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胰腺脂肪化与其他胰腺疾病和代谢疾病的关系

丁 崧^{1,2} 张晓艺³ 郭守亮^{1,2} 石 乔^{1,4}

¹武汉大学人民医院胰腺外科 湖北 武汉 430060;

²武汉大学第一临床学院 湖北 武汉 430060;

³武汉大学中南医院重症医学科 湖北 武汉 430071;

⁴武汉大学人民医院普外科实验室 湖北 武汉 430060

摘要 肥胖在世界范围内流行,胰腺脂肪化的患病率也逐渐升高。胰腺脂肪细胞通过旁分泌诱发胰内低度炎症反应参与多种胰腺和代谢疾病的发生发展,包括胰腺炎、胰腺肿瘤、糖尿病及代谢综合征等。本文就胰腺脂肪化的流行病学、发病机制、诊断、治疗,及其与其他胰腺和代谢疾病间的关系作一综述。

关键词 胰腺脂肪化;炎症;代谢综合征

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Relationship between pancreatic steatosis and other pancreatic and metabolic diseases

DING Song^{1,2}, ZHANG Xiaoyi³, GUO Shouliang^{1,2}, SHI Qiao^{1,4}

¹Department of Pancreatic Surgery, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China;

²First Clinical College, Wuhan University, Wuhan 430060, Hubei, China;

³Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan 430071, Hubei, China;

⁴Laboratory of General Surgery, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China

Abstract

Obesity has become a worldwide epidemic, and the prevalence of pancreatic steatosis has gradually increased. Pancreatic adipocytes are involved in the occurrence and development of a variety of pancreatic and metabolic diseases, including pancreatitis, pancreatic cancer, diabetes and metabolic syndrome, by inducing low-grade intra-pancreatic inflammation through paracrine. This article reviews the epidemiology, pathogenesis, diagnosis and treatment of pancreatic steatosis, and its relationship with other pancreatic and metabolic diseases.

Key Words Pancreatic Steatosis; Inflammation; Metabolic Syndrome

胰腺脂肪化(pancreatic steatosis, PS)通常指非酯化脂肪酸在胰腺实质内异常沉积的现象,可导致胰腺慢性炎症和纤维化^[1-2]。有研究^[3-4]报道PS不仅损伤胰腺内、外分泌功能,也导致急性胰腺炎

(acute pancreatitis, AP)、慢性胰腺炎(chronic pancreatitis, CP)和胰腺癌的发生。此外,有研究^[5]证实PS增加多种慢性代谢疾病的患病风险,如代谢综合征(metabolic syndrome, MetS)、2型糖尿病

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作者简介:丁崧,男,2001—,医学博士生,主要从事糖尿病相关组织纤维化研究,E-mail:whudsong@whu.edu.cn。

通信作者:石乔,E-mail:shiqiao614@whu.edu.cn。

(type 2 diabetes mellitus, T2DM)、非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)、动脉粥样硬化(atherosclerosis, AS)等。因此,理解PS的特征及其与其他胰腺疾病和代谢疾病间的关系有着重要的意义。

1 流行病学及危险因素

目前,尚无大规模流行病学调查报道PS的发生率与人口学特征,已有的数据几乎都为基于影像学的回顾性分析。由于采用的影像学方法和诊断标准的不统一,综合多项报道^[6-12],PS在健康成人中的患病率约为10%~35%;在健康儿童中约为10%^[13]。SINGH等^[14]对11项研究(12 675人)的PS数据进行了Meta分析,得出其患病率约为33%(95%CI:24%~41%)。PS发病率随年龄增长而增加,男性有更高患病风险,且存在种族差异,西班牙裔美国人有更高的患病风险^[15-18]。

有研究^[19-20]指出中心性肥胖和脂肪肝是PS的独立危险因素,NAFLD与PS呈正相关。在NAFLD人群中,PS的患病率显著高于健康人群^[21]。有学者^[4, 19, 22]认为NAFLD可能为PS的最强风险因素,其他风险因素包括MetS、高血压、高血糖等。过量饮酒、长期大量吸烟、过量摄入肉类等生活方式也可能为PS的风险因素^[8, 23]。此外,KOC和TAYDAS^[24]报道胆囊切除术患者中PS发生率高于年龄和性别匹配的健康人群。

2 胰腺脂肪化与胰腺损伤的发病机制

PS的具体发病机制尚不明确,目前较多学者认为PS是肥胖所致脂肪异位沉积的表现之一^[25]。在多种致病因素作用下,脂肪细胞通过“脂肪浸润”与“脂肪替代”两种方式在胰腺内沉积,通过旁分泌引起炎症反应,导致胰腺功能受损^[26-27]。

