

胰岛素抵抗的实用标志物：TyG指数在代谢性疾病中的研究现状

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摘 要

胰岛素抵抗是2型糖尿病、代谢综合征、代谢相关脂肪性肝病和动脉粥样硬化性心血管疾病等多种代谢性疾病的共同病理基础。近年来，肌少症及肌少性肥胖被认为是以胰岛素抵抗为核心的传统代谢性疾病谱系的新成员。甘油三酯-葡萄糖指数作为一种基于空腹甘油三酯和血糖计算的新型标志物，因其简便、经济的优点，已成为评估胰岛素抵抗的有效替代指标。本综述系统梳理了甘油三酯葡萄糖指数在上述代谢性疾病中的研究进展。

关键词

胰岛素抵抗，甘油三酯葡萄糖指数，代谢相关性疾病，肌少症

Practical Markers of Insulin Resistance: The Current Research Status of TyG Index in Metabolic Diseases

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Abstract

Insulin resistance serves as a common pathological basis for various metabolic diseases, including type 2 diabetes, metabolic syndrome, metabolic dysfunction-associated steatotic liver disease, and

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atherosclerotic cardiovascular disease. In recent years, sarcopenia and sarcopenic obesity have been recognized as new components of the traditional metabolic disease spectrum centered on insulin resistance. The triglyceride-glucose (TyG) index, a novel marker derived from fasting triglyceride and blood glucose levels, has emerged as an effective and economical alternative for assessing insulin resistance due to its simplicity and accessibility. This review systematically summarizes recent research advances regarding the TyG index in the context of these metabolic diseases.

Keywords

Insulin Resistance, Triglyceride-Glucose Index, Metabolic-Related Diseases, Sarcopenia

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1. 引言

胰岛素抵抗(insulin resistance, IR)是指机体对胰岛素敏感性下降,从而导致体内产生过多胰岛素的一种疾病状态。IR与糖尿病、代谢综合征、代谢相关脂肪性肝病以及动脉粥样硬化性心血管疾病的发生密切相关,是上述疾病共同的主要致病机制[1]。近年来,骨骼肌作为一种重要代谢器官,其与代谢紊乱的双向作用日益受到关注,其中肌少症及肌少性肥胖是关注的焦点。随着研究深入,肌少症及肌少性肥胖被认为是以IR为核心的传统代谢性疾病谱系的新成员[2][3]。因此早期识别、评估IR对上述疾病的诊治有重要意义。高胰岛素正常葡萄糖钳夹试验(hyperinsulinemic-euglycemic clamp, HEC)是评估IR的金标准,但其操作难度大、费用昂贵,故临床应用受限[4]。近年来甘油三酯葡萄糖指数(triglyceride-glucose index, TyG)作为一种新型的评估IR的有效替代指标日益受到关注[5],具备易获取、价格低廉的优点,仅需空腹血糖及甘油三酯两组常规检测数据即可获得。

因此,本综述旨在系统梳理TyG指数在以IR为共同病理基础的代谢性疾病中的应用进展,其中不仅包括2型糖尿病和代谢综合征两种经典的内分泌代谢疾病,也涵盖了以IR为病理机制而驱动的重要器官并发症,如代谢相关脂肪性肝病和动脉粥样硬化性心血管疾病。此外,我们还将探讨TyG在肌少症与肌少性肥胖中的新兴证据,以提供一个更全面的视角。

