

内脏肥胖及相关指标与2型糖尿病关系的研究进展

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摘 要

肥胖或体重过度增加被确认为2型糖尿病(T2DM)发生和进展中最重要且显著的危险因素, 特别是内脏肥胖。肥胖问题已达到大流行的程度, 使得对肥胖的治疗在预防和管理T2DM中显得尤为重要。关于不同内脏肥胖指标对T2DM和内脏肥胖风险的预测效果仍存在争议。本文旨在综述体重指数(BMI)、腰围(WC)、腰臀比(WHR)、腰高比(WHtR)、内脏脂肪指数(VAI)、中国内脏脂肪指数(CVAI)、内脏脂肪代谢评分(METS-VF)、新的内脏肥胖指数(NVAI)内脏肥胖相关指标与T2DM和内脏肥胖风险之间关系的研究进展, 以更好地应对日益流行的T2DM及肥胖。

关键词

内脏肥胖, 2型糖尿病, 内脏肥胖相关指标

Research Progress on the Relationship between Visceral Obesity and Related Indices and Type 2 Diabetes Mellitus

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Abstract

Obesity or excessive weight gain has been identified as one of the most significant risk factors for the development and progression of type 2 diabetes mellitus (T2DM), especially visceral obesity. The obesity epidemic has reached pandemic proportions, making obesity treatment crucial in the prevention and management of T2DM. However, there is still controversy regarding the predictive effectiveness of different visceral obesity indices on the risks of T2DM and visceral obesity. This article aims to review the research progress on the relationship between visceral obesity-related indices, including Body Mass Index (BMI), Waist Circumference (WC), Waist-to-Hip Ratio (WHR), Waist-to-Height Ratio (WHtR), Visceral Adiposity Index (VAI), Chinese Visceral Adiposity Index (CVAI), new Metabolic Score for Visceral fat (METS-VF), and New Visceral Adiposity Index (NVAI), and the risks of T2DM and visceral obesity. This review aims to better address the increasingly prevalent issues of T2DM and obesity.

Keywords

Visceral Obesity, Type 2 Diabetes Mellitus, Visceral Obesity-Related Indices

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1. 前言

根据最新的中国 2 型糖尿病(T2DM)防治指南,糖尿病总体患病率为 11.2%,其中约 90%以上为 T2DM [1]。中国 18 岁以上成年人中超重率为 28.1%,而肥胖症的患病率则达到 5.2%。此外,腹型肥胖的发生率也不容忽视,达到了 29.1% [2]。在糖尿病患者中,超重和肥胖的比例更加严重,分别为 41.0%和 24.3%,而腹型肥胖患者的比例高达 45.4% [3]。糖尿病的发生主要与胰岛素抵抗(IR)密切相关,其中腹型肥胖的特点是内脏脂肪的积聚,这种脂肪沉积与 IR 之间存在紧密的联系[4]。因此,关注肥胖对 T2DM 的管理至关重要。

目前评价内脏肥胖的黄金标准是核磁共振(MRI),然而, MRI 检查费用较高,且需要专业人员操作和解读结果。其他成像技术包括计算机断层扫描(CT)、双能 X 线吸收测定法(DXA)和生物电阻抗分析(BIA),这些技术易于使用且安全,与 MRI 评价高度相关[5]。但其在日常临床中的应用受限于设备和技术难度。因此开发了以人体测量为基础的估计内脏脂肪组织(VAT)的措施。包括腰围(WC)、体重指数(BMI)、腰高指数(WHtR)和腰臀比(WHR),这些指标的局限性在于区分皮下脂肪组织和 VAT 的挑战。研究表明 WC 和 WHtR 与 WHR 和 BMI 相比, WHR 和 BMI 是更好的测量中心性和内脏性肥胖的指标。然而,这些发现尚未在印度人和亚洲人中得到证实[6]。

