2 型糖尿病心外膜脂肪:冠心病新的防治靶点

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摘要 异位脂肪的过量堆积是 2 型糖尿病(T2DM)发生冠心病的高危因素。心外膜脂肪(EAT)是紧邻心肌和冠状动脉的一种异位脂肪。在 T2DM 患者体内,EAT 的容积和功能学发生变化,通过分泌脂肪因子、炎症因子和游离脂肪酸等,促进冠状动脉的内皮及平滑肌发生胰岛素抵抗、损伤和炎症反应,并引起心肌的损伤,进而加快冠心病的发生及发展,增加心肌缺血和斑块破裂等冠心病事件的发生。现有证据表明 EAT 可能是 T2DM 合并冠心病的治疗靶点,本文将对这一领域的研究进展进行总结及展望。

关键词 2 型糖尿病; 冠心病; 心外膜脂肪; 炎症反应
中图分类号 R587.1 **文献标识码** A DOI 10.11768/nkjwzzzz20230206

Epicardial adipose tissue in type 2 diabetes mellitus: a new intervention target for coronary heart diseases *SU Ying, YU Xue-feng, HE Wen-tao*. Department of Endocrinology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Branch of National Clinical Research Center for Metabolic Diseases, Hubei Wuhan 430030, China*
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Abstract Excessive accumulation of ectopic adipose tissue is a high-risk factor for coronary heart disease in type 2 diabetes mellitus (T2DM). Epicardial adipose tissue (EAT) is a type of ectopic fat adjacent to the myocardium and coronary arteries. In T2DM settings, the volume and function of EAT have undergone dramastic alteration. By secreting adipokines, inflammatory factors and free fatty acids, EAT promotes local insulin resistance, damage and inflammation in cellular components of coronary arteries. Moreover, factors from EAT directly cause damage to myocardium. Thereby, EAT in T2DM increases the occurrence of coronary heart disease and susceptibility of myocardium to ischemic events. Existing evidence suggests that EAT may be potential therapeutic target for T2DM combined with coronary heart disease. This review intends to probe into the current proceedings in this field and future research highlights.

Key words Type 2 diabetes mellitus; Coronary heart disease; Epicardial adipose tissue; Inflammatory response

2 型糖尿病(type 2 diabetes mellitus,T2DM)占糖尿病患者的绝大多数,冠心病是其主要死因之一。T2DM 常伴随有异位脂肪的堆积,尽管心外膜脂肪(epicardial adipose tissue, EAT)相对于其他部位的异位脂肪含量甚微,但是由于其紧邻冠状动脉和心肌,其对冠心病的影响日益引起人们的重视。本文对 T2DM 患者 EAT 与冠心病的相关性研究予以总结和展望。

EAT 生理概述

EAT 包括心肌脂肪和冠状动脉外膜脂肪[1],常见于房室沟和室间沟,与心肌及冠状动脉联系紧密。EAT 几乎覆盖心脏表面的 80%,具有棕色化特征[2]。其生理作用包括:①局部产热:为心肌直接提供热量保护心脏;②代谢调节:分泌血管保护性脂肪因子如脂联素和肾上腺髓质素[1];释放游离脂肪酸为心肌提供能量底物[3];合成脂肪酸结合蛋白 4 以储存游离脂肪酸。③缓冲保护冠脉:EAT 具有弹性,可以通过缓冲作用保护冠状动脉,避免其在动脉搏动和心脏收缩时过度变形[4]。

T2DM 患者体内 EAT 含量和功能的变化与冠心病

不同于正常生理状态,T2DM 患者体内的 EAT 在含量和功能上有所改变,通过释放过多的有害成分影响冠状动脉和心肌功能,对冠心病的发生发展起到推波助澜的作用[5~9]。EAT 与腹型肥胖有较好的相关性,但也是独立的影响冠心病预后的指标。

EAT 释放 oxLDL 促进冠心病的发生与发展 氧化低密度脂蛋白(oxidized low-density lipoproteins, oxLDL)已证实是动脉粥样硬化的重要致病因素[10~12]。OxLDL 主要由 oxLDL 受体-1(oxLDL receptor-1,LOX-1)识别后内化清除。在冠心病患者的

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EAT 组织中,LOX-1 的表达水平和吞噬 oxLDL 的巨噬细胞明显增加。EAT 中的冠状动脉周围脂肪组织来源的 oxLDL,通过巨噬细胞或新生血管源源不断地输送到冠状动脉内膜,促使冠状动脉发生粥样硬化[13]。众所周知,T2DM 伴随着大量氧化应激反应,对比非糖尿病患者 oxLDL 的生成更为显著。T2DM 患者的 EAT 可能作为冠状动脉内膜 oxLDL 的储存库[14],这一病理过程的重要性尚待进一步研究。