2. IR与甘油三酯葡萄糖指数

2008年, Simental-Mendía等[6]首次提出TyG指数的概念,其计算公式为 $TyG = \ln [空腹甘油三酯(mg/dl) \times 空腹血糖(mg/dl)/2]$ 。TyG包含糖代谢和脂代谢的参数,是其反映IR的基础。研究证明TyG是评估IR的有效指标,与HEC、HOMA-IR有高度的一致性。Guerrero-Romero等[7]人的研究表明TyG在诊断IR方面与HEC金标准方法有极好的相关性($AUC = 0.858$), TyG取值4.68,其估计IR的敏感性为96.5%,特异性为85%。因HEC操作复杂,有研究基于胰岛素稳态模型(homeostatic model assessment for insulin resistance, HOMA-IR)评估TyG与IR间的关系。一项横断面研究表明, TyG与IR强烈相关, TyG与IR风险呈正线性关系[8]。另一项纳入7629例对象的研究也表明TyG与HOMA-IR间的相关性最强, ROC分析结果提示TyG显示出最大的AUC值(男性为0.709, 女性为0.711)[9]。TyG不仅能反映成人IR情况,对儿童、青少年及多囊卵巢综合征女性的IR也有良好的预测能力[10]-[12]。因此,基于其与HEC的良好相关性,以及相对于HEC和HOMA-IR的简便性、经济性及可及性, TyG被视为在各级医疗场景和大型流行病学调查中理想的新型IR标志物。

3. TyG 与其他简易 IR 指标的比较

近年来, 以 TyG 指数、胰岛素抵抗代谢指数(metabolic score for insulin resistance, METS-IR)和甘油三酯/高密度脂蛋白胆固醇比值(triglyceride-to-high-density lipoprotein cholesterol ratio, TG/HDL-C)为代表的系列 IR 替代指标获得广泛关注。系统比较这些指标在不同疾病中的优劣, 对于临床疾病评估选择合适的工具有重要指导意义。

METS-IR 指标涵盖了血糖、血脂、肥胖相关指标, 其计算公式为 $METS-IR = [2 \times FPG \text{ (mg/dl)} + TG \text{ (mg/dl)}] \times BMI \text{ (kg/m}^2\text{)} / \ln[HDL \text{ (mg/dl)}]$ [13]。TG/HDL-C 仅含血脂相关指标, 其计算公式为 $TG/HDL-C = \ln [TG \text{ (mg/dl)} \times HDL-C \text{ (mg/dl)} / 2]$ [14]。研究指出, 相较于 TyG、TG/HDL-C, METS-IR 对糖尿病前期、牙周炎疾病有更强的预测能力[15] [16]。但 Li 等研究发现在预测正常血糖人群的 T2DM 发病率时, TyG 比 TG/HDL-C 和 METS-IR 更有用[17]。一项回顾性研究对不同 IR 指标预测 T2DM 患者发生糖尿病肾病进行受试者工作曲线分析, 结果表明, TyG、METS-IR、TG/HDL-C 的曲线下面积无明显差别, 但均优于 HOMA-IR [18]。Zhu 等的研究表明 TyG 对 T2DM 人群肌少症发生有更高的预测价值与 G/HDL-C、METS-IR 相比[19]。在心血管疾病方面, 研究发现, METS-IR 与全因死亡和心血管死亡有明显相关性[20]。关于三种指标在代谢相关脂肪性肝病、代谢综合征以及肌少性肥胖中的比较的研究目前尚少。TyG 在简便性和综合性方面得到了良好平衡; TG/HDL-C 更侧重脂代谢; 而 METS-IR 则通过纳入肥胖参数提供了更全面的视角。实际工作中, 结合患者情况选择合适的指标, 但总体来说, TyG 的可靠性和简便性更优。

4. TyG 在代谢性疾病中的研究

4.1. TyG 与糖尿病

据估计, 到 2045 年, 全球糖尿病患者人数将达到 7.83 亿, 糖尿病前期患病人数将高达 11.7 亿[21]。作为一种累及全身的慢性代谢性疾病, 糖尿病引起的各器官系统的并发症极大增加疾病负担, 因此对糖尿病前期和糖尿病的防治尤为重要。IR 引起的血糖升高是 2 型糖尿病(type 2 diabetes mellitus, T2DM)的标志, 是 T2DM 发生发展的主要病理生理机制[22]。准确评估 IR 对 T2DM 高危人群的早期识别和 T2DM 及并发症的诊治有重要意义。