近年来,许多国内外学者提出了一些与内脏肥胖相关的指标,以评估内脏肥胖情况。包括中国内脏肥胖指数(CVAI) [7]、内脏脂肪代谢评分(METS-VF) [8]、新的内脏肥胖指数(NVAI) [9]、内脏肥胖指数(VAI) [10]。新提出的相关指标在预测内脏肥胖方面展现出了显著的优势,尤其是相较于传统指标,其表现更加出色。然而,关于这些新指标在不同种族群体中的预测效果,仍存在一些争议。因此,本文将对内脏肥胖及其相关指标与 2 型糖尿病(T2DM)之间的关系进行深入研究的综述,旨在为 T2DM 与内脏肥胖的防治工作提供重要的参考依据。

2. 内脏肥胖与 2 型糖尿病

糖尿病是一种慢性代谢疾病，其主要特征在于胰岛素的分泌或功能发生缺陷，最终导致血糖水平升高。研究指出，VAT 被认为是肥胖与非肥胖个体中 T2DM 的主要驱动力之一。肥胖个体在葡萄糖代谢后会分泌出更多的胰岛素，这一过程通常会对胰腺 β 细胞的功能造成损害，这种情况会导致 IR，进而提高个体患 T2DM 的风险。此外，随着 VAT 的逐步累积，非肥胖个体在 T2DM 病例中所占的比例也日益显著[4]。

VAT 位于腹腔附近的器官，如肠道、肝脏和胰腺，属于一种以大量脂肪细胞为特征白色脂肪组织[11]。它与多种病理状况明显相关，包括葡萄糖和脂质代谢受损以及 IR，并且是代谢综合征的一个独立组成部分[12]。如此过量的脂肪组织会改变游离脂肪酸(FFAs)、脂肪因子、生长因子和促炎细胞因子的分泌。此外，肥胖会增加脂肪组织内巨噬细胞的浸润，从而增加促炎细胞因子的水平。随着炎症反应的改变扩散，在肝脏、胰腺和肌肉组织中也可以清楚地检测到葡萄糖和脂质代谢的改变。因此，炎症过程对 IR 的贡献不仅限于脂肪组织，而且是全身性的[13]。重要的是，在脂肪组织和巨噬细胞分泌的促炎因子中，有那些可以直接导致 IR 的因子，包括肿瘤坏死因子- α 、白细胞介素-1 β 、白细胞介素-6、白细胞介素-18 和血管紧张素 II [14]。

VAT 的脂肪细胞无法维持更长的代谢稳态，因为脂质超负荷导致内质网应激、炎症调节因子 NF- κ B 表达增加以及炎症诱导信号的产生[15]。这种慢性代谢诱导的炎症或代谢性炎症会激活常驻免疫细胞，包括巨噬细胞、B 细胞、T 细胞和抗原呈递细胞[16]。高脂饮食、坏死脂肪组织中累积的损伤相关分子模式的 FFAs 通量增加，以及缺氧诱导因子 1 (HIF-1) 可触发先天性和适应性免疫反应[15]。由此产生的低级别慢性脂肪组织炎症表现为促炎脂肪因子和细胞因子的水平显著升高，以及活性氧(ROS)的过度产生[14]。这种炎性环境会干扰胰岛素信号通路，其通过针对胰岛素(INS)和胰岛素受体(INSR)的抗体/自身抗体影响胰岛素受体(INSR) [17] [18]，还会通过抑制 INSR 内的酪氨酸自磷酸化和(或)胰岛素受体底物(IRSs)的丝氨酸/苏氨酸磷酸化来影响肿瘤坏死因子受体(TNFR1) [19] [20]。并通过异常磷酸化 INSR 和 IRSs，这与 TNFR1 信号传导中观察到的现象类似，进而影响其他促炎细胞因子的受体[19] [21]。通过丝裂原活化蛋白激酶/细胞外信号调节激酶(MAPK/ERK)和磷脂酰肌醇 3-激酶/蛋白激酶 B/雷帕霉素哺乳动物靶标(PI3K/AKT/mTOR)途径的下游信号传导中断，最终会导致 IR。由此产生的高血糖本身可能会增加炎症反应，并导致全身性炎症[22] [23]。

VAT 可能在预测 T2DM 方面发挥重要的代谢作用，原因在于它减少了 FFAs 的摄取，并增加了 FFAs 的释放。当 FFAs 在血液中的浓度增加到过高的水平时，可能会引发 IR [24] [25]。IR 会导致细胞内脂肪的分解，进而使甘油三酯被分解，释放出 FFAs 进入血液中。随着 FFAs 从脂肪组织释放进入血浆，并通过门静脉及骨骼肌的血管系统到达肝脏等其他组织，这一过程会加重其它组织中的 IR 问题[26]。

