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·综　述·

脂质积累产物在肥胖儿童胰岛素抵抗评估中的应用进展

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【摘要】　为有效评估肥胖儿童胰岛素抵抗(IR)、预防慢性疾病,本研究系统阐述了脂质积累产物(LAP)在肥胖儿童 IR 评估中的生理意义及临床应用价值。LAP 能有效反映内脏脂肪堆积及脂代谢紊乱,与 IR 核心病理指标相关,且在识别 IR 方面展现出优于传统人体测量指标的诊断效能;其动态变化可监测生活方式干预及药物治疗效果,助力肥胖儿童个性化干预方案制定。未来研究应聚焦中国儿童青少年代谢特征,建立本土化、标准化 LAP 参考值,为探究精准综合干预措施、提升肥胖儿童代谢健康提供循证依据。

【关键词】　脂质积累产物;肥胖症;胰岛素抵抗;儿童

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Progress in the application of lipid accumulation product in the assessment of insulin resistance in obese children

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【Abstract】　To effectively evaluate insulin resistance (IR) in obese children and prevent chronic diseases, the review systematically elucidates the physiological significance and clinical utility of lipid accumulation product (LAP) in IR assessment of obese children. LAP can effectively reflect visceral fat accumulation and lipid metabolism disorders, and correlates with the core pathological indicators of IR. It also shows better diagnostic efficacy in identifying IR than traditional anthropometric measurement indicators; its dynamic changes can monitor the effectiveness of lifestyle interventions and drug treatments, facilitating the formulation of personalized intervention plans strategies for obese children. Future research should focus on the metabolic characteristics of Chinese children and adolescents, establish localized and standardized LAP reference values, and provide evidence-based support for exploring precise comprehensive intervention measures and improving the metabolic health of obese children.

【Keywords】　Lipid accumulation products; Obesity; Insulin resistance; Child

儿童肥胖是一项日益严峻的全球公共卫生问题,严重危及患者身心健康,使医疗系统承受诸多压力[1]。《儿童青少年肥胖食养指南(2024 版)》指出,我国 6~17 岁儿童青少年超重率和肥胖率分别为 11.1%和 7.9%,6 岁以下儿童的超重率和肥胖率分别为 6.8%和 3.6%[2]。儿童超重肥胖率的激增,导致胰岛素抵抗(insulin resistance, IR)在儿童中更加常见[3]。IR 是肥胖儿童最早出现的病理状况,主要表现为胰岛素促进葡萄糖摄取和利用的效率下降,身体代偿分泌过量的胰岛素会产生高胰岛素血症,以维持血糖的稳定,是引发冠心病、代谢综合征(metabolic syndrome, MetS)、2 型糖尿病、非酒精性脂肪肝及心血管疾病的主要风险因素,并与其他代谢异常密切相关,且影响可能持续至成年期,增加终身慢性病风险[4-5]。因此,准确评估肥胖儿童 IR 是实现早期干预的关键,临床和公共卫生实践亟需一种简便、经济、可靠且不依赖胰岛素测定的工具以识别 IR 高风险肥胖儿童。

脂质积累产物(lipid accumulation products, LAP)是基于腰围(waist circumference, WC)和空腹甘油三酯(triglycerides, TG)的复合指标。LAP 可有效反映成人肥胖患者内脏脂肪蓄积及异位脂质沉积程度,与 IR 密切相关[6]。研究证实,LAP 适用于儿童,与肥胖儿童 IR 及心血管代谢风险相关,其在预测 IR、高血压和空腹血糖受损方面均优于传统肥胖指标[7]。鉴于此,本研究系统梳理 LAP 在肥胖儿童 IR 评估中的进展,为临床诊断及预防提供依据。

