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Perspective

Interconnected epidemics: obesity, metabolic syndrome, diabetes and cardiovascular diseases—insights from research and prevention strategies

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Abstract
The global surge in obesity, metabolic syndrome (MetS), and diabetes has led to a heightened prevalence of cardiovascular diseases (CVDs), posing a major public health challenge. This short communication outlines contemporary research approaches addressing the association between these interconnected conditions. Epidemiological studies, such as the Framingham Heart Study and INTERHEART, have confirmed the strong link between obesity, MetS, and diabetes as predictors of CVDs. Advances in genomics and biomarker discovery, including studies on adipokines and single nucleotide polymorphisms (SNPs), are providing insights into the genetic predispositions that influence the progression from obesity to metabolic disorders. Molecular research has focused on insulin resistance, endothelial dysfunction, and inflammation as key pathways driving these conditions. Furthermore, multi-omics approaches, combining genomics, proteomics, and metabolomics, are offering new opportunities for personalized interventions and precision medicine. Public health strategies, such as lifestyle interventions and policy changes, are also crucial in addressing the rising burden of these diseases. The integration of these innovative research methodologies will be essential in developing personalized treatment strategies and preventive approaches to curb the growing impact of metabolic and cardiovascular diseases.

Keywords Metabolic syndrome · Genomics · Diabetes · CVD · Metabolomics · Proteomics

1 Introduction

The global rise in obesity, metabolic syndrome (MetS), and diabetes has significantly increased the prevalence of cardiovascular diseases (CVDs), creating a pressing public health challenge. These interconnected conditions share complex biological mechanisms and risk factors [1], leading to higher morbidity and mortality worldwide. As their incidence continues to escalate across diverse populations, understanding their interrelationship has become a critical focus. Researchers are investigating the epidemiological, genomic, molecular, and clinical dimensions to elucidate the links between obesity, MetS, and diabetes, and their contribution to cardiovascular pathologies, while striving to develop effective prevention and management strategies.

Epidemiological studies have played a crucial role in identifying the correlation between obesity, diabetes, and CVDs. Cohort studies such as the Framingham Heart Study and global efforts like the INTERHEART study have provided robust evidence on how obesity-related metabolic disturbances, including insulin resistance and chronic inflammation, act as

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precursors to MetS and diabetes—key risk factors for CVDs [2]. Meanwhile, genomic research has identified specific gene variants associated with obesity and metabolic disorders, highlighting the role of genetic predisposition in exacerbating cardiovascular risk.

Advances in molecular biology have further enhanced our understanding of the pathophysiological pathways underlying these conditions. Studies have demonstrated how obesity-induced insulin resistance disrupts glucose regulation and drives chronic inflammation, contributing to endothelial dysfunction and atherosclerosis—major causes of cardiovascular complications. Additionally, the identification of biomarkers such as adipokines (e.g., leptin, adiponectin) and inflammatory markers (e.g., C-reactive protein) has been instrumental in tracing the progression from obesity to CVDs.

This article provides an overview of the latest research approaches aimed at deciphering the intricate interplay between obesity, MetS, diabetes, and CVDs. It emphasizes the contributions of epidemiological studies, genomic discoveries, and molecular insights, while exploring clinical interventions and the integration of 'omics' technologies. As the global burden of these interconnected diseases continues to grow, leveraging these advancements is essential to develop more personalized and effective strategies for prevention and treatment.

2 Epidemiological studies

Epidemiological research has played a key role in establishing the association between obesity, diabetes, and CVDs. Such research highlights the interplay of metabolic risk factors, including high body mass index (BMI), high fasting plasma glucose, and hypertension [3]. Longitudinal cohort studies and cross-sectional surveys have demonstrated how obesity increases the risk of MetS and diabetes, both of which are major predictors of CVDs. Large-scale prospective studies, such as the Framingham Heart Study, continue to provide valuable insights into how metabolic markers contribute to cardiovascular risk, emphasizing the role of lifestyle factors like diet and physical activity in mitigating these risks [4]. Several studies, such as INTERHEART, have further highlighted how central obesity raises cardiovascular risk factors globally, underscoring the need for lifestyle modifications and early interventions, particularly to reduce abdominal fat.

Researchers' understanding of metabolic health has also increased as a result of epidemiological studies using the clustering concept. According to recent article, individuals with similar BMI values may be at radically different risks based on their metabolic health, as seen by phenotypes such as metabolically healthy obesity (MHO) and metabolically unhealthy normal weight (MUHNW). The distribution of fat, especially visceral adiposity, has a substantial effect on cardiometabolic risk, according to these studies. Among populations, cluster analysis has shown subphenotypes including mild diabetes associated with obesity and severe insulin-resistant diabetes. Diabetes-related consequences, such as cardiovascular diseases, renal dysfunction, and mortality, are associated with different risks in these clusters [3]. By reducing the variety of risk phenotypes, these clustering approaches go beyond conventional binary classifications. These approaches support the objectives of precision medicine by identifying a range of pathophysiological processes, including insulin resistance and decreased insulin secretion. There are still issues, nevertheless, such as the requirement for data availability in clinical practice and established definitions. Notwithstanding these challenges, a potential path toward applying precision medicine in cardiometabolic research and clinical care is provided by the combination of accurate phenotyping and clustering.