当血液中的 FFAs 浓度过高时，骨骼肌会吸收更多的 FFAs，这种情况可能导致肌肉纤维的过度积累[27]。储存的脂肪在分解过程中会转化为多种代谢物，其中包括长链酰基辅酶 A、神经酰胺以及二酰基甘油等。这些代谢物在体内的积聚直接导致组织出现 IR 的现象。相关研究表明，长链酰基辅酶 A 具有抑制己糖激酶活性的作用，而己糖激酶在葡萄糖代谢过程中则扮演着关键酶的角色。此外，二酰基甘油可能通过直接或间接激活蛋白激酶 C 的某些特定同工型，以至于通过丝氨酸磷酸化的方式损害胰岛素受体底物 1 (IRS-1)途径的正常功能。这一过程还会进一步影响磷脂酰肌醇-3-激酶信号通路，进而导致骨骼肌在葡萄糖的摄取和代谢能力上出现下降。与此同时，神经酰胺具有降低 IRS-1 通路中酪氨酸磷酸化水平的作用，这一过程进一步抑制了蛋白激酶 B 的磷酸化。这两种机制相互作用，直接导致葡萄糖转运蛋白 4 转位的减少，最终导致骨骼肌对葡萄糖的摄取能力显著下降[28]。

综上，VAT 通过增加 FFAs 释放、炎症因子分泌、脂肪因子失衡等机制引发 IR，进而导致代谢紊乱，

所以减少内脏脂肪是改善胰岛素敏感性和预防代谢疾病的关键。

3. 内脏肥胖相关指数与 T2DM 及内脏肥胖

3.1. 传统肥胖指数

3.1.1. 体重指数(BMI)

BMI 是最常用的肥胖分类工具,也是评估全身肥胖的通用标准。它与体质比具有良好的相关性,能够反映肥胖相关疾病的患病风险[29]。T2DM 患者的 BMI 与微血管并发症呈正相关,例如糖尿病肾病(DKD),但与大血管疾病之间的关系尚不明确[30][31]。但是在一项因果关系研究中发现,虽然中国 T2DM 患者的 BMI 与总体微血管并发症事件风险增加相关。肥胖的类型与 DKD 之间存在明显的因果关系,说明不同的肥胖表现会影响肾脏健康。然而,肥胖类型与糖尿病视网膜病变(DR)之间并不存在这种因果关系,表明两者之间没有直接的影响关系[32]。相关研究也发现肥胖本身可能与 T2DM 患者的心血管疾病风险(CVD)及死亡风险的增加并没有直接关系,而 BMI 变异性增加,特别是迅速增加,才是真正的 CVD 和死亡危险因素。因此,应关注 BMI 的动态变化过程,而不仅仅是其单纯的数值[33][34]。而且,与 BMI 相比,其他肥胖相关指标对 T2DM 的预测能力更强,发生 T2DM 的风险也更高[35][36]。此外,不同种族中, BMI 与 T2DM 之间的关系并不稳定, BMI 作为 T2DM 的预测指标受到了不必要的关注[37]。总的来说,关于 BMI 这个传统指标对中国人群 2 型糖尿病风险及相关并发症预测有限,可能 BMI 是一种基于体重和身高的指标,用于评估整体肥胖程度。然而, BMI 无法区分体内的内脏脂肪和皮下脂肪,也会将一些肌肉质量较高的不具有健康风险的个体被错误地归类为肥胖。

