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Research on Weight-Adjusted Waist Circumference Index in Type 2 Diabetes and Complications: Current Development Status

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Abstract: Weight-adjusted Waist Index (WWI) is a novel tool for evaluating human metabolism. By standardizing waist circumference with body weight, it compensates for the limitations of traditional Body Mass Index (BMI). It performs remarkably well in predicting health risks, including type 2 diabetes mellitus (T2DM), cardiovascular diseases, and metabolic syndrome. This paper summarizes the research progress of WWI in T2DM and its complications. It is found that WWI can effectively predict the onset of diabetes and various complications, with superior assessment efficacy compared with conventional indicators, and combined indexes possess higher predictive value. At present, WWI has not been widely applied clinically, and its diagnostic criteria and action mechanism remain to be further explored. After relevant research is improved, WWI is expected to serve as an effective assessment method for diabetes risk screening and complication early warning.

Keywords: Type 2 diabetes mellitus; Weight-adjusted waist index; Obesity; Diabetic complications

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1. Introduction

DM is a metabolic disease caused by multiple factors, which can lead to chronic progressive lesions in tissues and organs such as nerves, the cardiovascular system, the kidneys, and the eyes. In 2021, there were approximately 529 million DM patients worldwide, with a total prevalence of 6.1%. It is estimated that by 2045, this will rise to 12.2% (about 783.2 million people) with DM. DM and its complications are a financial burden for patients' families, and also a major public health issue that is more serious for our country. Relevant surveys show that the prevalence of DM was 11.9% in 2018–2019 [1]. Obesity is a chronic disease and a precursor to various diseases, such as T2DM. Comprehensive assessment and prevention of T2DM with obesity is a key direction in medical development. As an emerging evaluation tool, WWI has the characteristics of being simple and easy to use, providing a new perspective for assessing health risks related to T2DM. Its core lies in standardizing waist circumference and weight, accurately reflecting the relationship between fat distribution and muscle mass, and offering advantages in cardiovascular diseases, metabolic syndrome, and other areas. In practical application, combining traditional indicators such as body mass index (BMI) and waist-to-hip ratio (WHR) enables more optimal individualized health management and provides more scientific intervention targets for the prevention and treatment of metabolic diseases.

2. Background of WWI and its clinical advantages

T2DM and obesity are closely related in terms of metabolism, sharing key physiological and pathological mechanisms [2]. BMI and WHR are traditional indices commonly used to assess body weight and fat distribution in patients with T2DM, but both are considered to have an "obesity paradox", which is more prominent in Asian populations. The obesity paradox refers to the abnormal phenomenon where obesity, which is a risk factor for chronic diseases, shows a lower mortality risk and better prognosis in mildly overweight populations. Based on this, some scholars believe that the obesity paradox is a statistical illusion caused by research design bias, measurement limitations, and other factors, rather than a real biological protective effect. They found that most of these studies were retrospective analyses, containing many confounding variables, and were not primarily aimed at studying the obesity paradox. Regarding the shortcomings of traditional indicators, Jaitovich et al. suggested that examinations such as CT should be combined for precise body composition assessment to distinguish between protective fat stores and harmful ectopic fat. In this context, Park et al. proposed a new index, WWI, by standardizing waist circumference by weight, achieving a weak correlation with BMI and a negative correlation with height. The formula for WWI is WWI = WC/√weight (cm/√kg), and it was validated using a large Korean cohort for its predictive value for the incidence and mortality of cardiometabolic diseases. In subsequent studies, Ji Yoon Kim, Jimi Choi, and others used CT data to study the relationship between WWI and abdominal fat and muscle indicators, further demonstrating that WWI is positively correlated with total abdominal fat, subcutaneous and visceral fat, and negatively correlated with abdominal muscle area and muscle density.

