its receptor, a series of intracellular events is triggered, leading to glucose uptake and metabolism. However, in MetS, insulin signaling becomes impaired due to the dysregulation of caveolae dynamics (Varela-Guruceaga et al., 2020). This disruption hampers glucose uptake and increases hepatic glucose production, perpetuating IR and metabolic dysfunction (Crewe et al., 2022). In

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addition to insulin signaling, caveolae play a crucial role in lipid metabolism. CD36, a protein found in caveolae, facilitates the uptake of FAs and the transport of lipoproteins (Peche et al., 2023). In MetS, altered caveolae function contributes to dyslipidemia, characterized by elevated triglyceride levels and reduced high-density lipoprotein cholesterol (HDL-C) (Frank et al., 2008). This disruption in lipid trafficking within caveolae may lead to the accumulation of toxic lipid intermediates, further exacerbating IR and promoting inflammation. Caveolae also influence vascular function through their association with endothelial nitric oxide synthase (eNOS), which regulates blood pressure by producing nitric oxide (NO) (W. Z. Zhang et al., 2008). In MetS, the disarray of caveolae can impair eNOS activity, reducing NO production and contributing to hypertension (W. Z. Zhang et al., 2008).

Caveolae continuously cycle between intracellular and extracellular compartments, and their dysregulation in MetS can reduce the functional number of caveolae present on the cell surface (W. Zhang, 2014). This reduction impedes the proper delivery of glucose, FAs, arginine, and other molecules to their respective receptors or transporters. The resulting metabolic disruptions manifest as the constellation of symptoms seen in metabolic syndrome, including IR, dyslipidemia, inflammation, and hypertension.

Clinical Implications of MetS

MetS has significant clinical implications, acting as a precursor to various chronic diseases. Below are the key areas affected:

1. **CVD**

Cardiovascular disease is an important complication of MetS, resulting in subclinical or symptomatic coronary artery disease, alterations in cardiac structure and function with potential progression to heart failure, and systemic vascular disease (Kalisz et al., 2024). MetS is closely linked to CVD through the clustering of risk factors such as hypertension, dyslipidemia, and IR. These factors contribute to the development of atherosclerosis and cardiovascular events. Caveolae, specialized membrane structures involved in vascular function, play a crucial role in endothelial health (Luchetti et al., 2021). Impaired caveolae function is associated with endothelial dysfunction, which is a precursor to cardiovascular disease.

2. **T2DM**

MetS is a major predictor of T2DM due to IR, a hallmark feature of MetS. Restoring caveolae function has been suggested as a potential strategy for improving insulin sensitivity (Westall et al., 2022), thereby mitigating the risk of T2DM and improving glycemic control.

3. **Metabolic Fatty Liver Disease (MAFLD)**

MAFLD and MetS share pathophysiological features such as IR and dyslipidemia (Fabris et al., 2024). Dysfunctional caveolae may impair lipid metabolism in the liver, contributing to the development and progression of MAFLD (Jaffe & Karumanchi, 2024).

4. **Hyperuricemia and Renal Implications**

Elevated serum uric acid levels are associated with MetS and may contribute to renal function decline (Xu et al., 2024), particularly in individuals with newly diagnosed MetS. MetS is also highly prevalent in patients with end-stage renal disease, highlighting its impact on renal health (Du et al., 2024). MetS is a major contributor to the premature development and progression of CKD. The metabolic abnormalities in MetS, such as hypertension and hyperglycemia, accelerate renal damage (Scurt et al., 2024).

5. **Peripheral Arterial Disease (PAD)**

MetS is a risk factor for PAD, further linking metabolic dysfunction to vascular disease. Impaired blood flow to peripheral tissues due to atherosclerosis is a common complication in MetS patients (Soriano-Moreno et al., 2024).

6. **Hypothyroidism**

MetS has been associated with hypothyroidism, suggesting that thyroid dysfunction may exacerbate the metabolic disturbances seen in MetS (Biondi, 2024)

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7. **Osteoarthritis**

MetS links to the development and progression of osteoarthritis, evidenced by that 12 genes shared between MetS and OA, with functional implications in several biological pathways (Huang et al., 2024).

8. **Psoriasis**

Psoriasis, a chronic inflammatory skin condition, has been linked to MetS, emphasizing the broader systemic inflammatory burden associated with metabolic dysfunction (Matwiejuk et al., 2024).