脂肪浸润指在过量卡路里摄入后肝脏合成过量脂肪酸异位沉积于内脏,脂肪细胞浸润以储存甘油三酯,释放脂肪细胞因子,改变周围组织微环境。该现象在肝脏、骨骼肌、心脏和肾脏中均有报道^[28-29]。脂肪细胞释放多种细胞因子和趋化因子,包括白细胞介素(IL-6、IL-8、IL-10、IL-15、IL-18)、巨噬细胞移动抑制因子(MIF)、单核细胞趋化蛋白(MCP-1)、巨噬细胞炎症蛋白(MIP)等,可诱导局部炎症损伤^[29-30]。同时,脂肪细胞分泌的IL-6、IL-1 β 、TNF- α 、瘦素和血清淀粉样蛋白A等在前体脂

肪细胞中降低CCAAT增强子结合蛋白的表达,抑制前体脂肪细胞的成熟分化,导致其储脂能力下降,甘油三酯持续“外溢”,形成加剧炎症的恶性循环^[31]。脂肪替代指慢性低度炎症直接刺激胰腺实质细胞使其发生转分化成为脂肪细胞,也指炎症诱发胰腺实质细胞凋亡后脂肪细胞增生代替原有组织,形成胰腺实质细胞减少、脂肪细胞增多的恶性循环。在上述两个恶性循环的作用下,局部慢性炎症损伤胰岛和腺泡实质,导致胰腺内、外分泌功能不全及其他胰腺疾病的形成^[32-33]。

3 胰腺脂肪化的诊断

目前,尚缺乏PS的诊断标准,但传统的病理检查和影像学检查仍是PS及其严重程度诊断的有效方法。常见的诊断方法包括胰腺病理活组织检查、超声、CT、MRI检查等。SINGH等^[14]发现健康人群中脂肪约占胰腺体积的4.48% $\pm$ 0.87%,当胰腺脂肪体积占比超过6.2%可作为诊断胰腺脂肪化的标准。

病理活组织检查:尽管活检被认为是诊断PS的金标准^[3, 34],但其具有如下缺点:(1)需通过手术或内镜下穿刺获取样本,患者难以接受;(2)局部获取胰腺样本不能代表全胰腺PS情况,难以获得准确的诊断结果^[1]。因此,在没有其他有创检查指证时,病检不作为PS诊断的推荐方法。

超声检查:为最常用的非侵入性方法,可分为腹部超声与内镜超声。超声检查是通过将胰腺与脾或肾脏的回声强度作对比判断PS严重程度^[2]。内镜超声因位置更接近于胰腺,超声成像质量更佳,但有操作复杂、费用高、依赖于诊断医师的经验等缺点^[34-36]。因此,超声仅作为PS的筛查方法之一。

CT检查:为常用的可半定量脂肪含量的影像学方法。胰腺脂肪化的诊断通常采用CT平扫,增强CT的造影剂在胰腺实质中集聚,于脂肪背景下易被误判为实性病变^[1]。尽管CT在国内检查方便、价格相对较低,但其诊断准确性有限且存在辐射,在一定程度上限制了其使用^[20]。

MRI检查:为目前测量胰腺脂肪含量最精确的影像学手段,常见方法为质子磁共振波谱(¹H-MRS)、化学位移编码MRI(chemical shift-encoded MRI,或Dixon MRI)。¹H-MRS是无创定量胰腺脂肪含量的金标准^[1],已有研究证明其诊断准确性与

活检相当^[37]。但因成本高、可获得性有限且可重复性差等,¹H-MRS 通常不用于 PS 诊断^[38-39]。相较之下,Dixon MRI 可重复性高、结果相对准确且耗时相对少,但需观察者在获得的脂肪分数图上绘制兴趣区域来量化脂肪^[40],因此,结果判定在不同观察者之间会有一定差异^[34]。Dixon MRI 是目前最先进可靠的无创定量胰腺脂肪的方法^[3, 41]。基于此,AL-MRABEH 等^[38]提出了一种名为“MRI‘组织活检’(MR-opsy)”的方法,显著提高了 PS 诊断的准确性。

4 胰腺脂肪化与其他胰腺疾病的关系

与 NAFLD 进展为非酒精性脂肪性肝炎、肝纤维化、肝硬化甚至肝细胞癌相似,有学者^[25]认为 PS 可作为始动因素诱发 AP、CP 和胰腺癌等疾病。胰腺脂肪细胞可分泌脂肪因子、细胞因子和趋化因子等,通过诱导炎症及细胞增殖、迁移、凋亡等参与 AP、CP 和胰腺癌等疾病的发生发展。