3. The role of WWI in the prediction and assessment of diabetes and its complications

3.1. Prediction and assessment of diabetes by WWI

WWI is closely related to T2DM. In the state of obesity, it triggers lipotoxicity and IR, leading to the occurrence of T2DM. Studies have shown that WWI is the best obesity indicator for predicting T2DM, outperforming traditional indicators (WC, BMI, WHR, body weight) [3]. At the same time, multiple large-scale studies show that WWI is significantly positively associated with the risk of T2DM. When WWI is at a high value, the risk of developing T2DM increases by 127%. Another research team conducted a longitudinal study using a Japanese database, and after fully adjusting the model, found that for each 1-unit increase in WWI, the risk of T2DM increases by 1.96 times, and the highest quartile of WWI has a 2.33 times higher risk of T2DM compared to the lowest quartile. In a cross-sectional stratified study based on the 2017–2020 National Health and Nutrition Examination Survey (NHANES) database in the United States, Researchers included 7,973 participants and found that for each 1-unit increase in WWI, the risk of developing diabetes increased by 111%. In comparison, for each 1-unit increase in BMI and WC, the risk of T2DM only increased by 5% and 3%, respectively. Different research results also exist, and researchers used the Cox regression model to verify whether WWI could predict T2DM. It was found that the effectiveness was lower than that of traditional indicators such as BMI and WC. The possible reason is that the original data limited the secondary analysis and could not completely rule out confounding factors (such as dietary details, exercise intensity, etc.), and no dynamic diagnosis was conducted during follow-up, which underestimated the incidence of T2DM. Additionally, the study population being a single Japanese ethnicity may also be an influencing factor. In a small-sample study in Iran, Researchers included 215 participants with prediabetes at baseline (≥ 35 years old, 40.5% male) from the prospective cohort of the Isfahan Cohort Study (ICS) in Iran and conducted a 13-year follow-up. They found that WWI had no significant predictive value for T2DM progression in this population. The study analyzed the reasons, which may be related to the sample coming from a specific population in central Iran, the lack of dynamic analysis of relevant indicators, baseline HbA1c not being measured, and diagnoses relying only on fasting blood glucose (FBG) and 2-hour postprandial glucose (2hPPG), leading to certain biases in the results.

Regarding patient characteristics, Zheng et al conducted a cross-sectional study using NHANES data from 2007–2018 and found that the association between WWI and T2DM was particularly significant in the population under 60 years of age, suggesting that WWI is more suitable for assessing T2DM risk in young adults [4]. In another study based on the same NHANES data. Scholars have found that a high WWI value is significantly associated with the prevalence of T2DM in American adults under 40 years old. In different racial populations, a longitudinal study in Japan found an interaction between WWI and age (p = 0.023), with WWI being more sensitive in predicting young adults. There are also studies based on rural and urban populations. Wu Qingzheng, Li Bing, and others used the REACTION study database (Cancer Risk Assessment in Chinese People with Diabetes), including 50,978 adults from eight urban areas in China (Dalian, Lanzhou, Zhengzhou, Guangzhou, Guangxi, Luzhou, Shanghai, and Wuhan), and found that WWI was significantly positively associated with the risk of T2DM in Chinese urban adults. This association was more pronounced in younger middle-aged (< 60 years) overweight/obese (BMI ≥ 24 kg/m^2) men, reflecting T2DM-related central obesity characteristics more accurately than traditional indicators. Another study focused on rural areas in Liaoning, China. WWI is considered an independent factor for T2DM patients in rural areas, unrelated to traditional risk factors, and can serve as a simple and effective tool for early identification and prevention, with significant public health implications. Regarding education level, interaction tests in studies have shown that the association between WWI and T2DM remains stable across subgroups with different ages, races, education levels, marital status, hypertension status, moderate activity levels, and smoking status. Education levels above high school more significantly affect the relationship between WWI and T2DM and show a significant positive correlation, with the association strength clearly exceeding that of BMI and WC.