EAT 与冠状动脉局部的炎症反应 冠状动脉粥样硬化的病理基础是斑块发生侵蚀或破裂,炎症在动脉粥样硬化发生发展中起到了核心作用,而 EAT 病理状态下大量分泌的炎症因子可能会加速斑块损伤进展。研究发现冠心病患者 EAT 来源的趋化因子和炎性细胞因子如白介素 1(interleukin-1,IL-1)、白介素 6(interleukin-6,IL-6)和肿瘤坏死因子(tumor necrosis factor-α,TNF-α)等水平明显高于皮下脂肪来源[15, 16],这说明 EAT 具有局部促炎作用。冠心病患者的 EAT 存在以巨噬细胞为主的炎性细胞浸润,且以具有促炎的 M1 型巨噬细胞为主[17]。M1 型巨噬细胞通过释放各种趋化因子刺激未极化的巨噬细胞转化为 M1。以 M1 释放的 TNF-α 为例,可诱导内皮细胞表达黏附分子配体,TNF-α 通过免疫细胞的募集,趋化因子与细胞因子的调节和释放,触发炎症级联反应[18, 19]。营养过剩和局部的脂肪炎症反应使 EAT 的脂肪细胞肥大或增生,脂肪细胞肥大使得促炎脂肪因子高表达,进一步加重脂肪增生和炎症反应,形成恶性循环[19]。相比于 EAT 的面积或体积,EAT 引起的炎症反应可能会更好的体现心血管疾病的风险。

有研究对 EAT 进行全转录组分析发现 T2DM 与非 T2DM 的 EAT 基因表达有明显差异,尤其是与炎症相关的基因,包括晚期糖基化终产物受体(receptor for advanced glycation endproducts,RAGE)、TNF-α 和核因子-κB(nuclear factor-κB,NF-κB)[20]。糖基化终产物(advanced glycation endproducts,AGE)是非酶糖基化反应的产物,在 T2DM 患者的组织内大量存在。AGE-RAGE 通路的过度激活已被证实与 EAT 的炎症反应、脂肪细胞肥大、脂联素降低和胰岛素抵抗相关。体外试验表明高糖减少 EAT 产生脂联素,一种抗动脉粥样硬化的因子;EAT 通过旁分泌作用增加血管内皮表达炎症因子[21, 22]。模仿糖尿病的致病因子(高血糖、高游离脂肪酸和脂多糖)对 T2DM 的 EAT 进行刺激发现,EAT 分泌大量的炎症因子,且 EAT 条件培养基使血管内皮发生炎性表型转变[23]。另一项近期的研究也发现:肥胖和糖尿病患者来源的 EAT 大量分泌 IL-1、IL-6 和 TNF-α 等多种因子[24]。因此,EAT 的炎症反应可能通过旁分泌影响冠脉内皮的炎症、动脉粥样硬化斑块的进展和斑块的稳定性,最终导致冠心病事件的发生。

EAT 与糖尿病心肌代谢受损 胰岛素抵抗是 T2DM 的一个重要特征,影响了心肌和血管的代谢、结构及功能,其机制涉及到促炎症环境及血脂代谢异常等系列因素。EAT 局部产生的炎症可导致心肌胰岛素抵抗。EAT 过度释放的促炎因子中 TNF-α 会增加蛋白酪氨酸磷酸酶的表达[25],通过胰岛素受体底物-1 磷酸化破坏胰岛素信号,诱导胰岛素抵抗,影响心肌细胞和脂肪细胞对葡萄糖的摄取。TNF-α 和 IL-1 还可通过激活 Jun 氨基末端激酶(Jun N-terminal kinase,JNK)或 IκB 激酶(IκB kinase,IKK)/NF-κB 的表达,导致胰岛素抵抗[26, 27]。在胰岛素抵抗的环境下,T2DM 患者心肌能量更多由游离脂肪酸提供,随着循环来源的游离脂肪酸不断输入,脂质代谢中间产物及心肌脂质的积累损害了细胞和心脏的功能[28]。过量的循环脂肪酸也可损害胰岛素信号导致胰岛素抵抗。参与冠状动脉粥样硬化的内皮细胞、血管平滑肌细胞和巨噬细胞均含有胰岛素受体及其介导的信号通路[29]。EAT 通过局部炎症效应诱导胰岛素抵抗,促进了动脉粥样硬化及晚期斑块的形成和进展,导致心血管事件发生的风险增加。