在急性胰腺炎初期,炎性细胞可清除应激源,使胰腺恢复其生理功能。但当应激持续存在(如大量脂肪组织持续存在),炎性细胞可导致胰腺炎的发生^[42-43]。在 AP 条件下,腺泡细胞中脂肪酶释放,其周围脂肪细胞溶解,甘油三酯水解,释放出更多的脂肪酸^[44],加重胰腺炎症和坏死,故 PS 与 AP 严重程度相关^[45]。SBEIT 和 KHOURY^[43]发现 6 个月内有 AP 病史的患者发生 PS 概率显著高于无 AP 病史者。PS 患者发生 AP 时,其疾病严重程度与脂肪的严重程度独立相关^[46]。

若低度慢性炎症持续存在或 AP 反复发生,导致胰腺纤维化及钙化,导致 CP 的发生^[47]。TIRKES 等^[48]发现 PS 与轻、中、重度 CP 均显著相关,胰腺脂肪分数可以作为 CP 极具潜力的诊断指标,胰腺脂肪分数 56% 对 CP 的诊断敏感性为 74%,特异性为 85%。

胰腺慢性炎症和脂肪细胞因子可协同造成促肿瘤微环境,导致胰腺癌的发生。例如,在胰腺癌患者血清中,脂联素水平下降,瘦素水平上升^[49-50],而脂联素可促进细胞凋亡并降低促生长因子的功能,瘦素可参与血管生成、炎症、抗凋亡、诱导细胞迁移和侵袭并抑制干扰素诱导基因表达等,故二者变化可参与促肿瘤微环境的形成。DESAI 等^[51]根据胰腺内脂肪浸润估计的胰腺导管腺癌(PDAC)的发生风险(*OR* 值)为 3.75($P < 0.001$),且与年龄、性别、BMI 和糖尿病等因素无关。胰腺 CT 低密度

(≤ 0.70)是 PDAC 的独立危险因素^[52]。此外,胰腺脂肪含量与胰腺导管内乳头状黏液瘤(IPMNs)相关,PS 可能为 IPMN 和胰腺导管腺癌的风险因素^[53]。

综上,PS 与 AP、CP、胰腺癌等均有着密切的关系,其间的病理生理学基础也逐渐被揭示。

5 胰腺脂肪化与代谢疾病的关系

5.1 代谢综合征(MetS) 根据美国国家胆固醇教育计划(The National Cholesterol Education Program, NCEP)成人治疗小组 III 专家给出的标准, MetS 是一组以腹型肥胖为主,伴有下列两种及以上疾病的综合征,这些疾病包括高血压、高脂血症、胰岛素抵抗与 T2DM 等^[54]。

BI 等^[5]对 13 项临床研究(49 329 人)进行 Meta 分析,发现 PS 与 MetS、高血压、中心性肥胖和糖尿病之间均存在相关性。另有学者^[55]纳入 17 项研究(11 967 人)进行 Meta 分析显示,高甘油三酯与 PS 之间存在显著相关性。两项研究结果均支持 PS 是 MetS 一部分的假设。有学者^[56]认为 PS 可作为 MetS 的影像标志。KIM 等^[57]提出胰腺-肝周脂肪指数(PPHFI)是诊断 MetS 的独立因素,PPHFI 诊断 MetS 的最佳截止值为 2.34,敏感性为 0.96,特异性为 0.70。

5.2 非酒精性脂肪性肝病(NAFLD) 由于肥胖正在世界范围内流行,NAFLD 已成为最常见的肝脏疾病^[58-59]。研究^[60-61]表明 NAFLD 与 PS 之间有显著相关性,NAFLD 患者中 PS 发生率显著增高且 PS 患者中 NAFLD 患病率也显著增高。

NAFLD 与 PS 除均受肥胖作用外,其二者间也存在相互联系。LÓPEZ-BERMUDO 等^[62]总结了在肥胖条件下胰腺与肝脏交通的信号蛋白及其各自作用。一方面,脂肪肝通过改变 Fetuin-A、Sep、ANGPTL8、HGF、FGF21、KISS1、Activin A、Follistatin、SerpinB1、IGFBPs、SHBG 等分泌,调控胰腺 β 细胞的增殖、凋亡、葡萄糖刺激的胰岛素分泌(GSIS)等生理活动,破坏体内糖脂代谢稳态。另一方面,当胰腺被过量的葡萄糖和脂肪酸刺激后,其分泌的 PANDER 因子(pancreatic derived factor)大量增加,作用于肝脏后促进肝脏脂肪、葡萄糖的合成代谢,在促进 PS 的同时,刺激 β 细胞分泌更多的 PANDER 因子,形成损害胰腺内分泌功能和促脂肪沉积的恶性循环^[63-64]。

