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肥胖指数与慢性肾脏病的研究进展

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【摘要】 慢性肾脏病 (chronic kidney disease, CKD) 是一个日益严重的公共健康问题, 其患病率在全球范围内逐年增加。肥胖是肾脏疾病发生和发展的重要危险因素, 且伴随而来的代谢异常又会进一步加剧疾病进展。因此早期识别和制定预防策略对于改善 CKD 高危人群的临床结果至关重要。目前肥胖的临床评估指数有很多, 但其与 CKD 发病的相关性研究结果却不尽相同。现对近年来报道的肥胖指数与 CKD 的相关研究进展进行阐述, 为其临床应用与未来研究提供参考。

【关键词】 慢性肾脏病; 肥胖指数; 相关性

Research progress of obesity index and chronic kidney disease

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【Abstract】 Chronic kidney disease (CKD) is a growing public health problem, with its prevalence increasing year by year worldwide. Obesity is an important risk factor for the development and progression of kidney disease, and the associated metabolic abnormalities further exacerbate disease progression. Therefore, early identification and the formulation of preventative measures are crucial in improving clinical outcomes for individuals predisposed to developing CKD. There are numerous indices available for the clinical evaluation of obesity. However, the findings from studies examining their correlation with incident CKD have been inconsistent. In this paper, the research progress on obesity index and CKD in recent years is reviewed, aiming to offer valuable insights for clinical application and future research.

【Key words】 Chronic kidney disease; Obesity index; Correlation

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慢性肾脏病 (chronic kidney disease, CKD) 是一个全球公共健康问题, 具有患病率高、知晓率低、预后差和医疗费用高等特点^[1]。全球疾病负担研究显示, 从 1990 年到 2017 年, CKD 死亡人数增加了 41.5%^[2]。CKD 患病率仍呈逐年上升趋势, 全球患病率高达 13.4%^[3]。肥胖是糖尿病、心血管疾病、多种癌症的危险因素^[4], 同时它也是 CKD 的独立危险因素^[5]。

近年来, 全球超重/肥胖的患病率快速增长, 人口占比不断增加, 并且逐渐向年轻化发展。肥

胖症已经成为一种严重影响国人身心健康的全球流行病。在中国, 超重率和肥胖率持续攀升, 一项来自中国 1 580 万成年人的真实世界研究显示超重率和肥胖率分别达到 34.8% 和 14.1%^[6], 预测至 2030 年, 中国将有 65.3% 的成年人和 31.8% 的学龄儿童及青少年出现超重或肥胖^[7]。肥胖的流行伴随着 CKD 的增加, 肥胖已经成为 CKD 发生的重要危险因素, 据估计, 全球肾脏疾病患者的肥胖率可达到 20%~25%^[8], 2011—2014 年美国国家卫生与营养调查 (National Health and Nutri-

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tion Examination Survey, NHANES) 的数据显示, 在美国 CKD 成人患者中, 肥胖率从 1999—2002 年的 38.1% 增加至 2011—2014 年的 44.1%^[9]。但肥胖引起的肾脏损伤的机制仍然不清楚, 可能机制如下。血流动力学改变: 肾小球高灌注、高滤过导致肾小球结构改变, 包括肾小球肥大和足细胞损伤; 肾素-血管紧张素-醛固酮系统 (rennin-angiotensin-aldosterone system, RAAS) 过度激活; 胰岛素抵抗; 脂肪因子分泌异常与持续的炎症反应; 脂代谢紊乱与脂毒性; 氧化应激与肠道菌群紊乱等^[10-17]。因此未来早期识别和预防策略的制定对于改善 CKD 的高危人群的临床结果至关重要。