T2DM 患者 EAT 含量的变化与冠心病 越来越多的研究发现 EAT 可以作为冠心病的独立相关因素,可能对冠状动脉粥样硬化发生发展有预测价值。空腹血糖受损的非糖尿病患者的 EAT 厚度明显增加[30],而 T2DM 患者的 EAT 含量明显高于健康人群[31],这说明在糖代谢异常的人群中,EAT 可能是一个独立的异常指标。T2DM 患者的 EAT 含量是否可以作为冠心病的高危因素呢? 有研究认为 EAT 的容积和炎症活动是冠心病的危险因素[32, 33],但也有研究发现在没有发生冠脉钙化的人群中,EAT 的容积及其未来一段时间的变化与冠脉钙化无关[34, 35]。如前所述,EAT 的炎症活动状态通过局部影响心肌代谢和冠脉血管,可能是 T2DM 发生冠心病的促进因素。EAT 的容积、炎症活动和持续时间等均参与了冠心病的发生和发展。由于冠心病是一类异质性大且发病周期长的疾病,容易受到年龄、病程、性别、血压、血糖、血脂、体质指数、吸烟和药物等

多种因素的影响,所以在不同的研究人群中研究 EAT 得到的结论会有所差异,需要寻找更为严格且更大规模的研究人群进行分析。

T2DM 患者 EAT 与内脏型肥胖

病理解剖发现,EAT 与心肌重量、腰围和年龄独立相关[36]。一项荟萃分析表明:EAT 与内脏肥胖显著相关,尤其是与相关指数如体重指数等相关[37]。这种相关性在不同的种群中存在显著差异[38]。例如,日裔美国人的 EAT 含量明显高于白种人和非裔美国人,这也许可以部分解释不同人种的冠心病风险不一样。超重和肥胖患者的 EAT 更高[39],这可能是他们发生心血管事件风险增加的原因之一。肥胖型 T2DM 患者的 EAT 含量较非肥胖型更高,相应的心功能更差,发生心血管事件的风险也更高。肥胖型 T2DM 患者的 EAT 在形态和功能上的变化表现出由棕色脂肪向类似白色脂肪表型的转变,具体表现为:脂肪细胞内含大量脂滴且线粒体活性降低[40]。而对于非肥胖的冠心病患者来说,EAT 含量更多,合并胰岛素抵抗和腹围增加[41]。因此,EAT 容积增加可能是独立于体重指数的预测冠心病的因素。

EAT:治疗 T2DM 合并冠心病的新靶点?

当前,针对 EAT 进行特异性干预性治疗,从而缓解 T2DM 患者的冠心病这一理念尚未成型,相关研究未见报道。目前相关研究主要聚焦于药物干预前后 EAT 容积的改变,而这种改变是否减少了冠心病事件的发生尚不清楚。有研究表明二甲双胍对 EAT 含量并无明显影响,而吡格列酮在减少肝脏脂肪含量的同时却增加了 EAT 含量[42]。达格列净使 EAT 分泌炎性趋化因子减少,改善了 EAT 对胰岛素的敏感性[43]。胰高血糖素样肽 1 受体激动剂(glucagon-like peptide 1 receptor agonist,GLP-1RA)是近年来推崇的减少冠心病事件的药物之一[44]。血糖控制良好的 T2DM 患者使用 GLP-1RA 艾塞那肽后 EAT 和肝脏脂肪组织的含量显著下降,并且独立于对血糖水平的改善[45]。通过对饮食控制以及有氧运动对肥胖患者的 EAT 有减少作用[46, 47],但在 T2DM 患者中进行饮食及中等强度运动后腹部内脏脂肪和心旁脂肪减少了,而 EAT 含量并无明显改变[48]。多维度对 T2DM 患者 EAT 的评估,例如:炎症状态、容积及内分泌功能,也许对冠心病的预测及预后改善有一定的帮助,但目前在临床实践中难以操作。今后针对 EAT 的研究也许需要多维度的在体检测手段。

总 结

EAT 具有特殊的内分泌学特征,主要通过旁分泌影响心肌代谢和冠状动脉发生粥样硬化。在 T2DM 患者中,营养过剩、氧化应激和炎症激活可能加速了 EAT 促冠脉粥样硬化这一过程,对冠心病的发生发展有一定的诊断预测价值。未来,T2DM 的相关治疗方案有望通过靶向调节 EAT,拮抗 EAT 对冠心病的不良影响,从而达到预期的治疗效果。

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(2022-02-23 收稿)