

A SYSTEMIC REVIEW ON INTEGRATING CARDIOMETABOLIC RISK: UNITING DIABETOLOGY AND CARDIOLOGY.

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Page | 1 **ABSTRACT.**

The principal catalyst behind the worldwide obesity pandemic is the dearth of physical activity and the adoption of unfavorable dietary patterns. The clinical presentation of metabolic syndrome, a modifiable risk factor for type 2 diabetes (T2 DM) and cardiovascular disease (CVD), commonly manifests as an augmentation in the mass of adipose tissue, specifically within the visceral adipose tissue compartment. Waist measurement functions as a fundamental indicator of the accumulation of visceral fat and provides valuable insights into the risks associated with CVD and type 2 DM, irrespective of an individual's BMI. However, an increased waist measurement may also be associated with an enlarged "cardioprotective" subcutaneous adipose tissue volume. The concept of the "hypertriglyceridemic waist" has been introduced, wherein the measurement of plasma triglycerides is combined with waist measurement assessment. The utilization of this approach is purported to provide a more precise evaluation of visceral adiposity and its concomitant health hazards in contrast to solely relying on waist measurement. The phrase "hypertriglyceridemic waist" denotes an aberrant, malfunctioning, and exceedingly lipolytic adipose tissue, which assumes a pivotal role in the pathogenesis of MetS and its associated cardiometabolic hazards. Significantly, this concept is applicable irrespective of conventional risk factors associated with cardiovascular disease, such as age, gender, and plasma LDL cholesterol levels. This study aims to explore the concept of the "hypertriglyceridemic waist" as an indicator of visceral adiposity and its relationship with metabolic syndrome (MetS), type 2 diabetes (T2 DM), and cardiovascular disease (CVD) risk factors, independent of traditional risk factors. Further research should focus on validating the "hypertriglyceridemic waist" concept through large-scale longitudinal studies. Investigating the relationship between this novel indicator and the development of MetS, T2 DM, and CVD in diverse populations can provide valuable insights into its clinical relevance.

Keywords: Visceral Adipose Tissue, Hypertriglyceridemic Waist, Cardiometabolic Risk, Metabolic Syndrome.

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INTRODUCTION.

During the American Diabetes Association's annual meeting in 1988, Gerald Reaven presented the concept that insulin resistance serves as a pivotal factor in elevating the susceptibility to both type 2 diabetes (T2 DM) and cardiovascular disease (CVD). Reaven's seminal discourse postulated that insulin resistance serves as the central pathophysiological mechanism underlying a constellation of metabolic aberrations, encompassing hypertriglyceridemia, reduced levels of HDL cholesterol, hyperglycemia, and raised blood pressure, collectively denoted as "syndrome X" [1]

Expanding upon this fundamental notion, subsequent investigations have consistently demonstrated that insulin resistance is intricately linked to these metabolic aberrations, thereby augmenting the susceptibility to both diabetes and CVD. Acknowledging the inherent difficulties in quantifying insulin resistance within the realm of clinical practice, the National Cholesterol Education Program Adult

Treatment Panel III (NCEP ATPIII) implemented a pragmatic methodology aimed at discerning individuals who are prone to insulin resistance and the concomitant metabolic complications it entails [2]. The emergence of the "MetS" ensued, thereby furnishing a concise modality for diagnosing said condition within clinical environments.

After that time, a multitude of investigations has substantiated that individuals who satisfy the clinical parameters for the MetS, as delineated by the NCEP ATPIII, are confronted with a 1.5 to 2-fold augmented susceptibility to CVD and a 3- to 5-fold amplified vulnerability to T2 DM [3].

Controversies have emerged about the clinical criteria and threshold values utilized in the assessment of metabolic syndrome (MetS). Notwithstanding their inherent limitations, the screening instruments put forth by the NCEP ATPIII have demonstrated utility in the identification of individuals in clinical settings who exhibit an elevated relative risk of developing diabetes and CVD. The MetS has garnered considerable attention owing to its correlation with heightened relative risk, thereby prompting certain

pharmaceutical companies to contemplate it as a potential therapeutic target.

In the year 2005, a critical appraisal was published by the American Diabetes Association and the European Association for the Study of Diabetes [4]. This appraisal raised concerns regarding the clinical significance of diagnosing the MetS and the underlying physiological rationale for its existence. This matter elicited significant concerns; however, deliberations within the non-specialized literature resulted in perplexity among medical practitioners and the general populace.