脂肪组织分布于机体各处, 不同部位脂肪组织的结构与功能有所不同。脂肪分布主要包括皮下脂肪组织 (subcutaneous adipose tissue, SAT) 和内脏脂肪组织 (visceral adipose tissue, VAT)。SAT 是指贮存于皮下的脂肪组织, 在真皮层和深层筋膜层之间, SAT 对疾病发生发展的作用比较有争议^[18-20]。相比之下, VAT 与代谢性结局关系的研究结论相对一致^[21-24]。尽管与 SAT 相比, VAT 在全身脂肪中占比较小, 但内脏脂肪的增加显著增加了代谢综合征的发病风险^[22]。在与 CKD 的相关研究中, Kataoka 等^[25]发现内脏与皮下脂肪比 (visceral to subcutaneous adipose ratio, VSR) 与 CKD 进展相关, 尤其是内脏脂肪面积 (visceral fat area, VFA) $\geq 100 \text{ cm}^2$ 时。Chen 等^[26]通过计算机断层扫描 (computed tomography, CT) 检测糖尿病患者的肾周脂肪厚度 (perirenal fat thickness, PRFT) 和总脂肪 (total body fat, TBF), 并通过双能 X 线吸收法 (dual energy X-ray absorption method, DEXA) 评估其 SAT 和 VAT, 研究结果发现肾周脂肪对 2 型糖尿病患者的 CKD 风险的预测价值高于总脂肪、皮下脂肪和内脏脂肪。最近一项研究探讨了通过 CT 获得的脂肪组织面积相关指数和脂肪组织放射密度与 CKD 患者预后的关系, 发现皮下脂肪组织密度 (subcutaneous adipose tissue density, SATd) 不仅在总体 CKD 患者中而且在男性、女性、非糖尿病、非高血压和高血压 CKD 患者亚组中都是肾功能进展的独立预

测因子, 肾窦脂肪密度 (renal sinus fat density, RSFd) 则对糖尿病 CKD 患者的预测有意义, 而 VSR 是非高血压和糖尿病 CKD 患者的重要预测因子, 该研究提示脂肪组织的质量而不是数量可能是提示 CKD 患者预后的新指标^[27]。目前上述测量指数与 CKD 发病风险仍有待进一步研究, 同时, 虽然 CT 和磁共振成像 (magnetic resonance imaging, MRI) 是目前定量判断内脏脂肪分布的“金标准”, 可以鉴别内脏、深部及浅部脂肪, 但 CT 检查辐射高, MRI 扫描时间长, 且价格昂贵, 不适合于临床常规应用或大规模人群筛查。因此出现了一些简单的肥胖指数来替代影像学检查, 但这些指数均有一定的优缺点, 我们可能还需要更严格的辅助方法来评估和管理肥胖。因此, 本文通过中国知网、万方、Pubmed 等数据库进行检索, 总结近年来报道的肥胖指数, 并探讨它们与 CKD 的相关性, 为进一步的研究方向及临床指导提供信息。

1 人体测量学的肥胖指数与慢性肾脏病

1.1 体质量指数

体质量指数 (body mass index, BMI) 被认为是全身性肥胖发生的传统标志, 它的计算公式为: $\text{BMI} (\text{kg}/\text{m}^2) = \text{体重} (\text{kg}) / \text{身高}^2 (\text{m}^2)$ 。根据世界卫生组织 (World Health Organization, WHO) 的定义: 成年人 $25 \text{ kg}/\text{m}^2 \leq \text{BMI} < 30 \text{ kg}/\text{m}^2$ 为超重; $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$ 为肥胖。中国根据实际情况进行调整, $24 \text{ kg}/\text{m}^2 \leq \text{BMI} < 28 \text{ kg}/\text{m}^2$ 为超重, $\text{BMI} \geq 28 \text{ kg}/\text{m}^2$ 为肥胖^[28]。

Sun 等^[29]的荟萃分析汇总了来自中国、印度、俄罗斯、新加坡和韩国的 8 项基于人群的研究, 将 BMI 作为肥胖的指标, 根据 BMI 将人群分为正常体重、超重和肥胖三组, 发现超重和肥胖都与 CKD 风险增加有关, 而当 BMI 作为连续变量时, BMI 与 CKD 无明显相关性。Herrington 等^[30]对 140 万英国成年人随访 7.5 年后发现, 无论有没有糖尿病、高血压或心血管疾病, 超重和肥胖会增加晚期 CKD 的风险, 采取减肥策略, BMI 每减少 1 个单位, CKD 风险可相应降低。最新研究发现青春期晚期的高 BMI 与成年早期 CKD 风险增加有关^[31]。虽然 BMI 测量简便, 但 BMI 不能准确反映

脂肪空间分布,同时BMI正常而体脂含量高于正常的情况普遍存在,因此,BMI不足以预测CKD的发病风险。

1.2 腰围、臀围和腰臀比

腰围(waist circumference, WC)作为判断代谢性肥胖和中心性肥胖的简易辅助指标,中国目前参考WHO标准,成年男性 $WC \geq 90$ cm、女性 $WC \geq 85$ cm即可诊断为腹型肥胖,或腰臀比(waist-to-hip ratio, WHR) > 1.0 即称为腹型肥胖^[1]。