3 Clinical trials and therapeutic interventions

Clinical trials are critical for assessing the efficacy of treatments targeting obesity and its associated comorbidities. Pharmacological agents like GLP-1 receptor agonists, SGLT2 inhibitors, and statins are being studied for their dual benefits in managing diabetes and reducing cardiovascular risk. Lifestyle interventions have shown that weight loss, increased physical activity, and dietary improvements can prevent MetS and CVDs. Emerging therapies targeting inflammation, insulin sensitivity, and lipid metabolism offer new avenues for obesity, diabetes, and CVD treatment [5]. Furthermore, large studies such as the UK Biobank are integrating clinical outcomes with genetic data to provide a deeper understanding of the interplay between obesity, diabetes, and CVDs [6].

4 Genomic and biomarker approaches

Advances in genomics and biomarker research have enhanced our understanding of the genetic predisposition to obesity, diabetes, and CVDs. Studies on adipokines like leptin and adiponectin have shown their importance in maintaining metabolic balance and cardiovascular health. Additionally, research on single nucleotide polymorphisms (SNPs) in genes regulating insulin sensitivity, lipid metabolism, and inflammation is helping to identify genetic factors that influence the transition from obesity to MetS and diabetes. Biomarkers like C-reactive protein (CRP) and interleukin-6 (IL-6) are also being studied for their role in linking obesity and diabetes to cardiovascular outcomes.

The integration of multi-omics technologies—genomics, proteomics, metabolomics, and lipidomics—has advanced our understanding of how obesity, diabetes, and CVDs are metabolically linked. By utilizing advanced computational tools, artificial intelligence and machine learning, researchers can analyse large datasets to identify new biomarkers, therapeutic targets, and metabolic pathways involved in these conditions [7, 8]. This systems biology approach enhances the development of precision medicine, allowing for more accurate predictions and management of disease risk based on individual metabolic profiles and the recent metabolomics research has identified novel biomarkers such as branched-chain amino acids [9], which are elevated in obese individuals and associated with insulin resistance and CVD risk. Additionally, genome-wide association studies (GWAS) have uncovered variants in genes such as FTO and TCF7L2, contributing to the understanding of obesity's pathogenesis. Combining omics with machine learning enables researchers to better predict disease progression and develop personalized treatment strategies [10].

5 Molecular mechanisms and pathophysiology

Research on the molecular mechanisms behind these interrelated conditions focuses on insulin resistance, endothelial dysfunction, and chronic inflammation. Obesity, defined by excessive fat accumulation, is primarily driven by an imbalance between energy intake and expenditure. The hypertrophy of adipocytes leads to a state of chronic low-grade inflammation, with increased secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines contribute to insulin resistance by impairing insulin signaling pathways, particularly the insulin receptor substrate (IRS) pathway. This insulin resistance is a hallmark of metabolic syndrome, which encompasses a cluster of conditions, including hypertension, dyslipidemia, and hyperglycemia [11].

The progression from obesity to type 2 diabetes is marked by further deterioration in insulin sensitivity and pancreatic beta-cell dysfunction. In obesity, free fatty acids released from enlarged adipocytes contribute to lipotoxicity, damaging pancreatic beta cells and impairing insulin secretion. Additionally, the accumulation of ectopic fat in the liver leads to metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease (NAFLD), further exacerbating insulin resistance and promoting hyperglycemia. By raising hepatic glucose synthesis and releasing proinflammatory mediators, the liver's compromised insulin response aggravates systemic metabolic dysfunction and raises cardiovascular risks even more. There is considerable heterogeneity in the pathophysiology of MASLD, which includes dietary variables, adipose tissue malfunction, and hereditary factors [12]. For example, variations in genes such as TM6SF2 and PNPLA3 predispose people to severe hepatic fibrosis and fat build-up, but they also paradoxically reduce cardiovascular risk. Adipose tissue inflammation and insulin resistance, on the other hand, are metabolic variables that cause MASLD, which is associated with a higher risk of type 2 diabetes and cardiovascular disease [12]. The necessity for accurate identification of MASLD-related cardiovascular risk is highlighted by its unpredictability.