1　肥胖儿童 IR 病理机制

肥胖儿童普遍存在 IR,IR 是影响其代谢健康的核心因素[8]。IR 是身体靶组织对胰岛素的生理反应缺陷,表现为身体对胰岛素的敏感性下降、靶细胞对

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葡萄糖的摄取利用效能降低,致使胰岛素信号传导通路的多层次功能障碍[4]。肥胖儿童肌细胞内脂质的过度积累,尤其是内脏脂肪组织的过度堆积与扩张,使游离脂肪酸(free fatty acids, FFAs)释放增加,进而产生二酰甘油和神经酰胺等脂质代谢产物。上述代谢产物会干扰胰岛素信号通路,激活蛋白激酶 C (protein kinase C,PKC)及其他抑制胰岛素受体底物的蛋白激酶,进而损害胰岛素信号级联反应,减少骨骼肌细胞的葡萄糖摄取,此类脂质诱导的 IR 是肥胖相关代谢疾病发展的关键因素[9]。此外,脂肪组织扩张诱导局部缺氧和氧化应激,进一步加剧炎症反应和细胞功能障碍,在肥胖儿童 IR 的病理过程中起到重要作用[10]。肥胖儿童脂肪组织中的免疫细胞浸润增加,引发单核细胞趋化蛋白-1、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、白介素-1β (interleukin-1β,IL-1β)及白介素-6 等促炎细胞因子水平升高[7,11]。单核细胞与炎症部位脂肪组织结合后分化为巨噬细胞;随着巨噬细胞比例增加,功能失调的脂肪组织进一步诱导 FFAs、活性氧及促炎反应[12]。肥胖儿童体内 TNF-α 水平升高,可激活核因子 κB 抑制蛋白激酶、p38 丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase,p38MAPK)、c-Jun 氨基末端激酶以及 PKC 等激酶。这些激酶直接作用于 IR 蛋白的丝氨酸残基,抑制其酪氨酸磷酸化,从而导致脂肪组织和肝脏的 IR[13]。此外,IL-1β 通过其受体激活 p38MAPK,经由丝氨酸磷酸化阻断胰岛素信号转导;TNF-α 还可能损害一氧化氮介导的 β 细胞胰岛素敏感性。然而,目前尚无实质性证据表明促炎作用可直接干扰 β 细胞功能[14-15]。

2　LAP 的生物学基础与生理意义

2.1　*LAP 计算与生物学基础*　成人 LAP 指标由 Kahn 等[16]提出,通过 WC 和 TG 等复合指标更准确地量化脂质过度储存及相关代谢风险,其计算公式为男性 LAP=[WC(cm)-65]×TG(mmol/L),女性 LAP=[WC(cm)-58]×TG(mmol/L),整合了 IR 评估中心性肥胖和脂质代谢异常等两个核心要素。从生物学机制解析 LAP 指标构成:WC 为内脏脂肪组织堆积程度的简易指标,TG 水平升高则反映极低密度脂蛋白合成增加及脂质代谢的动态平衡失调[3,17]。肥胖儿童 IR 生理病理特征具有独特性,其发生机制、发展轨迹及预后与成人期相比均存在差异[9]。当肥胖儿童内脏脂肪增加时,脂肪细胞对胰岛素的抗脂解作用增强,使 FFAs 增多,同时进入肝脏等器官促进肝脏糖异生,刺激肝脏合成并分泌大量富含 TG 的极低密度脂蛋白,进而导致身体循环过程中 TG 水平不断升高[1,4]。鉴于儿童青少年 WC、TG 水平存在年龄、性别和青春期发育阶段特异性变化,直接套用成人 LAP 公式存在争议,因此,肥胖儿童的 LAP 计算方式在成人公式基础上进行适应性调整[18]。除了 WC 和 TG 外,腹部皮褶厚度(abdominal skinfold thickness, AST)亦为揭示肥胖儿童腹部脂肪积累的重要指标,现有研究多采用绝对值而非减去常数、将成人 LAP 指数替换为基于儿童生长曲线的特定百分位数值或使用年龄、性别特异性公式等进行调整,如儿童 LAP = WC(cm)×AST(mm)×TG(mmol/L)/100[6,19]。该指标整合了腹部肥胖和血脂异常两类代谢风险因素,可应用于评估脂毒性及 IR 风险[20-21]。综上,目前涉及儿童 LAP 公式的研究尚未达成共识,未来研究应开展大样本前瞻性研究,系统比较不同公式预测肥胖儿童 IR 的效能,以推动肥胖儿童 LAP 标准化进程。