有研究提示由WC和WHR定义的腹部肥胖是比BMI更重要的死亡风险评估预测指标^[32]。Bae等^[33]的大型队列研究中,以WC作为腹部肥胖评估指标,结果表明腹型肥胖与CKD发生风险增加有关,WC与CKD风险呈U型关系,其年轻人群中的WC临界值为72 cm,但在糖尿病患者中得出了相反的结论。最近的一项中国成年人前瞻性研究分析了WC和BMI与CKD及其各个亚型发病风险的关联,其中WC与除高血压肾病和小管间质性肾炎外的所有亚型发病风险均呈正相关^[34]。WHR是权衡了WC和臀围两种身体指标后得到的一个相对值,但是WHR与CKD的关系仍然存在争议。一项研究表明较高的WC和WHR与白蛋白尿和CKD存在显著关联^[35]。另一项研究以BMI、WC、臀围和WHR为预测指数,观察与CKD之间的关系,基线BMI和WC以及BMI和WC轨迹与CKD发病有关,而WHR则与其无关^[36]。Song等^[37]的最新研究则提示BMI和WHR都与CKD发病风险相关且WHR优于BMI。因此,仍然有待进行长期的前瞻性研究以明确WHR预测CKD的价值以及性别差异性。

1.3 体脂百分比

体脂百分比(percentage body fat, PBF)是指体内脂肪的含量或脂肪占总体重的百分比,DEXA是目前公认的检测方法,生物电阻抗法(bioelectrical impedance method, BIA)存在一定的误差,可作为初步筛查应用。目前多以体脂量男性 $\geq 25\%$ 、女性 $\geq 30\%$ 作为肥胖的判定标准^[38]。

一项瑞典的大型前瞻性研究探索了BMI、WC、腰围身高比(waist-to-height ratio, WHtR)、

WHR、PBF、体重、身高和因CKD住院的发生率之间的关系。结果显示BMI、WC、WHR、WHtR和体重的值越高,患CKD的风险越高,只有在女性中,较高的PBF与较高的CKD风险相关,这项研究是肥胖和CKD之间存在关联的有力证据,同时提示PBF预测CKD的作用上存在性别差异^[39]。另一项研究也同样提示脂肪百分比衡量的肥胖状态在女性中是肾功能下降的危险因素^[40]。因此,在女性人群中,PBF对于识别CKD发病高危人群可能具有一定的参考价值。

1.4 人体肥胖指数

2011年Bergman等^[41]采用DEXA测量的体脂百分比作为验证“金标准”,提出了一种新的反映人体脂肪含量的测量指标,即人体肥胖指数(Body Adiposity Index, BAI)。BAI = 臀围(cm) / 身高(m)^{1.5} - 18,可用于反映不同种族的成年男性和女性的体脂百分比。Stepień等^[42]研究评估了早期CKD和非CKD肥胖患者的WC、WHR、WHtR、内脏脂肪指数(Visceral Adiposity Index, VAI)、BAI和血清脂肪因子(瘦素、脂联素、抵抗素)及其与估计肾小球滤过、血肌酐和微量白蛋白尿的关系,提出BAI可以作为预测肥胖患者CKD早期阶段的指数。

1.5 身体形态指数和身体圆度指数

身体形态指数(A Body Shape Index, ABSI)是Krakauer等^[43]根据身高、体质量和WC计算的一种人体测量指标,计算公式如下: $ABSI = WC(m) / [BMI^{2/3} (kg/m^2) \times 身高^{1/2} (m)]$ 。身体圆度指数(Body Roundness Index, BRI)联合了身高和WC,是识别中心性肥胖的有效指标,计算公式如下: $BRI = 364.2 - 365.5 \times \{1 - [WC(cm) / 2\pi]^2 / [0.5 \times 身高(cm)]^2\}^{0.5}$ ^[44]。中国的一项大型横断面研究评估了腰围、ABSI、BRI、WHR、臀围和WHtR等6项人体测量指标,发现CKD仅在体重正常的男性中与腰围、ABSI、BRI、WHR和WHtR呈显著相关^[45]。目前ABSI和BRI与CKD的关系研究较为有限。