9. **Cancer Risk**

MetS is associated with increased risks of lung (M. Li et al., 2024), endometrial (Yang & Wang, 2019) and pancreatic cancer (Miyashita et al., 2024), possibly due to chronic inflammation, IR, and altered metabolic signaling pathways.

10. **Autonomic Dysfunction**

The components of MetS (hypertension, obesity, dyslipidemia, and IR) have been shown to alter autonomic nervous system function (Birant et al., 2023). These disturbances affect the regulation of heart rate and peripheral blood flow, especially during physical activity (Mannozzi et al., 2024).

11. **Epigenetics**

MetS is linked to accelerated epigenetic aging, potentially driven by genetic factors rather than lifestyle choices alone (Föhr et al., 2024). Dietary supplement intervention can modify interconnected processes of metabolism and epigenetics (Kumar et al., 2024),

12. **Systemic Lupus Erythematosus (SLE)**

Individuals with MetS exhibit higher disease activity in conditions like SLE, suggesting that metabolic disturbances can exacerbate autoimmune conditions (DelOlmo-Romero et al., 2024).

13. **Alzheimer's Disease, Schizophrenia and Dementia**

MetS and its components are linked to elevated serum levels of amyloid-beta (Aβ42) (K. Li et al., 2024), which could potentially serve as a biomarker for Alzheimer's disease diagnosis (34). Additionally, schizophrenia increases the risk of metabolic dysfunction, independent of environmental factors (Meyer & Stahl, 2009). Stronger associations were observed between MetS and dementia, especially those with a low genetic risk (43).

Therefore, MetS has extensive clinical implications that extend beyond its diagnostic components, affecting cardiovascular health, insulin regulation, liver function, renal health, and more. Its association with multiple chronic diseases highlights the need for early identification and intervention to mitigate these risks.

Current Management Strategies for MetS

Management of MetS focuses primarily on lifestyle modifications and pharmacological interventions aimed at controlling the individual components of the syndrome.

1. **Lifestyle Modifications**

A balanced diet, rich in whole foods, fiber, and healthy fats, is fundamental in managing MetS. Dietary patterns such as the Mediterranean Diet (MD) and Dietary Approaches to Stop Hypertension (DASH) diet are proven to improve metabolic parameters. MD adherence in individuals with obesity and MetS demonstrated with improved body composition, including values of phase angle (De Luis et al., 2024). Specific polyphenols, like those derived from sugarcane leaves (Sun et al., 2024) also exhibit health-promoting effects, though the mechanisms remain under investigation.

Regular exercise is essential for improving insulin sensitivity and promoting weight loss. Current guidelines recommend at least 150 minutes of moderate-intensity aerobic activity per week, combined with resistance training to enhance metabolic outcomes (https://www.who.int/news-room/fact-sheets/detail/physical-activity).

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Modern lifestyles, characterized by psychological stress and behavioral habits, contribute to the high prevalence of MetS. Stress-related dysregulation in metabolic and digestive functions can lead to conditions like functional dyspepsia, often seen in MetS patients (Volarić et al., 2024). Behavioral interventions, including counseling and support groups, are vital in maintaining adherence to lifestyle changes. They help patients make long-term psychological modifications in diet and physical activity, leading to sustained improvements in MetS parameters.

Exposure to environmental pollutants and chemicals has been implicated in the development of MetS (Jiang et al., 2025)(Jeong & Choi, 2024). Chronic exposure to organic arsenic has been shown to cause liver damage involving caveolae dysfunction, linking environmental toxins to MetS-related organ damage (Saharudin et al., 2018).

2. Pharmacological Interventions

Current pharmacotherapy for MetS focuses on the individual conditions of hypertension, hyperlipidaemia and hyperglycaemia with respective antihypertensive, lipid lowing agents and antidiabetic medications. Dapagliflozin combined with metformin showed more meaningful improvements in any of components of metabolic syndrome (Cheng et al., 2021).

Recent research is exploring the potential of targeting caveolae as a therapeutic strategy for MetS (W. Zhang, 2014). Enhancing the expression or function of caveolin-1, a key protein in caveolae, may improve insulin signaling and lipid metabolism (Amiri khosroshahi et al., 2024). This has led to interest in developing pharmacological agents or gene therapies aimed at restoring caveolae function in insulin-resistant conditions. Given the role of chronic inflammation in MetS, anti-inflammatory therapies targeting pathways associated with caveolae could also be effective (Komalla et al., 2020). These therapies may include specific inhibitors or dietary interventions to reduce systemic inflammation. Telmisartan, an angiotensin receptor blocker, has shown unique properties, including a longer half-life and higher antihypertensive activity due to its action on caveolae, a component critical in vascular function (Imenshahidi et al., 2024) . Additionally, the estrogen-related receptor (ERR) agonist SLU-PP-332 has been identified as a potential treatment, acting as an exercise mimetic to address the growing challenges of obesity and MetS (Ross, 2024). Since ERRs are linked to caveolae (Márquez et al., 2006), further research is needed to determine whether SLU-PP-332 exerts its effects on caveolae, potentially contributing to the multi-faceted treatment of MetS.