Ming Kong 等人利用多中心数据通过 CT 测量皮下脂肪和内脏脂肪,研究表明 VAT 和皮下脂肪组织的参数分布因性别、年龄和 BMI 而异,即使在 BMI 处于正常范围的男性和女性中,内脏肥胖的发生率仍然较高。这表明,即使外表看似健康,内脏脂肪的积累仍然可能对他们的健康产生潜在风险[38]。此外,对于 T2DM 患者, BMI 大于 25 kg/m²可能是诊断一般性肥胖的最佳界值[39]。这一现象可能部分是由于糖尿病患者与普通人群之间的身体成分差异所致。对于 T2DM 患者,肌肉和骨骼质量的减少可能导致体重减轻,从而在一定程度上降低他们的 BMI。因此,降低 T2DM 患者的 BMI 临界值是必要的[40]。综上,虽然 BMI 是一种广泛使用的衡量标准,但 BMI 只涉及身高和体重的测量,因此无法评估个体的体脂百分比和肌肉质量,在确定性别、年龄和种族与肥胖之间的关系时, BMI 测量也可能存在差异[41]。因此, BMI 需要与其他指标结合使用,以提高对 T2DM 及其并发症的评估能力。

3.1.2. 腰围(WC)

WHO 建议男性的 WC 诊断肥胖的临界点为 ≥ 90 cm,女性为 ≥ 80 cm。然而,基于中国成年人群的特点和健康风险评估,中国对中心性肥胖的标准为男性 ≥ 90 cm,女性 ≥ 85 cm [42]。利用中国队列研究数据发现,无论是基于 BMI 和 WC 分组的肥胖,还是通过 WC 和 WHtR 定义的腹部肥胖,都与 T2DM 相关。而且,无论 BMI 状态如何,腹型肥胖的受试者患 T2DM 的风险均更高[43][44]。因此,监测腹部肥胖和减少腹部脂肪至关重要。在 T2DM 患者中,高 WC 同样是糖尿病微血管并发症的潜在致病危险因素。而且根据 WC、WHR 和 WHtR 进行分类分析时发现,患有 DKD 的 T2DM 患者更可能存在腹部肥胖,因此体重控制可能独立于血糖控制而改变这些并发症的风险[45]-[47]。针对糖尿病或糖尿病前期患者,CVD 的风险也显示出线性增加的相关性[48]。然而,其他研究纳入了脂质积累产物指数(LAP)、VAI、WHR、CVAI、颈围等指标后,发现 WC 在预测 T2DM 并发症时,相比其他指标并没有明显优势[49]-[51]。Zhao 等人[40]利用日本的腹型肥胖病标准研究表明,WC 相较于 BMI 在预测 T2DM 内脏肥胖方面的能力更强,男性 WC > 93 cm 和女性 WC > 90 cm 被认为是诊断中国 T2DM 患者腹型肥胖的最佳界限。上述表明

T2DM 腹型肥胖临界值较正常人更高, 可能是 2 型糖尿病患者通常存在代谢综合征的表现, 包括肥胖、IR、血脂异常等, 这些代谢异常往往伴随着腹部脂肪的过度积累, 使得腰围显著增大。与中国人群不同, 在加纳 T2DM 患者临界值却为 $WC > 80.5\text{ cm}$ [52]。综上, 考虑到 WC 相较于新开发指标预测效能无明显优势, 且尚缺少利用中国腹型肥胖诊断标准取得 WC 诊断内脏肥胖最佳临界值, 需要更多研究去探索。

3.1.3. 腰高比(WHtR)和腰臀比(WHR)

与 BMI 相比, WC、WHtR 和 WHR 通常用于定义向心性肥胖, 并在内脏肥胖及 T2DM 中表现更好。有研究纳入 WHR 和 WHtR 及其他肥胖指标, 分析其预测 T2DM 发生风险效能表明, 相较于其他指标 WHtR 对 T2DM 的相关性和预测能力相对较强, 特别是在中国 18 岁以上的女性中, 但是也有研究纳入其他不同肥胖指标, 表明 WHtR 相较于其他肥胖指标却无明显优势[35] [53] [54]。目前尚不清楚 WHtR 和 WHR 相较于近期开发的肥胖指标更有优势, 需要进一步的研究去证明。与 WC 和 BMI 相比, WHtR 与 T2DM 受试者的糖尿病周围神经病变和 CVD 事件具有更强的相关性, WHtR 是评估 T2DM 患者糖尿病周围神经病变和 CVD 的更佳指标[55] [56]。一项对中国上海 1952 名 T2DM 患者的横断面研究中, WHtR 和 BMI 也是肥胖 T2DM 患者发生 DR 的危险因素, 而不是 WHR [57]。另一项横断面研究则显示, 在 BMI 正常的 T2DM 人群中, WC、WHR、WHtR 与 DR 之间的关系存在性别差异而且女性中显著相关, 但在男性中则无关联[58]。在糖尿病肾病中 WHtR 和 WHR 相较于 WC 预测能力也欠佳[45]。综上, WHtR 和 WHR 与 T2DM 及相关并发症之间相较传统指标关系针对不同人群存在差异, 与新的肥胖相关指标比较研究相对较少, 是否更优越值得进一步探究。