1.6 锥度指数和相对脂肪质量指数

锥度指数(Conicity Index, C-index)由Valdez^[46]提出,旨在识别腹部肥胖,并通过测量体

重、身高和 WC 来确定, 计算公式: $WC(m)/\{0.109 \times [\text{体重}(kg)/\text{身高}(m)]^{1/2}\}$ 。C-index 被认为是识别内脏脂肪、血脂异常、心血管和糖尿病风险的有效指标^[47-51]。虽然 C-index 提出较早, 但是涉及 C-index 与 CKD 的研究很少, Cordeiro 等^[52]发现 C-index 的增加与血液透析患者的生存率降低相关, Martins 等^[53]认为 C-index 能更准确地评估血液透析患者的腹型肥胖, 并确定该人群中 C-index 的切点(男性为 1.275, 女性为 1.285)。相对脂肪质量指数(Relative Fat Mass Index, RFM)是一种新开发的人体测量指数, 可以更准确地评估全身脂肪百分比, 与 DEXA 测定的脂肪量的相关性高于 BMI。RFM 根据 WC 和身高进行计算, 并且具有性别特异性, 男性: $RFM = 64 - \{20 \times [\text{身高}(m)/WC(m)]\}$; 女性: $RFM = 76 - \{20 \times [\text{身高}(m)/WC(m)]\}$ ^[54]。近年来, 越来越多的研究发现 RFM 与一系列的不良结局相关, 包括心血管事件、糖尿病和非酒精性脂肪肝病^[51,55-60]等。一项 Moli-sani 队列研究提示 RFM 与死亡率的关联呈 U 型, 该关联是由葡萄糖代谢、肾功能和肺功能介导的^[61]。值得注意的是, C-index 和 RFM 与 CKD 发病风险的关系以及其预测能力仍不清楚。

1.7 其他

Wu 等^[62]前瞻性队列研究首次提出使用胸围、WC 和大腿测量的组合, 即胸腿比(chest-to-thigh ratio, CHTR)和腰腿比(waist-to-thigh ratio, WTR)可作为预测 CKD 发展的可靠生物标志物。Yoon 等^[63]提出了反映人体上半身的皮下脂肪堆积的人体测量方法, 即颈围, 结果表明颈围可用于识别具有 CKD 风险的人群。除此之外, Li 等^[64]分析了体重调整 WC 指数(Weight-Adjusted-Waist Index, WWI)、BMI、WHtR、WC、身高和体重与 CKD 之间的关联, 其中 WWI 是预测 CKD 和白蛋白尿的最佳肥胖评估指标。

2 含有人体测量学及代谢指数的复合肥胖指数与 CKD

2.1 脂质蓄积指数

脂质蓄积指数(Lipid Accumulation Product, LAP)是一项简单有效的评估内脏脂肪的指标,

它通过 WC 和甘油三酯(triglyceride, TG)来反映内脏脂肪的堆积情况, 根据 Kahn 的理论, 男性: $LAP = (WC - 65) \times TG$; 女性: $LAP = (WC - 58) \times TG$ ^[65]。

2021 年 Yan 等^[66]首次探讨了中国普通人群中 LAP 与 CKD 的相关性, 结果显示高 LAP 水平可能与女性的 CKD 患病风险显著相关。另外一项随访 18 年的队列研究也发现女性 LAP 的异常轨迹模式与 CKD 患病风险增加有关^[67]。因此, 女性超重人群的 LAP 水平可能是 CKD 发病风险的有效预测指标。

2.2 内脏脂肪指数

2010 年 Amato 等^[68]首次根据性别、WC、BMI、TG 和高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)建立了内脏脂肪指数(Visceral Adiposity Index, VAI), 间接反映内脏脂肪蓄积情况。计算公式如下, 男性: $VAI = [WC / (39.68 + 1.88 \times BMI)] \times (TG / 1.03) \times (1.31 / HDL-C)$; 女性: $VAI = [WC / (36.58 + 1.89 \times BMI)] \times (TG / 0.81) \times (1.52 / HDL-C)$ 。

VAI 对肾功能的影响在不同地区和人群中进行了评估。Bamba 等^[69]对 15 159 例参与者进行的一项队列研究表明 VAI 可以成为日本男性和女性 CKD 的预测指标。另外几项研究发现 VAI 似乎只是男性肾功能下降的独立预测因子^[70-71]。最近一项研究侧重于 VAI 与肾功能下降之间的关联, 检测到较高的 VAI 与白蛋白尿和 CKD 的风险增加呈正相关, 强调了内脏脂肪对肾功能的负面影响^[72]。