Emerging research highlights the impact of gut microbiome composition on metabolic health. Modulating gut flora through diet, probiotics, and specific supplements can influence insulin sensitivity, lipid metabolism, and inflammation, offering new avenues for managing MetS (Horvath et al., 2024).

Several herbs, including *Lycium barbarum* (goji berries), have demonstrated potential benefits in treating obesity and T2DM, though more studies are needed to validate their role in MetS management (Sharifi-Rad et al., 2024). Apigenin, a flavonoid found in many fruits and vegetables, has anti-inflammatory and antioxidant properties that may be beneficial for MetS treatment (Javadi & Sobhani, 2024). Herbal treatments targeting hyperglycemia, inflammation, and mitochondrial health also show promise in slowing or reversing MetS progression (Tritel & Resh, 2001). Oleanolic acid, a five-cyclic triterpenoid, exhibits antihypertensive, anti-hyperlipidemic, and liver-protective effects. Its therapeutic role in managing MetS and CVD is gaining attention due to its multi-pathway actions (Luo et al., 2024).

Other natural agents, such as *Kaempferia parviflora* (Na Takuathung et al., 2024) and *Moringa oleifera* (Adarthaiya & Sehgal, 2024), are under investigation for their potential to improve metabolic parameters and treat associated conditions like impotence. Lactate, known for its involvement in MetS-related pathologies, is also being explored for its therapeutic potential (Cai et al., 2024). Specific supplements, such as dietary diacylglycerol, have been shown to reduce postprandial blood lipids, manage weight, and improve insulin sensitivity (Lyu, 2024). These supplements may serve as adjuncts to traditional lifestyle and pharmacological interventions.

Additionally, **individualized interventions and MetS with comorbidities should also be involved in the therapy.** Dietary and lifestyle interventions need to be tailored to

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individuals based on factors like gender and genetic predispositions. Accumulated poor dietary habits and gender-specific responses to dietary modifications underscore the need for personalized management strategies. MetS-related factors are also implicated in the pathogenesis of other conditions such as endometrial cancer, with evidence suggesting that components of MetS may accelerate cancer progression (Yang & Wang, 2019).

Conclusively, the management of MetS requires a multifaceted approach that incorporates lifestyle modifications, pharmacotherapy, and emerging natural therapies. Individualized treatment plans and novel strategies like microbiome modulation offer promising avenues for comprehensive MetS management.

Future Prospects

The precision diagnosis of MetS may involve the use of advanced technologies. CT and MRI are commonly employed for quantifying excess fat, including subcutaneous and visceral adipose tissue, as well as fat around organs, all of which are linked to increased cardiovascular risk (Kalisz et al., 2024). PET imaging can detect signs of IR and may also identify ectopic deposits of brown fat (Succurro et al., 2022).

The shift toward precision medicine offers the potential for customized interventions based on individual genetic, metabolic, and lifestyle factors (Gharipour et al., 2022). Future MetS management could benefit from a deeper understanding of the role of caveolae in metabolic regulation. Caveolae dynamics, which may vary among individuals, could guide more targeted therapeutic strategies (Wei-zheng Zhang, 2025).

Identifying reliable biomarkers related to caveolae function could greatly enhance the understanding of MetS pathophysiology and enable targeted treatments. Dysfunction in caveolae-related proteins, particularly caveolin-1, is linked to various metabolic disorders seen in MetS (Abaj & Mirzaei, 2022). Circulating caveolin-1 levels are being explored as biomarkers for assessing metabolic health, as caveolin-1 is a key regulator of endothelial function, insulin signaling, and lipid metabolism. Tracking caveolin-1 levels may offer prognostic insights into the risk and progression of MetS, particularly in relation to IR and cardiovascular risk (Amiri khosroshahi et al., 2024).