西澳大利亚人群的研究表明, 在男性中, WC、WHR 和 WHtR 与 VAT 呈高度相关性, 在女性中, 只有 WHtR 与 VAT 高度相关[59]。同时, 在高加索人群中, 与 BMI、WC、WHR 和 WHtR 相比, WHtR 是脂肪量百分比和 VAT 质量的最佳预测指标。WHtR 在评估内脏肥胖时的临界值在男性和女性之间的差异不大分别为 0.53 和 0.54 [60]。值得注意的是, Ke 等[56]在一项针对 191 名成人的横断面研究中表明, 预测内脏肥胖($VFA \geq 130\text{ cm}$, 由 CT 确定) WHtR 切点范围为 0.54 至 0.59。在加纳 T2DM 患者中评估内脏肥胖的最佳临界值为 $WHtR > 0.5$, $WHR > 0.82$ 。而且 WHtR 在识别内脏肥胖方面优于 BMI、WC 和 WHR [52]。以上研究显示针对不同研究人群 WHtR 和 WHR 识别内脏肥胖临界值不同, 故针对不同人群需要重新寻找临界值筛查内脏肥胖。

3.2. 新型内脏肥胖相关指数

3.2.1. 中国内脏脂肪指数(CVAI)

Xia 等人结合中国成人特征, 利用临床非侵入性指标开发并进一步外部验证了 CVAI。与 WC、BMI、VAI 相比, CVAI 与 VAT 关系更为密切, 并能更好地预测代谢紊乱[7]。在一项针对 12,237 名中国成年人为期 6 年的队列研究中, 结果表明 VCAI 在预测 T2DM 发病率方面优于其他内脏肥胖指数(VAI、WHtR、WC 和 BMI) [61]。在中国上海的 7 个社区中, 对 4658 名 T2DM 患者的研究显示, CVAI 与 CVD 和 DKD 患病率的相关性相较于 BMI、WC、WHR 和 VAI 最强, 是预防和治疗 CVD 及 DKD 的有用且有效的工具[49]。而且在中国新疆的多民族队列研究中, CVAI 被强调为识别 T2DM 人群中高风险 CVD 事件的有价值的腹部肥胖指标[50]。同时, CVAI 已被证明与脂肪肝、代谢综合征、高血压、动脉硬化等 T2DM 及其并发症的危险因素密切相关[62]-[65]。总的来说 CVAI 是基于中国沿海成年人开发的一个指数, 如今在其他种族、地区及 2 型糖尿病预测内脏肥胖的应用仍需进一步研究。

3.2.2. 新的内脏脂肪代谢评分(METS-VF)

Bello-Chavolla 等人利用美国人群开发了 METS-VF。该开发人群包括正常、超重、肥胖、高血压和糖

尿病患者, 并进行了三次验证[8]。经过 6 年随访健康检查的 15,464 名受试者的研究表明, METS-VF 是一种评估内脏肥胖的新指标, 与糖尿病风险呈显著正相关。与 BMI、WC、WHtR 和 VAI 相比, METS-VF 被证明是预测未来糖尿病发作的优越风险标志物, 特别是在预测中长期糖尿病风险方面[66]。同时, 在不同葡萄糖耐量状况人群中也发现 METS-VF 与 CVD 事件和全因死亡率风险增加相关[67]。此外, METS-VF 与不同人群中冠状动脉钙化、非酒精性脂肪肝病以及高血压之间存在明显的相关性[68]-[71]。对于印度 BMI $\geq 35 \text{ kg/m}^2$ 的病态肥胖个体而言, METS-VF 在评估 VAT 升高方面表现出良好的敏感性和合理的特异性, 可以作为南印度病态肥胖个体内脏肥胖的替代测量指标[72]。值得注意的是, 在对 185 名接受 CT 检查以测量 VFA 的土耳其青中年研究对象的研究中, 虽然 METS-VF 与内脏肥胖密切相关, 并更能预测 VFA 增加, 但对 WC、BMI、BRI 和 LAP 的优越性并不显著[73]。所以针对不同种族其预测能力需要更多研究去进一步验证。