5.3 2型糖尿病(T2DM) 多项研究^[12, 17]发现T2DM与PS显著相关,但YAMAZAKI等^[65]发现PS与T2DM并不独立相关,而依赖于年龄、性别、BMI、肝功能不全和酒精摄入量等。鉴于该研究随访时间较短,且T2DM、PS的发生在不同种族中可能有差异,该结论仍需在日本以外人群中进一步证实。

肥胖是引起T2DM的重要因素之一,而PS可能在其间发挥着纽带作用,因为PS可基于糖脂毒性现象直接损伤胰腺 β 细胞^[66]。肥胖患者中,过高的葡萄糖浓度通过抑制 β 细胞中肉碱-棕榈酰转移酶-1的活性,减少脂肪酸的 β 氧化,导致甘油三酯在 β 细胞内沉积,造成胰岛素基因表达减少,GSIS不敏感,导致细胞凋亡,而这会进一步导致患者血糖升高。该恶性循环可导致 β 细胞功能持续受损且数量减少,引起糖脂代谢平衡紊乱。

5.4 动脉粥样硬化(AS) 主动脉内膜-中膜厚度增加被认为是AS的表现之一^[67],心外膜脂肪垫形成是亚临床AS的标志之一^[68]。基于此,一项土耳其的临床研究^[69]显示,PS患者主动脉内膜-中膜厚度和心外膜脂肪组织均增加,且与其二者均独立相关(均 $P<0.05$)。SAHIN和KARADENIZ^[70]发现与单纯脂肪肝患者相比,合并PS患者的颈动脉内膜中层厚度显著增加。以上研究提示我们PS与AS之间可能存在关联,但当前证据还不够充分,尚需更多的研究加以证实。

6 胰腺脂肪化的治疗

目前,规律运动和改善饮食习惯是改善PS的主要方法。规律运动是公认的可降低肥胖相关疾病发生风险的生活方式,包括NAFLD和T2DM等^[71]。已有研究^[72]证明2周的间歇冲刺或中等强度的持续训练均能显著减少男性的胰腺脂肪,促进 β 细胞分泌胰岛素。另外,已有研究^[73]表明,减少卡路里摄入的饮食习惯使T2DM患者的胰腺脂肪含量明显减少,胰岛素分泌恢复健康水平。MATHEUS等^[74]在肥胖小鼠饮食中添加丁酸钠,发现胰岛素分泌增加,胰腺内脂质显著减少。

药物方面,曲格列酮、利拉鲁肽、视黄酸受体 $\beta 2$ 激动剂等被证明可以改善PS及 β 细胞功能。曲格列酮在T2DM小鼠中可显著增加胰腺湿重、蛋白质含量,完全阻止或逆转炎症细胞浸润、脂肪替代和纤维化^[75]。利拉鲁肽可通过调节内质网应激和凋

亡信号通路来减轻PS^[76]。视黄酸受体 $\beta 2$ 激动剂可显著降低糖尿病小鼠肝、胰和肾的脂肪变性、脂质过氧化和氧化应激^[77]。这些动物实验为开发PS的治疗药物奠定了基础。手术方面,袖状胃切除术和/或Roux-en-Y吻合术(减重手术)被证明可以减少胰腺脂肪^[78]。肥胖患者在减重手术6个月后发现胰腺中脂肪量和脂肪酸摄取减少, β 细胞功能改善^[79]。

运动、食疗、药物及手术等对PS均有改善作用,但目前尚缺乏PS的标准化治疗方案。为实现其治疗的最优化,需要进一步理解PS的发病机制及其带来的病理生理变化,以期实现其相关疾病的一级和二级预防。

7 总结与展望

PS是以肥胖为始动因素的与糖和脂肪代谢紊乱相关的胰腺异位脂肪贮积疾病。与NAFLD不同,PS的脂肪主要存在于脂肪细胞中。脂肪细胞通过旁分泌方式在胰腺局部引起炎症细胞浸润和纤维化,炎症加剧或持续存在则可能诱发AP、CP、胰腺癌等疾病;当胰岛 β 细胞持续受损或数量减少,则会引起全身代谢平衡的紊乱,参与MetS、NAFLD、T2DM、AS等疾病的发生发展。因此,早期诊断和治疗PS对减轻患者及社会负担具有重要意义。目前,尚缺乏PS的标准治疗方案,但仍推荐以减重、改善生活方式等减少胰腺内脂肪含量、改善胰腺功能。