3.2. Correlation between WWI and Type 2 diabetes combined with cardiovascular disease (CVD)

DM is still significantly associated with all-cause mortality and cardiovascular diseases. The link between WWI and cardiovascular disease is related to the vicious cycle of dysfunctional adipose tissue, oxidative stress, and chronic inflammation. The core mechanism is as follows: long-term energy surplus exceeds the compensatory storage capacity of subcutaneous fat, causing pathological hypertrophy of adipocytes, leading to local hypoxia, immune infiltration, and dysregulated secretion of adipokines, such as reduced adiponectin and leptin resistance [5]. At the same time, it causes excessive lipids to accumulate in tissues such as internal organs, blood vessels, and the liver, inducing systemic metabolic disorders. On one hand, the free fatty acids released by visceral fat accumulation can activate related lipid metabolism pathways and block insulin signaling. Fatty degeneration of the liver further exacerbates glucose and lipid metabolism disorders, jointly inducing IR; On the other hand, dysfunctional adipose tissue produces a large amount of reactive oxygen species, Induce oxidative stress, And activate inflammatory pathways such as NF-κB and TLR, promoting the massive release of pro-inflammatory factors such as TNF-α and IL-6, Forming a vicious cycle in which oxidative stress and chronic inflammation reinforce each other, continuously aggravating insulin resistance. On this basis, the secretory function of perivascular adipose tissue becomes disordered, combined with the abnormal activation of oxidases by oxidized low-density lipoprotein, inducing macrophages to promote atherosclerotic transformation, damaging vascular endothelial function, and reducing nitric oxide utilization. At the same time, the visceral fat fibrosis caused by abnormal fat expansion further consolidates systemic metabolic disorders. The synergistic effect of multiple mechanisms ultimately promotes the occurrence and development of cardiovascular metabolic diseases such as hypertension and atherosclerosis.

A large-scale cross-sectional study based on NHANES collected 44,528 data samples and found that WWI is positively correlated with an increased risk of coronary heart disease, and it surpasses traditional indicators and other new indicators, making it a reliable independent predictor of adverse health outcomes [6]. Another study analyzed data from 4,937 participants across seven NHANES cycles between 2007 and 2020, finding that WWI increased the cardiovascular disease risk in patients with DM, and pointed out that sedentary behavior is an important risk factor. Maojun Liu, Junyu Pei, and others used the Cox proportional hazards regression model and found that for each one standard deviation increase in WWI, the risks of major adverse cardiovascular events (MACEs), composite cardiovascular outcomes, congestive heart failure (CHF), and total mortality (TM) in T2DM patients increased by 7%, 9%, 20%, and 11%, respectively, and it predicted heart failure (HF) more accurately in patients with a disease duration of less than 10 years. Qi Sun, Yang Yang, and others similarly used NHANES data and confirmed through a logistic regression model that WWI is significantly and independently positively correlated with the risk of hypertension (HTN), with the highest quartile group having a 2.94 times higher risk than the lowest group (95% CI: 2.65–3.27, $p < 0.001$). Daoliang Zhang, based on a study of 25,509 participants in NHANES, found that after adjusting for multiple confounding factors, for each 1-unit increase in WWI, the risk of HF increased by 19.5%; in quartile analysis, the highest group had a 1.670 times higher risk of HF compared to the lowest group. It can be seen that WWI is significantly linearly associated with HF risk and can be used for risk screening of HF in the general population. Arterial stiffness (AS) is an important condition for cardiovascular disease, and obesity is also an important risk factor for AS, CVD, and other diseases. Compared with other traditional obesity indices, WWI has a higher correlation with AS risk. Some researchers, while exploring the relationship between the incidence of carotid atherosclerosis (CAS) and WWI in Chinese patients with T2DM, included data from 801 adult patients and conducted a retrospective cross-sectional analysis, finding that WWI was independently associated with the occurrence of CAS, suggesting that WWI can be used as a simple indicator to assess the risk of CAS in Chinese T2DM patients. In another study exploring the association between WWI and the risk of CAS in the Chinese community, based on continuous health examination data from 2012 to 2018, 4,671 subjects without CAS at baseline were included. A prospective cohort study design was used, and after a follow-up of 6.62 years, a total of 2,806 new CAS events occurred. It was found that WWI was significantly positively associated with CAS risk, and it was also considered that WWI can serve as a simple and effective indicator for identifying high-risk individuals for CAS in the general adult population of the Chinese community.