3.2.3. 新的内脏肥胖指数(NVAI)

NVAI 是 Sung-Kwan Oh 等人提出的一种指标, 它结合了年龄、WC、甘油三酯、高密度脂蛋白胆固醇以及平均血压, 与韩国人 CT 测量的 VAT 显著相关, 能够比以前的替代指标, 如 BMI、WC 和 VAI, 更好地预测内脏肥胖[9]。作为一种新的内脏肥胖指数, 目前关于 NVAI 对内脏肥胖及 T2DM 相关性和预测效能的研究较少, 未来需要更多研究来证实其是否相较于其他指标更具优越性。

3.2.4. 内脏肥胖指数(VAI)

Marco 等人提出了一个新的指标 VAI, 用于评估 VAT。该评估工具基于量化血液甘油三酯和高密度脂蛋白水平的常规生化测试结果, 以及人体测量指数 BMI 和 WC [10]。VAI 被认为是内脏脂肪分布和内脏脂肪功能障碍的替代量度, 其灵敏度和特异性高于经典参数[74]。一项荟萃分析表明, VAI 是来自不同人群(包括中国人)的糖尿病风险的独立预测指标, 但不同的种族和国家之间存在差异, 导致对 VAI 临界值的定义缺乏共识且其预测准确性仍然有限, 需要进一步探索寻求新的指标[75]。在中国北方成人 T2DM 患者中, VAI 与 DKD 发生风险相关, 但与 DR 之间缺乏显著关联[76]。而在中国南方人群中, VAI 与新发 DR 风险增加显著相关[77]。同时针对印度人群, 与非 DM 患者相比 VAI 是 T2DM 患者预测 DR、DKD 和神经病变等微血管并发症的筛查工具[51]。这与利用美国人群的队列研究针对 T2DM 微血管病变研究一致[78][79]。研究也表明 VAI 与糖尿病人群发生大血管并发症的风险也相关[80][81]。然而, 在中国研究人群纳入其他肥胖替代指标后, 虽然 VAI 与并发症事件风险增加相关, 但 VAI 相较于其他新的替代肥胖指数在预测 T2DM 并发症能力上并无明显优势[49][82]。这可能是由于 VAI 是基于高加索人群开发的内脏肥胖相关指数, 而研究表明不同种族在体脂分布特征上存在差异, 亚洲人群似乎更容易发生内脏脂肪蓄积, 因此在中国人群中, VAI 对 T2DM 及其并发症的预测能力并不理想[83][84]。

针对 40 名男性巴西空军飞行员研究结果表明, VAI 在预测正常成人内脏肥胖方面, 相较于传统指标, 表现出更为明显的优势[85]。然而, 目前尚缺乏关于 VAI 对其他种族、不同职业以及伴随其他基础疾病人群内脏肥胖预测能力的研究。

4. 总结与展望

内脏肥胖与 T2DM 密切相关, VAT 通过增加 FFAs 释放、炎症因子分泌、脂肪因子失衡等机制引发 IR。因此, 对高危人群进行早期干预以防止内脏肥胖的发生显得尤为重要。这种干预措施不仅能够有效降低患 T2DM 的风险, 还能减轻这一疾病带来的整体负担。内脏肥胖相关的指标在预测 T2DM 风险方面具有良好的预测效能, 但仍存在一些局限性。首先, 目前尚不明确内脏肥胖相关指标与中国 T2DM 内脏肥胖统一的临界值。其次, 近期新开发的指标相关研究较少, 尚缺乏充分的研究证据, 需要更多严谨的

研究来验证这些指标的可靠性。同时, 继续寻找更加简单有效的方法, 以在临床实践和大型流行病学调查中以最经济的方式评估身体成分。

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