然而,目前PS在临床工作中尚未引起足够重视,多数患者因漏诊或未得到专业的治疗指导而导致胰腺炎和胰腺癌等不良结果的发生。在未来的临床和科研工作中,提高医患对胰腺脂肪化的认识,引导高风险人群进行PS筛查,探索更加准确的PS诊断方法,研发新的预防和治疗药物,减少胰腺脂肪化及其他胰腺和代谢疾病的发生等均具有重要意义。



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参考文献

- [1] RAMKISSOON R, GARDNER T B. Pancreatic steatosis: An emerging clinical entity [J]. Am J Gastroenterol, 2019, 114(11): 1726-1734.
- [2] SOTOUDEHMANESH R, TAHMASBI A, SADE-

- GHI A, et al. The prevalence of nonalcoholic fatty pancreas by endoscopic ultrasonography [J]. *Pancreas*, 2019, 48(9): 1220-1224.
- [3] WAGNER R, ECKSTEIN S S, YAMAZAKI H, et al. Metabolic implications of pancreatic fat accumulation [J]. *Nat Rev Endocrinol*, 2022, 18(1): 43-54.
- [4] CATANZARO R, CUFFARI B, ITALIA A, et al. Exploring the metabolic syndrome: Nonalcoholic fatty pancreas disease [J]. *World J Gastroenterol*, 2016, 22(34): 7660-7675.
- [5] BI Y, WANG J L, LI M L, et al. The association between pancreas steatosis and metabolic syndrome: A systematic review and meta-analysis [J]. *Diabetes Metab Res Rev*, 2019, 35(5): e3142.
- [6] OKADA K, WATAHIKI T, HORIE K, et al. The prevalence and clinical implications of pancreatic fat accumulation identified during a medical check-up [J]. *Medicine*, 2021, 100(41): e27487.
- [7] WANG C Y, OU H Y, CHEN M F, et al. Enigmatic ectopic fat: Prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population [J]. *J Am Heart Assoc*, 2014, 3(1): e000297.
- [8] ZHOU J, LI M L, ZHANG D D, et al. The correlation between pancreatic steatosis and metabolic syndrome in a Chinese population [J]. *Pancreatolog*, 2016, 16(4): 578-583.
- [9] WONG V W, WONG G L, YEUNG D K, et al. Fatty pancreas, insulin resistance, and β -cell function: A population study using fat-water magnetic resonance imaging [J]. *Am J Gastroenterol*, 2014, 109(4): 589-597.
- [10] LESMANA C R, PAKASI L S, INGGRANI S, et al. Prevalence of non-alcoholic fatty pancreas disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: A large cross sectional study [J]. *BMC Gastroenterol*, 2015, 15: 174.
- [11] FILIPPATOS T D. Non-alcoholic fatty pancreas disease: A diagnosis of increasing importance [J]. *Angiology*, 2022, 73(6): 495-596.
- [12] CHAN T T, TSE Y K, LUI R N, et al. Fatty pancreas is independently associated with subsequent diabetes mellitus development: A 10-year prospective cohort study [J]. *Clin Gastroenterol Hepatol*, 2022, 20(9): 2014-2022. e4.
- [13] PHAM Y H, BINGHAM B A, BELL C S, et al. Prevalence of pancreatic steatosis at a pediatric tertiary care center [J]. *South Med J*, 2016, 109(3): 196-198.
- [14] SINGH R G, YOON H D, WU L M, et al. Ectopic fat accumulation in the pancreas and its clinical relevance: A systematic review, meta-analysis, and meta-regression [J]. *Metabolism*, 2017, 69: 1-13.