2.2　*LAP 应用于肥胖儿童 IR 评估的生理意义*　异位脂质过量沉积于肝脏、肾脏、心脑血管和胰腺等非脂肪组织中,会干扰细胞代谢并加速凋亡,LAP 作为评估肥胖儿童内脏脂肪功能失调及 IR 的整合性标志物,能有效反映内脏脂肪堆积及其功能障碍,并与儿童内脏脂肪含量的 CT 测量结果高度相关[18,22]。研究证实,LAP 与肥胖儿童 IR 的核心病理生理指标密切相关,在识别 IR 方面具有显著效能,而 TG/高密度脂蛋白胆固醇(TG/high-density lipoprotein cholesterol, TG/HDL-C)的识别效能相对较低[23]。同时,LAP 与 IR 的关联独立于年龄、性别和体质量指数(body mass index,BMI);即使在相同 BMI 水平的肥胖儿童中,LAP 更高的个体仍面临着更严重的代谢紊乱和 IR 风险[24-25]。LAP 可有效识别代谢水平风险升高的肥胖儿童,即体重超标且伴随内脏脂肪堆积、脂代谢紊乱及 IR 高危特征的肥胖儿童,对于临床识别肥胖儿童 IR 风险和制定个性化干预策略具有重要意义[3,19]。LAP 不仅与肥胖儿童 IR 密切相关,更与 IR 所驱动的一系列心脑血管并发症存在关联[7,13]。虽然异位脂质沉积在儿童青少年中难以直接量化,但 LAP 值升高提示器官组织因脂质沉积更易受损[4,26]。相较于 BMI、腰臀比(waist-to-hip ratio, WHR)、腰高比(waist-height ratio, WHtR)等传统指标,LAP 对儿童高血压具有更优的预测效能[27]。LAP 的 WC 和 TG 等构成要素也属于 MetS 的核心组成部分,可有效识别肥胖儿童早期 MetS[10,28]。提示 LAP 与颈动脉内膜中层厚度、血压、可溶性细胞间黏附分子-1 等内皮功能障碍标志物相关,可作为肥胖儿童早期心血管风险评估与诊断的工具[16,29]。综上,LAP 是简便、有效且低成本的肥胖儿童 IR 识别指标,也是评估肥胖儿童内脏脂肪分布和脂肪组织功能障碍的新型标志物,值得进一步实践与推广。

3　LAP 在肥胖儿童 IR 评估中的临床实证

3.1　*LAP 在肥胖儿童 IR 筛查与评估中的应用*　目前评估肥胖儿童 IR 方法众多，高胰岛素-正葡萄糖钳夹技术虽为金标准，但操作复杂、有创且费用高，难以在临床常规开展[30]。人体测量指标如 BMI、WHR 及 WHtR 虽简便易行，却无法区分脂肪分布及代谢状态[29,31]。稳态模型评估的胰岛素抵抗指数（homeostasis model assessment of insulin resistance, HOMA-IR）是目前应用最广的 IR 替代指标，但其需采血测定胰岛素，且儿童参考值切点尚未统一[14]。近年来，复合代谢指标如甘油三酯-葡萄糖指数、内脏肥胖指数及 LAP 受到广泛关注[32]。研究表明，MetS 儿童的 BMI、WHtR 和 LAP 均高于非 MetS 儿童，且 LAP 与 MetS 显著相关；WHtR 与 TG/HDL-C 等指标仅反映肥胖儿童外周血脂质蓄积程度；LAP 综合了 WC、TG 和 AST 的叠加效应，因此其预测 MetS 儿童的效能显著优于 WHtR[16,33]。横断面研究显示，以 HOMA-IR≥3.0 为 IR 的界定值，LAP 是 MetS 最突出的风险因素，而 HDL-C 则呈保护性关联[34]。LAP 与肥胖儿童空腹胰岛素、糖化血红蛋白、丙氨酸氨基转移酶等指标呈正相关[35]。LAP 对伴有严重代谢紊乱的肥胖儿童 IR 群体识别优势更明显，对于同时存在腹型肥胖和高甘油三酯血症的肥胖儿童，患非酒精性脂肪肝、MetS 等疾病风险极高，LAP 对此类高危群体具有极佳的预警价值[36]。综上，LAP 在肥胖儿童临床管理中的首要价值是作为低成本、高效率的筛查工具。然而，目前儿童 LAP 切点尚未统一，现有研究报道的参考值因研究人群的种族、年龄、性别、青春期界定及 IR 评估标准不同而存在差异[13,37]。