To elucidate this perplexity, the American College of Endocrinology and the American Association of Clinical Endocrinologists have restated their 2003 ACE Insulin Resistance Syndrome (IRS) declaration in 2006 [5]. Insulin resistance has been underscored as a fundamental characteristic associated with a constellation of metabolic abnormalities, with a cautious approach taken towards categorizing the MetS as an independent pathological condition. This review aimed to prioritize the identification of patients presenting with a confluence of metabolic disorders.

The contribution of the International Diabetes Federation (IDF) to the ongoing discourse was manifested through the proposition of clinical criteria that bear resemblance to the NCEP ATP III guidelines [6]. These criteria serve the purpose of identifying individuals who exhibit a confluence of risk factors associated with this particular cluster. The IDF has placed significant emphasis on abdominal obesity as the primary component, in contrast to insulin resistance. The establishment of the International Chair on Cardiometabolic Risk in 2005 [7] aimed to create a forum for scholarly discourse surrounding topics such as abdominal obesity, the Mets, and the overall risk of CVD on a global scale. The primary aim of the study was to delineate the conceptual framework of the MetS from the diagnostic instruments employed in clinical practice. The phenotype known as "hypertriglyceridemic waist" has been proposed as a clinically significant marker associated with insulin resistance and cardiovascular risk. This phenotype is characterized by an elevated waist measurement accompanied by increased levels of triglycerides.

Furthermore, the inclusion of C-reactive protein (CRP) in CVD risk assessment has been contemplated owing to its established correlation with persistent inflammation. Elevated CRP levels have been observed in individuals who are obese, particularly those who exhibit a buildup of adipose tissue in the abdominal region [8]. The correlation between C-reactive protein (CRP) levels and abdominal obesity is thought to be impacted by increased secretion of interleukin-6 (IL-6) from adipocytes located in the intra-abdominal adipose depot that has been infiltrated by macrophages.

The identification of individuals with the "hypertriglyceridemic waist" diagnosis enables the

recognition of those who are insulin-resistant and have a heightened susceptibility to the Mets. Nevertheless, it fails to offer a comprehensive evaluation of the collective cardiovascular risk. Henceforth, clinicians must accord precedence to the assessment of comprehensive CVD risk, predicated upon classical risk factors, before contemplating the MetS. The concept of "cardiometabolic risk" has been suggested to encompass the potential increased risk of CVD associated with the clinical diagnosis of the MetS, irrespective of the estimated overall risk level determined by existing algorithms relying on traditional risk factors.

Relevance of Abdominal Obesity and MetS in Type 2 Diabetes Patients.

Epidemiological investigations have provided evidence supporting the correlation between T2DM and an increased susceptibility to CVD. Nevertheless, the exact mechanisms that are responsible for this association remain to be comprehensively elucidated. Dyslipidemia and hypertension are acknowledged as conventional indicators that are associated with the risk of CVD in people with hyperglycemic conditions. The impact of MetS on CVD risk in individuals with T2DM is significant. The examination of patients identified as having type 2 diabetes necessitates the utmost significance placed on the measurement of waist circumference and the assessment of additional criteria about MetS. The observation of abdominal obesity as an emerging treatment avenue for the management of CVD risk has been noted.

The implementation of moderate weight loss has been observed to yield favorable outcomes in terms of glycemic control and insulin sensitivity among individuals diagnosed with T2DM. Weight loss frequently results in the preferential reduction of visceral fat in patients who are viscerally obese. The evaluation of whether the reduction of visceral adipose tissue via modifications in lifestyle or the use of pharmacotherapy can yield additional benefits in mitigating cardiovascular disease risk among individuals with T2 DM, beyond the management of hypertension, dyslipidemia, and hyperglycemia, is of utmost importance. Furthermore, it has been observed that although the condition of being prediabetic is indicative of an increased risk of CVD, studies indicate that the presence of isolated dysglycemia alone may not be a substantial independent risk factor for coronary heart disease unless it is accompanied by concurrent abdominal obesity and a diagnosis of MetS. The aforementioned observations provide evidence in favor of the notion that hyperglycemic or dysglycemic conditions are merely a subset of the broader atherothrombotic inflammatory state, frequently observed in individuals afflicted with abdominal obesity and an excessive accumulation of visceral/ectopic adipose tissue [9, 10].