- [15] SZCZEPANIAK L S, VICTOR R G, MATHUR R, et al. Pancreatic steatosis and its relationship to β -cell dysfunction in humans: Racial and ethnic variations [J]. *Diabetes Care*, 2012, 35(11): 2377-2383.
- [16] TROUT A T, HUNTE D E, MOUZAKI M, et al. Relationship between abdominal fat stores and liver fat, pancreatic fat, and metabolic comorbidities in a pediatric population with non-alcoholic fatty liver disease [J]. *Abdom Radiol (NY)*, 2019, 44(9): 3107-3114.
- [17] OU H Y, WANG C Y, YANG Y C, et al. The association between nonalcoholic fatty pancreas disease and diabetes [J]. *PLoS One*, 2013, 8(5): e62561.
- [18] WENG S, ZHOU J, CHEN X, et al. Prevalence and factors associated with nonalcoholic fatty pancreas disease and its severity in China [J]. *Medicine*, 2018, 97(26): e11293.
- [19] WANG D, YU X P, XIAO W M, et al. Prevalence and clinical characteristics of fatty pancreas in Yangzhou, China: A cross-sectional study [J]. *Pancreatolog*, 2018, 18(3): 263-268.
- [20] KOYUNCU SOKMEN B, SAHIN T, ORAL A, et al. The comparison of pancreatic and hepatic steatosis in healthy liver donor candidates [J]. *Sci Rep*, 2021, 11(1): 4507.
- [21] CHO J Y, YOU S K, LIM H H, et al. Clinical significance of pancreatic fat in children: A single-center experience [J]. *Pancreas*, 2022, 51(8): 972-975.
- [22] LEE E H, KIM J Y, YANG H R. Ectopic pancreatic fat as a risk factor for hypertension in children and adolescents with nonalcoholic fatty liver disease [J]. *J Clin Hypertens (Greenwich)*, 2021, 23(8): 1506-1515.
- [23] MEZA V, ARNOLD J, DiAZ L A, et al. Alcohol consumption: Medical implications, the liver and beyond [J]. *Alcohol Alcohol*, 2022, 57(3): 283-291.
- [24] KOC U, TAYDAS O. Investigation of the relationship between fatty pancreas and cholecystectomy using noncontrast computed tomography [J]. *J Med Imaging Radiat Sci*, 2019, 50(2): 220-226.
- [25] TRUONG E, PANDOL S, JEON C. Uniting epidemiology and experimental models: Pancreatic steatosis and pancreatic cancer [J]. *EBioMedicine*, 2022, 79: 103996.
- [26] SMITS M M, VAN GEENEN E J. The clinical significance of pancreatic steatosis [J]. *Nat Rev Gastroenterol Hepatol*, 2011, 8(3): 169-177.
- [27] DITE P, BLAHO M, BOJKOVA M, et al. Nonalcoholic fatty pancreas disease: Clinical consequences [J]. *Dig Dis*, 2020, 38(2): 143-149.
- [28] LIU L, MEI M, YANG S, et al. Roles of chronic low-grade inflammation in the development of ectopic fat deposition [J]. *Mediators Inflamm*, 2014, 2014: 418185.
- [29] GERST F, WAGNER R, OQUENDO M B, et al. What role do fat cells play in pancreatic tissue? [J]. *Mol Meta*, 2019, 25: 1-10.