3.2　*LAP 在肥胖儿童 IR 综合干预中的应用*　LAP 在肥胖儿童综合干预中具有积极作用，可反映不同干预措施下肥胖儿童脂肪积累与代谢紊乱的动态变化[9,38]。研究发现，每周总身体活动量与 LAP 之间呈非线性负相关，每周总体育活动量达到 440 min 阈值可降低 LAP 水平；规律且达到一定强度的身体活动能有效控制 LAP，提示 LAP 可作为评估干预效果的敏感指标，激励肥胖儿童及家长坚持运动疗法[39]。此外，为期 12 周的抗高血压饮食法（dietary approaches to stop hypertension, DASH）对 MetS 儿童的 IR 和 LAP 具有显著影响，遵循 DASH 饮食可清除肝脏脂质、提高胰高血糖素水平、调节胰高血糖素样肽-1 和胰高血糖素样肽-2 的分泌，改善胰岛素敏感性，从而有效降低 MetS 患儿心血管风险[40]。LAP 数值波动使家长及患儿直观感知干预效果，可作为健康教育及增强依从性的监测工具[41]。对于少数生活方式干预效果不佳、合并重度脂肪肝或糖耐量异常等严重并发症的肥胖儿童，需考虑药物治疗[20,42]。当前评估药物疗效主要依赖血糖、胰岛素及肝酶等指标，当药物干预使 TG 下降但腰围变化不明显时，HOMA-IR 的改善可能有限，此时 LAP 的下降仍能捕捉到代谢风险的降低，可作为整合性指标提供补充信息[26,43]。尽管以 LAP 为监测指标的减重药物临床实践在肥胖儿童中尚少，但现有成人临床研究结果显示，降糖或降脂药物治疗后 LAP 的显著改善与心血管事件风险降低高度相关[44]。未来肥胖儿童药物临床实践可将 LAP 纳入疗效评估指标，以验证其在监测药物干预效果中的价值。

4　小结与展望

LAP 作为整合了 WC、AST 及 TG 的复合指标，在临床评估肥胖儿童 IR 及相关代谢紊乱中具有重要价值。LAP 与 2 型糖尿病、非酒精性脂肪肝、代谢综合征等肥胖并发症密切相关，其评估效能显著优于 BMI 等传统肥胖指标。在临床筛查与评估方面，LAP 具有测量简便、成本低廉、不依赖于胰岛素测定及生物学解释性强等多重优势，有望成为肥胖儿童 IR 评估的有效工具。在肥胖儿童 IR 综合干预中，LAP 的动态变化可作为肥胖儿童干预效果的敏感指标，有助于制定肥胖儿童个性化干预方案。未来研究方向应着力推动 LAP 在肥胖儿童 IR 评估中的标准化与精准化应用，需聚焦于以下方面：（1）建立不同年龄、性别和青春期阶段的儿童 LAP 正常参考值范围及 IR 评估切点，夯实临床应用的标准化基础；（2）适当增加前瞻性研究，明确 LAP 对儿童 2 型糖尿病及心血管疾病的长期预测价值；（3）进一步探究生活方式干预联合运动疗法、肠道微生态调节等综合干预措施对肥胖儿童 IR 的改善效果，并探析 LAP 与上述因素的交互作用。明确以上研究方向有助于早期识别肥胖儿童 IR 高危个体，构建标准化监测评价体系，实施精准化联合干预，为提升肥胖儿童代谢健康提供理论依据和实践指引。

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