Evaluating Cardiometabolic Risk: Is Waist Measurement the Key?

Despite the robust body of evidence suggesting that an increased waist circumference serves as a dependable prognosticator for an escalated susceptibility to CVD and T2 DM, irrespective of the total adipose tissue content, certain researchers persist in maintaining skepticism regarding the clinical relevance of waist circumference assessment. It is frequently noted that the accurate measurement of waist measurement poses challenges for clinicians and health professionals. Moreover, the clinical significance of evaluating waist circumference, alongside the evaluation of body mass index, remains a subject of continuous discourse. Regarding this issue, the results of the recently published study referred to as the International Day for the Evaluation of Abdominal Obesity (IDEA) study [11], have conclusively shown that the proper education of primary care physicians in the precise evaluation of waist circumference provides valuable insights into the potential risks of CVD and diabetes. These insights surpass the predictive abilities of BMI alone, irrespective of the individual's BMI category. Hence, the assessment of waist measurement enables the precise refinement of cardiometabolic risk evaluation linked to a specific BMI.

Waist measurement: Is It Always an Indicator of Visceral Fat?

While the measurement of waist measurement holds clinical significance, it is imperative to acknowledge that an augmented waistline may not solely signify the presence of visceral obesity. Rather, it can also arise from the accumulation of adipose tissue throughout the entire body. Henceforth, waist measurement functions as an indicator of overall adiposity. In instances characterized by severe obesity, it is important to note that the presence of a high waistline does not always correspond to a substantial accumulation of visceral or ectopic fat, nor does it consistently serve as a reliable predictor of metabolic risk factors.

Clinicians frequently contemplate the existence of alternative methods for more effectively evaluating visceral adiposity, surpassing the mere reliance on waist measurement. A proposition has been put forth regarding the potential utility of fasting triglyceride levels as a valuable diagnostic tool for distinguishing between visceral abdominal obesity as well as subcutaneous abdominal obesity. The presence of a raised waistline in the absence of hypertriglyceridemia may suggest the presence of subcutaneous obesity. In contrast, the simultaneous presence of hypertriglyceridemia alongside the identical waistline measurement may indicate an excessive buildup of visceral or ectopic fat [12]. This underscores the significance of assessing the existence or nonexistence of the "hypertriglyceridemic waist" in clinical settings.

Is There a Threshold for Waist Measurement and Health Risk?

The concept of establishing a precise threshold for the identification of high-risk abdominal obesity presents a notable challenge. The comprehensive investigation of the IDEA study has elucidated a direct correlation between waist measurement and susceptibility to diabetes and CVD. Consequently, it is impractical to suggest a solitary threshold value as a therapeutic objective. In the context of diagnosing the potential existence of the Mets, it has been proposed that elevated waist measurement measurements of 90 cm in males and 85 cm in females may serve as predictive indicators. However, it is important to note that these measurements are only considered significant when accompanied by the presence of hypertriglyceridemia, indicated by triglyceride levels equal to or exceeding 2.0 mmol/L in males and 1.5 mmol/L in females [13]. Henceforth, it is imperative for healthcare practitioners to duly acknowledge waist measurement measurements that surpass the established thresholds. Furthermore, they should contemplate the potential existence of hypertriglyceridemia, which serves as an indicator of the probable presence of surplus visceral and ectopic adipose tissue, in conjunction with associated cardiometabolic complications.

Nevertheless, it is imperative to acknowledge that the designation of 'hypertriglyceridemic waist' is dichotomous, signifying its presence or absence, and does not furnish a comprehensive understanding regarding the extent of the MetS about its correlation with CVD and risk of diabetes. The CVD risk among individuals exhibiting the 'hypertriglyceridemic waist' phenotype is not uniform, as there exists variability in both waist girth and triglyceride levels. The aforementioned constraint highlights the imperative for additional investigation to integrate the notion of 'severity' into novel global risk assessment algorithms for MetS.

Optimal Management of Cardiovascular Risk in MetS.

The efficient management of cardiovascular (cardiometabolic) risk on a worldwide level in patients diagnosed with the Mets poses a significant clinical challenge. During the preliminary stage, healthcare providers must perform a thorough assessment of the overall vulnerability to CVD and subsequently address the conventional risk factors, if identified. The utilization of well-established risk assessment algorithms, such as the Framingham or PROCAM models [14], proves to be highly advantageous in fulfilling this objective.