- [30] KHOURY T, ASOMBANG A W, BERZIN T M, et al. The clinical implications of fatty pancreas: A concise review [J]. *Dig Dis Sci*, 2017, 62(10): 2658-2667.
- [31] RONTI T, LUPATTELLI G, MANNARINO E. The endocrine function of adipose tissue: An update [J]. *Clin Endocrinol (Oxf)*, 2006, 64(4): 355-365.
- [32] SREEDHAR U L, DESOUZA S V, PARK B, et al. A systematic review of intra-pancreatic fat deposition and pancreatic carcinogenesis [J]. *J Gastrointest Surg*, 2020, 24(11): 2560-2569.
- [33] UYGUN A, KADAYIFCI A, DEMIRCI H, et al. The effect of fatty pancreas on serum glucose parameters in patients with nonalcoholic steatohepatitis [J]. *Eur J Intern Med*, 2015, 26(1): 37-41.
- [34] PETROV M S, TAYLOR R. Intra-pancreatic fat deposition: Bringing hidden fat to the fore [J]. *Nat Rev Gastroenterol Hepatol*, 2022, 19(3): 153-168.
- [35] MILOVANOVIC T, DRAGASEVIC S, STOJKOVIC LALOSEVIC M, et al. Ultrasonographic evaluation of fatty pancreas in serbian patients with non alcoholic fatty liver disease—A cross sectional study [J]. *Medicina (Kaunas)*, 2019, 55(10): 697.
- [36] FILIPPATOS T D, ALEXAKIS K, MAVRIKAKI V, et al. Nonalcoholic fatty pancreas disease: Role in metabolic syndrome, "Prediabetes," diabetes and atherosclerosis [J]. *Dig Dis Sci*, 2022, 67(1): 26-41.
- [37] GABORIT B, ABDESSELAM I, KOBER F, et al. Ectopic fat storage in the pancreas using ¹H-MRS: Importance of diabetic status and modulation with bariatric surgery - induced weight loss [J]. *Int J Obes (Lond)*, 2015, 39(3): 480-487.
- [38] AL-MRABEH A, HOLLINGSWORTH K G, STEVEN S, et al. Quantification of intrapancreatic fat in type 2 diabetes by MRI [J]. *PLoS one*, 2017, 12(4): e0174660.
- [39] SAKAI N S, TAYLOR S A, CHOUHAN M D. Obesity, metabolic disease and the pancreas - quantitative imaging of pancreatic fat [J]. *Br J Radiol*, 2018, 91(1089): 20180267.
- [40] IDILMAN I S, YILDIZ A E, KARAOSMANOGLU A D, et al. Proton density fat fraction: Magnetic resonance imaging applications beyond the liver [J]. *Diagn Interv Radiol*, 2022, 28(1): 83-91.
- [41] BLAHO M, MACHÁČKOVÁ J, DÍTĚ P, et al. Use of magnetic resonance imaging to quantify fat and steatosis in the pancreas in patients after bariatric surgery: A retrospective study [J]. *Obes Surg*, 2022, 32(11): 3666-3674.
- [42] MEDZHITOV R. Origin and physiological roles of inflammation [J]. *Nature*, 2008, 454(7203): 428-435.
- [43] SBEIT W, KHOURY T. Fatty pancreas represents a risk factor for acute pancreatitis: A pilot study [J]. *Pancreas*, 2021, 50(7): 990-993.
- [44] PANEK J, SZTEFKO K, DROZDZ W. Composition of free fatty acid and triglyceride fractions in human necrotic pancreatic tissue [J]. *Med Sci Monit*, 2001, 7(5): 894-898.
- [45] NAVINA S, ACHARYA C, DELANY J P, et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity [J]. *Sci Transl Med*, 2011, 3(107): 107ra10.
- [46] XIE J, XU L, PAN Y, et al. Nonalcoholic fatty pancreas disease is related independently to the severity of acute pancreatitis [J]. *Eur J Gastroenterol Hepatol*, 2019, 31(8): 973-978.
- [47] KLEEFF J, WHITCOMB D C, SHIMOSEGAWA T, et al. Chronic pancreatitis [J]. *Nat Rev Dis Primers*, 2017, 3: 17060.
- [48] TIRKES T, JEON C Y, LI L, et al. Association of pancreatic steatosis with chronic pancreatitis, obesity, and type 2 diabetes mellitus [J]. *Pancreas*, 2019, 48(3): 420-426.
- [49] BAO Y, GIOVANNUCCI E L, KRAFT P, et al. A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts [J]. *J Natl Cancer Inst*, 2013, 105(2): 95-103.
- [50] BOOTH A, MAGNUSON A, FOUTS J, et al. Adipose tissue, obesity and adipokines: Role in cancer promotion [J]. *Horm Mol Biol Clin Investig*, 2015, 21(1): 57-74.
- [51] DESAI V, PATEL K, SHETH R, et al. Pancreatic fat infiltration is associated with a higher risk of pancreatic ductal adenocarcinoma [J]. *Visc Med*, 2020, 36(3): 220-226.
- [52] FUKUDA Y, YAMADA D, EGUCHI H, et al. CT density in the pancreas is a promising imaging predictor for pancreatic ductal adenocarcinoma [J]. *Ann Surg Oncol*, 2017, 24(9): 2762-2769.
- [53] KASHIWAGI K, SEINO T, FUKUHARA S, et al. Pancreatic fat content detected by computed tomography and its significant relationship with intraductal papillary mucinous neoplasm [J]. *Pancreas*, 2018, 47(9): 1087-1092.
- [54] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) [J]. *JAMA*, 2001, 285(19): 2486-2497.
- [55] SINGH R G, YOON H D, POPPITT S D, et al. Ectopic fat accumulation in the pancreas and its biomarkers: A systematic review and meta-analysis [J]. *Diabetes Metab Res Rev*, 2017, 33:e2918.