In terms of all-cause mortality, a study based on the NHANES research indicated that WWI has a long-term synergistic negative effect on all-cause mortality and cardiovascular mortality in T2DM patients, and can serve as an independent predictor of mortality in T2DM patients [7]. Cardiometabolic syndrome (CMS) is closely related to an increased risk of cardiovascular disease, T2DM, and all-cause mortality. In this regard, a study based on the 2003–2018 U.S. NHANES data included 6,506 CMS patients to investigate the association between WWI and all-cause mortality in CMS patients, and to analyze the potential mediating role of inflammatory markers. The results showed that WWI is an independent predictor of all-cause mortality in CMS patients, with inflammation playing a key mediating role in this association. The mediation effects of neutrophils, systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and white blood cells were 24.52%, 22.64%, 17.7%, and 14.6%, respectively. Consistent with the population characteristics of this group, obesity itself represents a state of chronic low-grade inflammation, which can further drive the progression of cardiovascular disease and diabetes through mechanisms such as atherosclerosis, insulin resistance, and pancreatic β-cell dysfunction. Regarding research on WWI-related thresholds, some studies have found that in hypertensive patients with hypertension and obstructive sleep apnea (OSA), WWI has a J-shaped relationship with cardiovascular disease, especially when WWI exceeds 11.5 cm/√kg, at which point the risk of cardiovascular disease increases significantly. Another cross-sectional study including more than 30,000 participants based on the 1999–2014 NHANES found a nonlinear positive correlation between WWI and myocardial infarction, with a threshold of 11.15 cm/√kg that can be used to predict myocardial infarction, surpassing traditional indicators such as WC and BMI.

3.3. Correlation of WWI with diabetic nephropathy

3.3.1. Diabetic nephropathy

The pathogenesis of diabetic kidney disease (DKD) is a complex process in which multiple pathogenic pathways intertwine and amplify step by step, ultimately leading to irreversible renal function decline. It involves the following aspects:

(1) Metabolic disorder is the initiating factor, with hyperglycemia being the most upstream driving force. It initiates damage through three classical pathways: the polyol and protein kinase C pathways, advanced glycation end products, and gut microbiota dysbiosis. At the same time, hyperglycemia induces podocytes and renal tubular epithelial cells to produce large amounts of reactive oxygen species, promoting lesions through NLRP3 inflammasomes, epithelial-mesenchymal transition, and apoptosis.

(2) Obesity turns adipose tissue into a pro-inflammatory organ, with excessive secretion of pro-inflammatory factors such as TNF-α and IL-6, leading to macrophage infiltration and sustained activation of the NF-κB pathway. Protective factors like adiponectin decrease (adiponectin exerts renoprotective effects through the AdipoR1/AMPK and AdipoR2/PPAR-α pathways), and its deficiency aggravates oxidative stress, causing the inflammation-fibrosis cascade to go out of control. TNF-α mediates podocyte damage through NF-κB, and IL-1β links hyperglycemia to macrophage infiltration, participating in renal tubulointerstitial fibrosis.

(3) Fibrosis is a common final pathway. Under persistent inflammation and oxidative stress, the TGF-β/Smad2/3 axis becomes the central regulatory hub of fibrosis, with Smad3 mediating the cascade between inflammation and fibrosis, upregulating extracellular matrix components such as fibronectin, promoting the accumulation of myofibroblasts and extracellular matrix deposition, leading to renal tubular interstitial fibrosis and glomerulosclerosis, ultimately causing an irreversible decline in glomerular filtration rate.

(4) Early glomerular hyperfiltration and subsequent glomerular hypertension are closely related to excessive local RAAS activation and the strong vasoconstrictive effect of endothelin-1. Angiotensin II induces reactive oxygen species production and podocyte injury, while aldosterone upregulates profibrotic factors such as TGF-β; endothelin-1 activates pro-inflammatory and profibrotic pathways, promoting mesangial proliferation and proteinuria [8].

In summary, the four major mechanisms, namely, metabolic disorder, chronic inflammation, fibrosis, and hemodynamic abnormalities, work together to lead to progressive loss of kidney function. Using a study from NHANES, which included 10,661 patients diagnosed with T2DM, the overall prevalence of DKD was 20.74%. The study results indicate that WWI can serve as a new index to predict DKD, with a stronger predictive ability than BMI [9]. Another retrospective analysis from China, involving 860 adult patients, investigated the relationship between WWI and albuminuria in T2DM patients. It found that WWI is an independent risk factor for albuminuria in T2DM patients. The area under the curve (AUC) of WWI for predicting albuminuria was 0.605. WWI is independently associated with albuminuria in Chinese T2DM patients and may serve as a simple indicator for assessing the risk of albuminuria.