In individuals presenting with elevated global CVD risk, it is imperative to ensure the efficient management of conventional risk factors such as diabetes, hypertension, and dyslipidemia. This management should adhere to established guidelines and recommendations. Nevertheless,

given the prevailing manifestation of MetS characterized by an overabundance of visceral and ectopic adipose tissue, healthcare practitioners must accord utmost importance to the alteration of dietary and exercise patterns in individuals afflicted with elevated-risk visceral obesity.

The management of nutritional habits necessitates diligent oversight by dietitians, while the modification of physical activity routines necessitates the guidance and expertise of kinesiologists. The incorporation of these lifestyle modifications is crucial within a comprehensive regimen aimed at reducing abdominal adiposity and improving cardiometabolic risk variables and markers, which are often disregarded by current pharmacological interventions.

Numerous studies have substantiated that the achievement of modest weight loss in individuals afflicted with abdominal obesity can result in the targeted decrease of visceral adipose tissue and noteworthy enhancements in cardiometabolic risk profiles, irrespective of the magnitude of weight reduction [15]. Moreover, existing research indicates that the presence of abdominal visceral obesity, in conjunction with an excessive accumulation of ectopic fat, may potentially correlate with an augmented activation of the endocannabinoid system. The efficacy of employing an antagonist targeting this particular system has been demonstrated in clinical trials, wherein significant reductions in abdominal adipose tissue have been observed. These reductions have been accompanied by notable enhancements in cardiometabolic risk factors.

In summary, although certain experts maintain a skeptical stance regarding the clinical utility of diagnosing the MetS and its potential implications for therapeutic interventions, there is a growing acknowledgment of the paramount importance of identifying high-risk abdominal obesity. The coexistence of an increased waist measurement and hypertriglyceridemia, referred to as the 'hypertriglyceridemic waist' phenotype, markedly amplifies the cardiovascular (cardiometabolic) jeopardy in individuals [16]. Hence, it is imperative to adopt a comprehensive therapeutic strategy that encompasses not only conventional risk factors but also the modification of dietary and exercise patterns to specifically address the accumulation of atherogenic and diabetogenic visceral adipose tissue.

Considering that a significant proportion of people diagnosed with T2DM present with abdominal obesity and display characteristics associated with the MetS, they are predisposed to an elevated susceptibility for cardiovascular disease. As a result, it is imperative for diabetologists to effectively manage the microvascular complications that arise due to elevated blood glucose levels, as well as the macrovascular repercussions that stem from the MetS. Similarly, cardiologists are observing a growing number of patients with CAD who also present with MetS and/or T2 DM. This can be attributed to the evolving panorama of CVD risk factors. Hence, it is imperative to establish collaborative endeavors and foster open communication between diabetologists and cardiologists to proficiently

address the escalating prevalence of abdominally obese individuals.

LIMITATIONS.

The study evaluates disputed metabolic syndrome (MetS) clinical criteria and threshold values. Due to MetS's lack of definition and criteria, diagnosis and therapy may differ. Obesity can mask visceral fat, but waist measurement matters. Clinicians struggle to measure waist circumference, affecting cardiometabolic risk. The review shows 'hypertriglyceridemic waist' without MetS severity. More research is needed on waist circumference and triglyceride risk assessment. The article includes risk assessment methods but does not explain how to use them to manage cardiovascular risk in MetS patients. Pragmatic implementation advice is needed.

RECOMMENDATIONS.

To enhance MetS management, standardize diagnosis criteria across categories, train healthcare staff for precise waist measurements, and develop guidelines. Conduct comprehensive cardiovascular risk assessments, considering both metabolic and conventional factors, to tailor treatment. Emphasize nutrition and exercise for MetS patients with abdominal obesity, involving kinesiologists and nutritionists. Promote collaboration between cardiologists and diabetologists, using multidisciplinary teams for complex cases. Further research is needed to create severity-based risk assessment methods, advancing MetS cardiovascular risk understanding.

LIST OF ABBREVIATIONS.

T2 DM	:	type 2 diabetes mellitus
CVD	:	cardiovascular disease
MetS	:	metabolic syndrome
NCEP ATP III	:	National Cholesterol Education Program Adult Treatment Panel III
IDF	:	International Diabetes Federation
CRP	:	C-reactive protein
IDEA	:	International Day for the Evaluation of Abdominal Obesity

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CONFLICT OF INTEREST:

The authors report no conflicts of interest in this work.

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