研究表明 TyG 可预测 T2DM 的发生风险。一项长达 15 年的队列研究[23]发现 TyG 是 T2DM 发生发展最重要的独立预测因子, 该研究的结果显示 TyG 与 T2DM 发病之间存在非线性关联和阈值效应。当 TyG 在 8.51 附近时, T2DM 的发病风险最低。当 $TyG > 8.51$ 时, 其每增加一个标准差, T2DM 的发病风险增加 38%。Lee 等[24]对 2900 名非糖尿病患者数据进行分析, 结果表明 TyG 可作为评估患糖尿病风险的标志物。该研究发现 TyG 高的受试者患糖尿病的风险高, TyG 四分位数中, 第 3、4 分位数的风险比分别为 4.06、5.65。TyG 对妊娠期糖尿病(gestational diabetes mellitus, GDM)的发生也有一定预测价值。研究表明, 孕前、孕早期和整个孕期 TyG 升高与 GDM 风险增加密切相关[25]。

此外, 研究发现 TyG 可评估糖尿病并发症的发生风险。例如, Yao 等[26]对 858 名 T2DM 患者进行回顾性分析, 结果显示, TyG 为 9.31 时, 可预测 T2DM 患者的大血管并发症, 且独立于已知的心血管危险因素。Lv L 等[27]的研究发现 TyG 高的 T2DM 患者更易发生微量白蛋白尿及肾功能异常, 发生糖尿病肾脏病(diabetic kidney disease, DKD)的风险更高。另外, 研究发现 TyG 是 DKD 进展的独立预测因子[28], 与进展为终末期肾病(end-stage renal disease, ESRD)显著正相关, 其每增加一个单位, ESRD 的风险增加 1.5 倍[29]。Neelam 等[30]的队列研究表明 TyG 与糖尿病视网膜病变(diabetic retinopathy, DR)的发生显著相关。Yao 等[31]研究进一步揭示 TyG 与 DR 的严重程度相关。研究[32]观察到与 T2DM 未合并神经病变相比, 合并神经病变的 T2DM 患者具有更高的 TyG 值。Chen 等[33]发现较高的 TyG 与糖尿病足的严

重程度相关,且在男性、年龄 ≥ 65 岁、糖尿病病程超过 10 年且无外周动脉疾病的患者中关联更显著。

4.2. TyG 与代谢综合征

随着超重、肥胖发病率逐年增加,代谢综合征(metabolic syndrome, MetS)的患病率在全球范围内不断增长,且年轻化趋势明显[34]。全球超 10 亿人患有 MetS [35]。MetS 聚集 IR、糖脂代谢紊乱、血压升高以及肥胖等一众危险因素,极大增加了心血管事件、糖尿病以及众多慢性疾病的发病风险。

近年来,研究发现 TyG 可有效预测 MetS。例如, Kang 等[36]的前瞻性队列研究结果发现 TyG 对患 MetS 的高风险个体有很高的预测价值。Wan 等[37]基于美国国家健康与营养调查(national health and nutrition examination survey, NHANES)数据库进行的研究发现, TyG 预测 MetS 发病风险的能力优于 HOMA-IR。一项纳入 13 项研究的荟萃分析[38]进一步探究了 TyG 预测 MetS 的准确性,结果显示, TyG 在识别 MetS 方面展现出很高的诊断准确性,男性的 AUC 为 0.90 (特异性 79%, 灵敏度为 82%),女性的 AUC 为 0.87 (特异性 85%, 灵敏度 81%)。因此综合以上研究, TyG 不仅能预测 MetS,且较其他指标准确性更高,可成为预测 MetS 发生风险的优秀指标。