2.3 甘油三酯葡萄糖乘积指数结合肥胖指标

近年来, 甘油三酯葡萄糖乘积指数(Triglyceride Glucose Index, TyG)结合简单人体测量指数不断出现, 包括 TyG-BMI、TyG-WC 和 TyG-WHtR 等, 目前已有研究分析了 TyG 相关指标与各种代谢性疾病的关系^[73-78]。Chen 等^[79]分别评估了 TyG-BMI、TyG-WC 和 TyG-WHtR 与 CKD 的关联, 在 TyG 相关指标中, TyG-WHtR 对 CKD 有着更高的预测价值, 但由于这是一项横断面研究且样本量相对较小, 仍需进一步验证 TyG 相关指标对 CKD 进展的影响。

2.4 中国内脏脂肪指数

2016年中国学者建立了适合评估亚洲人内脏脂肪功能的临床指数,命名为中国内脏脂肪指数(Chinese Visceral Adiposity Index, CVAI),计算公式如下:男性 $CVAI = -267.93 + 0.68 \times \text{年龄} + 0.03 \times \text{BMI} (\text{kg}/\text{m}^2) + 4.00 \times \text{WC} (\text{cm}) + 22.00 \times \log_{10} \text{TG} (\text{mmol}/\text{L}) - 16.32 \times \text{HDL-C} (\text{mmol}/\text{L})$;女性 $CVAI = -187.32 + 1.71 \times \text{年龄} + 4.23 \times \text{BMI} (\text{kg}/\text{m}^2) + 1.12 \times \text{WC} (\text{cm}) + 39.76 \times \log_{10} \text{TG} (\text{mmol}/\text{L}) - 11.66 \times \text{HDL-C} (\text{mmol}/\text{L})$ 。CVAI与CT测定的内脏脂肪面积高度相关,且优于BMI和WC。该研究表明CVAI是评价中国人内脏脂肪功能障碍的可靠、实用的指数^[80]。

Xu等^[81]进行了一项回顾性横断面研究,结果表明,CVAI和估算肾小球滤过率(estimated glomerular filtration rate, eGFR)呈负相关,CVAI的受试者操作特征(receiver operating characteristic, ROC)曲线的曲线下面积大于其他肥胖指标(BMI、WHR、WC、LAP和VAI),尤其在女性人群中。Jin等^[82]也发现了相同的结果,CVAI与韩国人群的高CKD患病率显著相关,但在女性人群中,CVAI的AUC显著高于男性。最近一项前瞻性队列研究发现在肾功能正常的中国成年人中,相比于LAP、血浆动脉粥样硬化指数、TyG、TyG-BMI、TyG-WC,CVAI对进展为CKD具有更强的预测价值^[83]。

近年来,一些研究者提出将肥胖表型进行更精细的分类以便更高效识别疾病风险并实现个性化预防性干预^[84-86]。人工智能结合医疗数据已广泛应用于医学领域,数据驱动的机器学习建模可以挖掘大量多维数据以揭示肥胖的潜在表型。Lin等^[86]使用机器学习将多中心队列的常见临床变量进行无监督聚类,将肥胖分为代谢健康型肥胖(metabolic healthy obesity, MHO)、高代谢型肥胖-高尿酸亚型(hypermetabolic obesity-hyperuricemia, HMO-U)、高代谢型肥胖-高胰岛素亚型(hypermetabolic obesity-hyperinsulinemia, HMO-I)和低代谢型肥胖(hypometabolic obesity, LMO),这四种肥胖亚型临床特点和并发症发病风

险各异。基于肥胖代谢表型的提出,Khalili等^[87]探讨了代谢健康状态和肥胖的4种不同表型[代谢健康型非肥胖(metabolically healthy non-obese, MHNO)、代谢不健康型非肥胖(metabolically unhealthy non-obese, MUNO)、MHO和代谢不健康型肥胖(metabolically unhealthy obese, MUO)]与CKD风险的关系,发现超重和代谢健康及其组成部分都独立导致CKD风险增加,且对CKD进展的影响存在时间差异,有趣的是,从MHNO状态转变为MHO状态降低了CKD发病风险。因此,表征CKD高危人群的具体肥胖表型及针对不同肥胖表型的管理将有助于更精准地指导临床实践。

综上所述,肥胖是CKD发生发展的重要因素,使用简单的指标有效预测CKD的发病风险对疾病的防治尤为重要。目前国内外研究中评估肥胖的指数众多,但是肥胖指数与CKD的相关研究仍然有限且缺乏大样本、前瞻性临床研究,另外仍缺少关于特异性预测CKD风险的肥胖表型。因此应充分认识肥胖与CKD的内在机制,结合相应指数的优缺点,进而制定符合中国人群的控制目标,早期识别可能发生CKD的高危人群,实施预防策略,及时治疗改善临床结果。

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