3.3.2. WWI and kidney stones

Obesity, diabetes, hypertension, and metabolic syndrome are all considered risk factors for kidney stone formation. Kidney stones, in turn, may lead to hypertension, chronic kidney disease, and end-stage renal disease. The accumulation of non-esterified fatty acids in renal cells may interfere with cellular metabolism in proximal tubular cells, leading to a decrease in ammonia production. The reduced ammonia output may result in kidney damage, thereby promoting the formation of kidney stones. There is an independent association between WWI and an increased risk of kidney stones. Individuals in the highest third of WWI have a higher risk of disease compared to those in the lowest third. T2DM partially mediates this relationship. Firstly, IR can promote the excretion of uric acid and oxalate, thereby inducing stone formation; secondly, adipose-derived inflammatory mediators can lower urine pH and increase oxalate levels; chronic low-grade inflammation can disrupt calcium and uric acid metabolism and damage renal tubules; lipid metabolism disorders can independently increase the risk of kidney stones through oxidative stress and renal tubular injury. In addition, the aforementioned inflammatory and metabolic abnormal pathways can also interact with diabetic effects, further increasing the risk of kidney stones in individuals with a high waist-to-height ratio. A cross-sectional study based on the NHANES database, including 31,344 adult participants during the period from 2007 to 2018. Studies have shown that obesity increases the risk of kidney stones, regardless of whether the participants have metabolic syndrome. Other researchers used data from NHANES to conduct multiple logistic regression analyses. Assess the association between WWI and the prevalence of kidney stones, and perform subgroup analyses for susceptible populations. It was also found that WWI is positively associated with the incidence of kidney stones, and this association should be more pronounced in people aged 20 to 39, males, other U.S. ethnic groups, and participants without HTN or T2DM.

3.4. Development of research on WWI in diabetic peripheral neuropathy

Metabolic syndrome in DM patients is a major risk factor for diabetic peripheral neuropathy (DPN). However, obesity can independently damage the peripheral nervous system through two core pathways, leading to peripheral neuropathy: first, the chronic inflammation pathway, which disrupts the blood-nerve barrier, activates neuroinflammation, and directly damages nerve structures; second, the lipid metabolism disorder pathway, where excessive accumulation of long-chain fatty acids (LCFA) induces endoplasmic reticulum stress in Schwann cells, mitochondrial dysfunction, and calcium imbalance, causing an energy metabolism collapse, compounded by mitochondrial transport disorders, with lipid toxicity and inflammation synergistically aggravating nerve damage [10]. WWI is closely related to abdominal visceral fat. As abdominal obesity increases, the combination of chronic low-grade inflammation and insulin signaling impairment can weaken the ability of neurons to cope with metabolic stress and oxidative challenges, thereby promoting the development of neurodegenerative diseases. A study involving 1,790 participants analyzed the relationship between WWI, BMI, WC, and DPN using logistic regression and other methods, and assessed the diagnostic performance of obesity indices using ROC-AUC. It was found that when WWI was greater than 10.757 cm/√kg, WWI had a linear relationship with DPN (odds ratio: 1.375, 95% confidence interval: 1.115–1.7). ROC analysis showed that the diagnostic performance of WWI was better than that of BMI and WC. WWI is linearly and independently associated with DPN, and its stability and predictive value are superior to those of BMI and WC. Some researchers conducted a cross-sectional study based on the U.S. NHANES database to analyze the relationship between body shape index (ABSI), weight-adjusted waist index (WWI), and serum neurofilament light chain (sNfL) levels. They found that both indicators were positively linearly associated with sNfL.