4.3. TyG 与代谢相关脂肪性肝病

代谢相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD),既往称非酒精脂肪肝,是全球最常见的慢性肝病,也是健康体检转氨酶升高的主要病因[39][40]。据估计,全球 MASLD 的总患病率约 32.4% [39],且因 T2DM、肥胖等疾病人数的逐年增加, MASLD 的患病率不断增加,极大加重疾病负担[41]。脂肪变性是 MASLD 的特征,早期通过增加身体活动、饮食干预可逆转[42],但因 MASLD 早期往往没有症状,随着疾病进展,可能出现脂肪性肝炎、肝纤维化、肝硬化甚至肝癌[43]。

因 MASLD 的发生发展与 IR 密切相关[44], TyG 在 MASLD 相关研究中受到关注。研究指出 TyG 是 MASLD 的可靠预测标志物。例如, Su 等[45]结合 NHANES 数据库和孟德尔随机化分析,结果显示, TyG 是 MASLD 的独立危险因素。Liu 等[46]的研究也支持这一点,且研究指出随着 TyG 升高, MASLD 发病率增加。一项研究发现 TyG 筛查单纯脂肪变性和 MASLD 具有高敏感性[47]。TyG 筛查单纯脂肪变性的最佳截断值为 4.58 (敏感性 0.94, 特异性 0.69),筛查 MASLD 的最佳截断值为 4.59 (敏感性 0.87, 特异性 0.69)。除了筛查 MASLD,研究[44]还发现 TyG 能够预测患病人群的肝纤维化进展,高基线的 TyG 可能促进肝纤维化。因此, TyG 是预测 MASLD 的有效替代指标。

4.4. TyG 与动脉粥样硬化性心血管疾病

心血管疾病(cardiovascular disease, CVD)是全球死亡和疾病负担增加的主要原因,而动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD)是 CVD 的最主要部分,包括冠状动脉疾病(coronary artery disease, CAD)、缺血性卒中、外周动脉疾病三类,其中冠状动脉疾病及缺血性卒中是导致死亡和残疾的主要原因[48]-[50]。研究显示,2019 年 ASCVD 占总死亡人数的 22%以及 2.455 亿残疾人调整生命年[49],其中代谢功能障碍被认为是主要因素[51]。众所周知,血糖和血脂代谢异常是 ASCVD 发生的主要危险因素。因此,识别血糖、血脂等代谢性危险因素对 ASCVD 的预防至关重要。

IR 是 ASCVD 发生发展的关键因素[52]。作为评估 IR 的有效指标,研究证实 TyG 是预测 ASCVD 发生风险的有效指标。例如, Hong 等[53]对国家健康信息数据库(the national health information database, NHID)进行分析,结果显示, TyG 有助于早期识别 ASCVD 高风险个体,且 TyG 为最高四分位数组的受试者相较于最低四分位数组发生中风、心肌梗死以及两者同时发生的风险更高,HR 值分别为 1.259、1.313、1.282。Ding 等[54]的荟萃分析表明,高 TyG 水平与高 ASCVD 发生风险独立相关。上述研究的研究结局

为缺血性卒中和心肌梗死, 没有单独评估 TyG 与外周血管疾病(peripheral arterial disease, PAD)的关系。Sun 等[55]研究发现 TyG 与 PAD 呈 U 型相关: 当 TyG 为 8.67 时, PAD 发生风险最低, 与 CAD 和缺血性卒中的相关性与上述研究结果一致。TyG 还与 CAD 的死亡率相关。Wang 等[56]对 5425 名重症 CAD 患者数据进行分析, 结果显示, TyG 与重症 CAD 患者的短期(30 天)和长期(365 天)全因死亡率显著相关: TyG 越高, 短期和长期的全因死亡率越高, 且这种关系在短期全因死亡率风险评估中更显著。这提示对重症患者的代谢紊乱进行早期干预可改善患者的生存结果。Fiorentino 等[57]发现 TyG 可评估血管动脉粥样硬化和血管硬度, TyG 为 9.19 时可用于评估血管动脉粥样硬化的存在(AUC = 0.739, 灵敏度 82.5%, 特异性 59.2%), 为 8.99 可用于评估血管硬度(AUC = 0.579, 灵敏度 74.4%, 特异性 41.7%)。