- [56] BALLESTER-VALLÉS C, FLORES-MÉNDEZ J, DELGADO-MORALED A J, et al. Hepatic and pancreatic fat as imaging biomarkers of metabolic syndrome [J]. *Radiologia*, 2020, 62(2): 122-130.
- [57] KIM D R, LEE M S, LEE J S, et al. Ultrasonographic quantitative analysis of fatty pancreas in obese children: Its correlation with metabolic syndrome and homeostasis model assessment of insulin resistance [J]. *J Pediatr*, 2018, 193: 134-138. e1.
- [58] KATSIKI N, PEREZ - MARTINEZ P, ANAGNOSTIS P, et al. Is nonalcoholic fatty liver disease indeed the hepatic manifestation of metabolic syndrome? [J]. *Curr Vasc Pharmacol*, 2018, 16(3): 219-227.
- [59] MULLISH B H, FORLANO R, MANOUSOU P, et al. Non-alcoholic fatty liver disease and cardiovascular risk: An update [J]. *Expert Rev Gastroenterol Hepatol*, 2018, 12(12): 1175-1177.
- [60] VIEIRA J, AMORIM J, MARTÍ-BONMATÍ L, et al. Quantifying steatosis in the liver and pancreas with MRI in patient with chronic liver disease [J]. *Radiologia*, 2020, 62(3): 222-228.
- [61] SBEIT W, GREENER T, KADAH A, et al. Pancreatobiliary manifestations of nonalcoholic fatty liver disease: A retrospective case-control multicenter study [J]. *Eur J Gastroenterol Hepatol*, 2021, 33(5): 722-726.
- [62] LÓPEZ - BERMUDO L, LUQUE - SIERRA A, MAYA-MILES D, et al. Contribution of liver and pancreatic islet crosstalk to β -cell function/dysfunction in the presence of fatty liver [J]. *Front Endocrinol (Lausanne)*, 2022, 13: 892672.
- [63] ZHANG X, YANG W, WANG J, et al. FAM3 gene family: A promising therapeutical target for NAFLD and type 2 diabetes [J]. *Metabolism*, 2018, 81: 71-82.
- [64] WANG O, CAI K, PANG S, et al. Mechanisms of glucose-induced expression of pancreatic-derived factor in pancreatic beta-cells [J]. *Endocrinology*, 2008, 149(2): 672-680.
- [65] YAMAZAKI H, TAUCHI S, MACHANN J, et al. Fat distribution patterns and future type 2 diabetes [J]. *Diabetes*, 2022, 71(9): 1937-1945.
- [66] YU T Y, WANG C Y. Impact of non-alcoholic fatty pancreas disease on glucose metabolism [J]. *J Diabetes Investig*, 2017, 8(6): 735-747.
- [67] SKILTON M R, CELERMAJER D S, COSMI E, et al. Natural history of atherosclerosis and abdominal aortic intima-media thickness: Rationale, evidence, and best practice for detection of atherosclerosis in the young [J]. *J Clin Med*, 2019, 8(8):1201.
- [68] KATSIKI N, MIKHAILIDIS D P. Epicardial fat: A novel marker of subclinical atherosclerosis in clinical practice? [J]. *Anatol J Cardiol*, 2017, 17(1): 64-65.
- [69] KUL S, KARADENIZ A, DURSUN İ, et al. Non-alcoholic fatty pancreas disease is associated with increased epicardial adipose tissue and aortic intima-media thickness [J]. *Acta Cardiol Sin*, 2019, 35(2): 118-125.
- [70] SAHIN S, KARADENIZ A. Pancretic fat accumulation is associated with subclinical atherosclerosis [J]. *Angiology*, 2022, 73(6): 508-513.
- [71] THYFAULT J P, BERGOUIGNAN A. Exercise and metabolic health: Beyond skeletal muscle [J]. *Diabetologia*, 2020, 63(8): 1464-1474.
- [72] HEISKANEN M A, MOTIANI K K, MARI A, et al. Exercise training decreases pancreatic fat content and improves beta cell function regardless of baseline glucose tolerance: A randomised controlled trial [J]. *Diabetologia*, 2018, 61(8): 1817-1828.
- [73] LEAN M E, LESLIE W S, BARNES A C, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial [J]. *Lancet*, 2018, 391(10120): 541-551.
- [74] MATHEUS V A, MONTEIRO L, OLIVEIRA R B, et al. Butyrate reduces high-fat diet-induced metabolic alterations, hepatic steatosis and pancreatic beta cell and intestinal barrier dysfunctions in prediabetic mice [J]. *Exp Biol Med (Maywood)*, 2017, 242(12): 1214-1226.
- [75] JIA D M, FUKUMITSU K I, TABARU A, et al. Troglitazone stimulates pancreatic growth in congenitally CCK-A receptor-deficient OLETF rats [J]. *Am J Physiol Regul Integr Comp Physiol*, 2001, 280(5): R1332-R1340.
- [76] FANG T, HUANG S, CHEN Y, et al. Glucagon like peptide-1 receptor agonists alter pancreatic and hepatic histology and regulation of endoplasmic reticulum stress in high-fat diet mouse model [J]. *Exp Clin Endocrinol Diabetes*, 2021, 129(9): 625-633.
- [77] TRASINO S E, TANG X H, JESSURUN J, et al. Retinoic acid receptor β 2 agonists restore glycaemic control in diabetes and reduce steatosis [J]. *Diabetes Obes Metab*, 2016, 18(2): 142-151.
- [78] REBOURS V, GARTEISER P, RIBEIRO-PARENTI L, et al. Obesity-induced pancreatopathy in rats is reversible after bariatric surgery [J]. *Sci Rep*, 2018, 8(1): 16295.
- [79] HUI S C N, WONG S K H, AI Q, et al. Observed changes in brown, white, hepatic and pancreatic fat after bariatric surgery: Evaluation with MRI [J]. *Eur Radiol*, 2019, 29(2): 849-856.

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