3.5. Development of the WWI index

The triglyceride-glucose index (TyG) is a reliable alternative biomarker for assessing insulin resistance in diabetic patients and is closely related to the incidence of various cardiovascular and kidney diseases. However, it does not take into account the impact of obesity on insulin resistance, and its accuracy in assessing IR is superior to HOMA-IR, with lower cost; WWI can more accurately reflect visceral fat accumulation, differentiate between fat and muscle mass, avoid the “obesity paradox” of BMI and WC, and visceral fat is a key risk factor for the development of DM, having a mutually reinforcing pathological relationship with IR; therefore, a large-sample study based on NHANES. For the first time, TyG was combined with WWI to form the TyG-WWI composite index. Studies have shown that it is significantly superior to the TyG index alone and other TyG-derived indices such as TyG-WC, TyG-BMI, and TyG-WHR. The ROC curves indicate that TyG-WWI has the highest AUC for all outcomes: diabetes (0.81), all-cause mortality (0.69), CVD mortality (0.71), and diabetes-related mortality (0.85). In other studies, related to TyG-WWI, it also reached similar conclusions. Another prospective cohort study was based on the China Health and Retirement Longitudinal Study (CHARLS) database. A total of 5,555 middle-aged and elderly individuals aged 45 and above without T2DM were included and followed up for 9 years. For the first time, the interaction between TyG and WWI was investigated for its impact on the risk of developing T2DM in the Chinese middle-aged and elderly population. It was confirmed that both are independent risk factors for DM, and their combined predictive clinical value is significantly higher than that of a single indicator. Essentially, this reflects the pathological overlay of IR and central obesity. Combined evaluation can simultaneously capture metabolic abnormalities and abnormal fat distribution, compensating for the limitations of a single indicator.

In terms of cardiovascular and cerebrovascular diseases, TyG-WWI also shows advantages in an ACCORD/ACCORDION cohort. Researchers have found that higher TyG-WWI is significantly associated with an increased risk of major adverse cardiovascular events (MACEs), severe coronary heart disease (CHD), congestive heart failure (CHF), and total mortality (TM). TyG-WWI outperforms TyG in predictive accuracy, and for patients under 65 years old, TyG-WWI shows stronger predictive ability for CHF. Another study, based on middle-aged and elderly populations, revealed a significant association between TyG-WWI and stroke, with a 11% increase in stroke risk for each standard unit increase in TyG-WWI. Insulin resistance (IR) and obesity are important components of metabolic syndrome, both of which may increase the risk of stroke. IR is known to contribute to the development of atherosclerosis, leading to vascular intimal hyperplasia and the formation of atherosclerotic plaques, and is significantly associated with the incidence of stroke. It may also hinder the utilization of nitric oxide, thereby impairing endothelial function and increasing the risk of stroke.

4. Summary

WWI compensates for the shortcomings of traditional indicators such as BMI and WC, can to some extent avoid the obesity paradox, reflects fat and muscle distribution, and has good predictive effects on the onset of T2DM and IR. This index can also assess the risk of various complications, including cardiovascular, renal, and peripheral nerve diseases, with predictive performance superior to conventional body fat indicators. The TyG-WWI combined index integrates features of IR and abdominal obesity, further enhancing the ability to predict diseases and adverse outcomes. Most studies recognize the excellent evaluation value of WWI, but a few studies have results that contradict it. These differences arise from individual variations in population ethnicity, age, and lifestyle habits, the size of the study sample, follow-up methods, inconsistent diagnostic standards, and differing levels of confounding variable control, such as diet and exercise. WWI is associated with various forms of disease, and the critical thresholds differ. Currently, WWI remains at the research stage, has not been included in clinical guidelines, and lacks unified reference values for the Chinese population; the underlying mechanisms related to complications are not yet fully clarified; local population data are limited, and research on special populations is insufficient; multi-indicator combined evaluation systems are immature, and long-term follow-up studies for indicator-based stratified interventions are lacking. In the future, large-sample local studies should be conducted to establish WWI reference standards suitable for the Chinese population; further clarify the related pathogenic mechanisms such as inflammation and lipid metabolism; expand research data on populations with different characteristics; build multi-indicator combined evaluation models; carry out intervention trials to verify the practical value of the index in guiding clinical diagnosis and treatment, and promote its application in clinical practice.

5. Conclusion

WWI can objectively assess the degree of abdominal obesity and has prominent advantages in evaluating the risk of onset and complications of T2DM. The combined index detection is even more effective. At present, there are still many shortcomings in the application of this indicator. After further improvement of related studies, WWI is expected to become an effective auxiliary tool for T2DM screening and complication warning, providing a reference for chronic disease prevention and control.

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