4.5. TyG 与肌少症、肌少性肥胖

肌少症是一种以肌肉质量和力量降低为特征的疾病[58], 当肌少症与肥胖共存时称为肌少性肥胖[59]。根据 2022 年全球流行病学调查显示肌少症的患病率约 10%~27% [60], 肌少性肥胖的患病率为 7.9%~23% [61]。研究证实肌少症、肌少性肥胖分别与糖尿病、代谢综合征、心血管疾病等疾病风险增加相关, 成为威胁人类健康的重要公共卫生问题[62]-[65]。IR 是肌少症、肌少性肥胖发生的重要机制[2]。骨骼肌作为胰岛素作用的主要靶器官, 在调节糖代谢过程中起着重要作用。IR 发生时, 全身组织器官的糖脂代谢紊乱, 这造成肌肉分解增强及脂肪堆积增加[66], 而骨骼肌减少进一步加重 IR, 形成恶性循环。

有关 TyG 与肌少症的关系存在争议。Yang 等[67]的研究显示 TyG 与肌少症的发生呈正相关, 且在不伴 MetS 和 T2DM 人群中相关性更显著。一项单中心横断面研究通过对非糖尿病性的血液透析患者进行分析, 结果提示升高的 TyG 与肌少症发生风险增加相关[68]。但一项队列研究结果显示 TyG 与肌少症呈负相关[69]。同样, Li 等[70]对 460 例非糖尿病中年、老年中国女性的数据进行分析, 结果显示, 较高的 TyG 及 TyG-BMI 可预防肌少症。这可能是由于不同数据来源的样本比例、种族、调查方法的差异以及使用的数据库的差异造成。

研究指出 TyG 升高与肌少性肥胖的发生风险正相关。例如, Xu 等[71]的研究发现, TyG 及其相关指标与肌少性肥胖的发生率显著正相关。Zhao 等[72]的研究结果与之相同, 且 TyG 对肌少性肥胖的影响不受年龄、性别及其他临床并发症的影响。一项对韩国 60 岁以上人群开展的研究发现, TyG 是肌少性肥胖的有效预测指标[73]。随着 TyG 增加, 男女的肥胖率和肌少症发病率增加, 男性和女性肌少性肥胖的 TyG 临界值分别为 8.72 和 8.67。此外, 研究[74]发现 TyG 与肌少性肥胖患者的全因死亡呈 U 型相关, 提示 TyG 在中等水平能降低肌少性肥胖的全因死亡率。

5. 总结及展望

IR 是许多代谢性疾病的重要病理机制, 因此准确评估 IR 对疾病的早期发现和治疗有重要意义。TyG 是评估 IR 的良好指标, 具有简单易获取的优点。尽管存在 METS-IR 等包含肥胖参数的综合指标, 但总体而言, TyG 在简便性、普适性和证据支持方面仍展现出优势。TyG 与多种代谢性疾病相关, 对糖尿病及并发症、代谢综合征、代谢相关脂肪性肝病、动脉粥样硬化性心血管病以及肌少症和肌少性肥胖有预测价值, 甚至能预测心血管疾病的全因死亡。有研究还发现 TyG 与甲状腺疾病、多囊卵巢综合征相关[75] [76]。关于 TyG 在不同疾病中的诊断阈值各不相同, 目前尚无统一论。关于 TyG 的相关研究多基于数据库进行, 国内外数据库差异较大, 导致研究结果存在差异, 未来需要更多大型临床和基础研究进一步探究 TyG 与代谢相关疾病的关系, 以及在不同疾病中 TyG 的参考范围或诊断阈值, 为 TyG 在实际临床工作中广泛运用提供理论支持。目前, 对肌少症及肌少性肥胖作为代谢相关疾病的研究还比较少, 未来需要更多研究进一步探究肌少症、肌少性肥胖与 IR 的关系。

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