Distinguishing the roles of fatty liver and visceral obesity in insulin resistance and cardiovascular disease (CVD) risk highlights important nuances in metabolic biology. Despite the fact that these conditions often coexist, they impact metabolic health through distinct mechanisms. Hepatic insulin resistance and the release of hepatokines such as fetuin-A are strongly linked to fatty liver, also known as NAFLD [13]. These factors compromise systemic insulin signaling, increase inflammation, and encourage atherogenic dyslipidemia, all of which directly increase the risk of CVD. Conversely, visceral obesity, which is characterized by excess fat surrounding abdominal organs, causes dysregulated adipokine synthesis, which results in low levels of adiponectin and increased levels of pro-inflammatory cytokines [13]. This leads to systemic insulin resistance. Visceral fat, rather than fatty liver alone, is a better predictor of

prediabetes and diabetes, according to studies like the Dallas Heart Study [14]. Only those with high visceral and liver fat have a markedly increased risk of CVD. With precision medicine and customized treatments for certain metabolic dysfunctions, integrative clustering methods that measure liver and visceral fat levels in addition to hepatokines and adipokines, such as fetuin-A and adiponectin, offer insights into their separate and combined functions.

Cardiovascular diseases often manifest as a consequence of the metabolic derangements associated with obesity and diabetes. The interplay between insulin resistance and dyslipidemia contributes to the development of atherosclerosis. Elevated levels of low-density lipoprotein (LDL) cholesterol and triglycerides, along with decreased high-density lipoprotein (HDL) cholesterol, enhance endothelial dysfunction and promote vascular inflammation. Furthermore, increased oxidative stress and the production of reactive oxygen species (ROS) lead to vascular injury, culminating in hypertension and increased risk of myocardial infarction and stroke [15].

Emerging evidence suggests that adipokines, the signalling molecules secreted by adipose tissue, play crucial roles in this interconnection [16–18]. Adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, is often decreased in obesity, while resistin and leptin levels are elevated, further promoting insulin resistance and inflammation [19]. The altered adipokine profile contributes to the pathogenesis of both metabolic syndrome and cardiovascular diseases, highlighting the need for targeted therapeutic strategies.

The interconnection among obesity, metabolic syndrome, diabetes, and cardiovascular diseases is underpinned by intricate molecular mechanisms and pathophysiological processes (Fig. 1). Addressing these conditions requires a comprehensive understanding of their shared pathways, with a focus on early intervention and personalized treatment approaches to mitigate their impact on public health. Understanding these pathways is crucial for uncovering how metabolic disorders lead to cardiovascular complications.

6 Public health and preventive strategies

Public health research has shifted focus to preventive measures aimed at curbing the rise of obesity and its metabolic consequences. Initiatives that promote healthier diets, increased physical activity, and reduced consumption of sugary beverages have shown promise in lowering obesity rates and reducing the associated risk of MetS, diabetes, and CVDs. Early screening for MetS and prediabetes in at-risk populations is being emphasized as a cost-effective way to prevent the onset of diabetes and CVDs. Program like the national policies, including sugar taxes and food labelling, are instrumental in addressing these issues at a societal level [20].

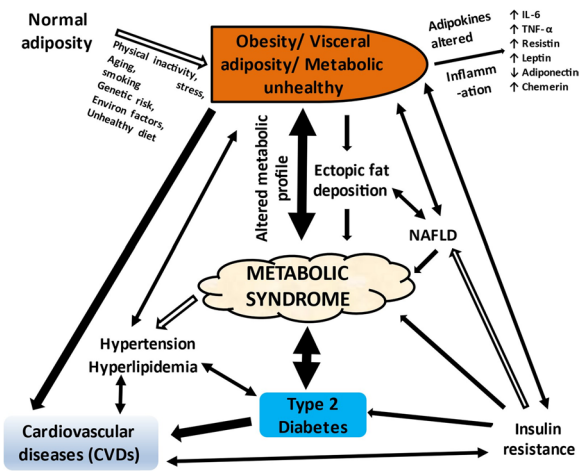

Fig. 1 The complex interactions among obesity, MetS, T2D, and CVDs. This figure draws attention to the ways that obesity and visceral adiposity are caused by age, poor diets, genetic susceptibility, physical inactivity, and altered adipokine secretion, which in turn causes systemic inflammation. This cascade contributes to the development of metabolic syndrome by causing ectopic fat deposition, insulin resistance, NAFLD, and a changed metabolic profile. The figure goes on to link these metabolic abnormalities to hypertension, hyperlipidemia, and type 2 diabetes, all of which increase the risk of cardiovascular diseases

7 Conclusion

The interconnected nature of obesity, MetS, diabetes, and CVDs continues to be a central focus of biomedical research. Advances in understanding genetic, molecular, and environmental factors have paved the way for developing personalized interventions and prevention strategies. Bridging the gap between fundamental research and clinical application will be vital in mitigating the global burden of these interrelated conditions.

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Declarations

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