Other biomarkers may also be valuable in MetS management. The Carbohydrate Quality Index (CQI), which considers dietary fiber intake, glycemic index (GI), the ratio of whole grains to total grains, and the solid-to-total carbohydrate ratio, has emerged as a significant marker (Farhadnejad et al., 2024). A higher CQI is inversely associated with obesity and overweight, with recent studies indicating its role in reducing the risk of developing MetS. The index helps fine-tune dietary strategies aimed at improving carbohydrate quality, crucial for metabolic health. Additionally, the uric acid to HDL cholesterol ratio is a promising biomarker for predicting MetS, particularly in patients with T2DM (Kocak et al., 2019). Elevated uric acid levels combined with low HDL are indicative of poor metabolic control and may serve as early indicators for MetS, allowing for earlier intervention. Furthermore, bioinformatics analysis has identified the coiled-coil domain containing 25 (CCDC25) as a potential biomarker associated with key proteins in metabolic pathways (Phimphila et al., 2024). Its link to metabolic dysfunction highlights its potential in predicting MetS progression, supporting a more personalized approach to treatment (Phimphila et al., 2024).

The discovery of biomarkers like caveolin-1, the uric acid to HDL ratio, and CCDC25 improves the ability to predict the onset and progression of MetS. Integrating these biomarkers into clinical practice allows for better patient stratification by metabolic risk, enabling more targeted interventions and enhancing health outcomes. These markers hold significant potential for advancing MetS diagnosis and management, helping to identify high-risk individuals and optimize therapeutic strategies.

Tackling the growing epidemic of MetS requires coordinated public health initiatives that promote healthier lifestyles and raise awareness of the associated risk factors. These strategies should prioritize prevention, education, and ongoing monitoring to reduce the burden of MetS and its related comorbidities.

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Public health campaigns should highlight the importance of physical activity, balanced nutrition, and stress management in reducing the risk of MetS. Educational programs targeting diverse populations can emphasize the benefits of regular exercise, including both aerobic and strength training, and encourage dietary patterns such as the Mediterranean and DASH diets, which have been shown to improve metabolic health (Wiśniewska et al., 2024).

Incorporating mind-body exercises like yoga and tai chi into public health initiatives can also be effective in addressing MetS risk factors (S. Li et al., 2024). These practices not only promote physical activity but also reduce stress and enhance mental well-being, which are critical in preventing and managing MetS.

Breastfeeding duration plays a significant role in predicting long-term metabolic health in women (Lee et al., 2024). Public health programs should advocate for extended breastfeeding, particularly for women at higher risk due to factors like high body mass index (BMI), hypertension, cardiovascular disease, or advancing age (Lee et al., 2024). Promoting breastfeeding can help reduce long-term metabolic risks for both mothers and children.

Sustained monitoring and management of MetS are essential for reducing the risk of chronic diseases, including cancer. Public health strategies should incorporate routine screening and long-term management of MetS components such as hypertension, dyslipidemia, and IR to lower the overall risk of cancer and other serious conditions (Deng et al., 2024).

Overall, comprehensive public health initiatives focused on education, physical activity, stress reduction, breastfeeding, and long-term management of MetS have the potential to significantly reduce the prevalence of MetS and improve population health outcomes.

Conclusions

MetS is a complex, multifaceted disorder that significantly increases the risk of CVD and T2DM. Since its first identification in 1923, MetS has evolved to encompass a range of metabolic abnormalities, including IR, dyslipidemia, hypertension, and central obesity. The global prevalence of MetS continues to rise, primarily driven by lifestyle factors such as poor diet and sedentary behavior, creating a considerable burden on healthcare systems.

Recent research has emphasized the critical role of caveolae, specialized membrane structures, in the pathophysiology of MetS, particularly in insulin signaling, lipid metabolism, and vascular function. These insights clarify the mechanisms underlying the interconnected metabolic disturbances characteristic of MetS. The condition is associated with various health complications, including MAFLD, CKD and increased risks for Alzheimer's disease and cancer.

To effectively combat MetS, a comprehensive approach integrating lifestyle modifications, pharmacological interventions, and emerging therapies is essential. Dietary strategies, such as the Mediterranean Diet and DASH, along with regular physical activity, are foundational. Pharmacological treatments, including antihypertensives and lipid-lowering agents, help manage MetS components. Furthermore, understanding the mechanisms of MetS, particularly the role of caveolae, opens avenues for innovative therapeutic interventions. Public health initiatives focusing on education, stress management, and physical activity promotion are vital for prevention and effective management of MetS.

Conflicts of interest: The author declares no conflicts of interest

Funding: Not applicable.

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