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Shijie Huaren Xiaohua Zazhi

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述评 EDITORIAL

吸烟与胰腺损伤研究进展

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Progress in understanding of relationship between smoking and pancreatic injury

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Abstract

There are numerous harmful chemicals present in smoke from cigarette, and smoking is strongly associated with the occurrence and development of various diseases, significantly impacting individuals' health. The correlation between smoking and pancreatic injury has gained increasing recognition. The detrimental components in cigarette smoking can induce endocrine dysfunction, inflammatory reactions, aberrant blood supply, and alterations in enzyme activity in the pancreas. Smoking substantially elevates the risk of pancreatic injury, encompassing acute pancreatitis, chronic pancreatitis, and pancreatic cancer. Furthermore, smoking cessation has been proven to reduce the likelihood of pancreatic injury and enhance pancreatic function. Nevertheless, the biological mechanisms underlying the effects of smoking on the pancreas and the long-term benefits of smoking cessation remain to be further explored. A comprehensive understanding of the impact of smoking on pancreatic tissue damage is crucial in formulating effective prevention and treatment strategies to safeguard individuals' health. Therefore, this article aims to provide a concise overview of the latest research progress concerning smoking-related pancreatic tissue damage.

Key Words: Smoking; Nicotine; Pancreatic damage; Pancreatitis; Pancreatic cancer

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摘要

香烟烟雾中有多种有害的化学物质, 吸烟与多种疾病的发生均密切相关, 对人们的健康有一定影响. 吸烟与胰腺损伤的关系日益受到关注. 香烟烟雾中的有害成分可导致胰腺内分泌功能障碍、炎症反应和血液

供应异常、以及酶活性的改变. 吸烟显著增加胰腺损伤的风险, 包括急性胰腺炎、慢性胰腺炎和胰腺癌. 此外, 戒烟已被证实可降低胰腺损伤风险, 改善胰腺功能. 然而, 吸烟对胰腺影响的生物学机制以及戒烟的长期效益仍需进一步探索. 全面了解吸烟对胰腺的影响有助于制定有效的预防和治疗策略, 以保护人们的健康. 因此, 本文将就吸烟对胰腺组织损伤的研究进展进行简要综述.

关键词: 吸烟; 尼古丁; 胰腺损伤; 胰腺炎; 胰腺癌

核心提要: 吸烟与胰腺损伤的关系密切. 烟草中的有害成分可导致胰腺功能障碍, 并显著增加胰腺炎及胰腺癌的风险. 全面了解吸烟对胰腺的影响有助于制定有效的预防和治疗策略, 以保护人们的健康.

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0 引言

吸烟与多种疾病的发生发展均有密切关系, 给人们的健康和生活质量带来严重影响[1,2]. 香烟烟雾中含有超过9500种不同的化学物质, 其中约80种具有潜在的毒性和致癌性[3]. 香烟烟雾中较为常见的物质除了最常见的尼古丁外, 多环芳烃等芳香烃类化合物占比较大, 其次是金属和亚硝胺类物质. 此外, 醛类、酮类、醇类和酚类等化合物也均有检测到[4].

香烟烟雾中所含的有害成分对人体的多个器官和系统都有不利影响, 如慢性阻塞性肺疾病、肺部感染和肺癌等呼吸系统疾病[5,6]; 冠心病和脑卒中等心脑血管系统疾病[7]; 类风湿性关节炎等自身免疫性疾病[8]; 以及皮肤癌、牙周病等其他系统疾病[9,10]. 尽管在戒烟的宣传下, 吸烟人数有所下降. 但根据美国疾病预防控制中心数据预测, 仅美国每年与吸烟有关的死亡就有45-48万例, 且这一数字将持续到2035年[11]. 因此, 吸烟导致的健康危害仍值得关注.

相较于吸烟与其他系统疾病的研究, 吸烟与胰腺的研究及相关综述较少. 因此, 本文将着眼于吸烟对胰腺的损伤, 旨在综述该领域最新的研究进展, 重点讨论吸烟对胰腺功能和结构的影响, 并探讨吸烟与胰腺炎、胰腺癌等疾病的关联.

1 吸烟对胰腺功能的影响

吸烟可导致胰腺内分泌功能异常. 香烟烟雾中的有害化学物质, 如一氧化碳和氰化物, 可以干扰胰岛素和胰高血糖素等内分泌物质的正常合成和分泌, 进而影响血糖调节, 导致血糖调节紊乱[12]. 香烟烟雾中的尼古丁可以与烟碱样乙酰胆碱受体(nicotinic acetylcholine receptor, nAChR)结合, 影响胰岛对葡萄糖稳态的调节. 同时, 吸烟会损害β细胞功能, 并与吸烟剂量成正相关[13,14]; 并且可以增加胰岛素受体底物-1的Ser636磷酸化, 激活哺乳动物雷帕霉素靶蛋白和丝裂原激活的蛋白激酶信号通路, 从而影响胰岛素敏感性[15]. 以上研究表明, 吸烟可能增加了胰岛素抵抗和胰岛素抵抗相关疾病(如2型糖尿病)的发生风险.

吸烟会促进胰腺炎症反应的发生和进展[16]. 香烟烟雾中的有害化学物质可以刺激胰腺组织, 引发炎症反应. 这种炎症反应可能导致胰腺组织的破坏和纤维化, 加重炎症过程, 进一步损害胰腺功能[17]. 同时, 吸烟也会改变胰腺的血液供应, 对胰腺的血液供应产生不利影响. 香烟烟雾中的化学物质可以引起血管收缩和血小板聚集, 导致胰腺血管收缩和缺血. 这可能降低胰腺组织的氧供应和营养供应, 使其更容易受到损伤和炎症的侵袭.

此外, 吸烟还会使酶活性发生改变. 研究发现, 吸烟者的胰腺酶活性明显增加, 这可能导致消化酶在胰腺内部的异常活化, 从而引发胰腺自消化的过程[18].

综上所述, 吸烟会对胰腺的功能产生负面影响. 它可以干扰胰岛素和胰高血糖素的正常合成和分泌, 增加胰腺炎症反应的风险, 影响胰腺的血液供应, 并改变胰腺酶的活性. 这些影响可能导致胰腺功能异常, 增加胰腺炎、胰腺癌和其他胰腺相关疾病的发生风险.

2 吸烟与胰腺炎的关联

吸烟被认为是胰腺炎的危险因素之一. 研究表明, 吸烟与急性胰腺炎和慢性胰腺炎(chronic pancreatitis, CP)的发生之间均存在明显的关联[19,20]. 吸烟可以增加胰腺炎的患病风险, 加重疾病的严重程度, 促进病情进展, 延长疾病持续时间, 并增加复发的可能性.

近年来, 很多研究致力于探究吸烟导致胰腺炎的潜在作用机制. 早期研究[21]就发现吸烟可导致大鼠胰腺损伤, 吸烟组大鼠从3周起就出现胰腺组织中胶原表达升高的情况, 9-12周起出现小叶间和导管旁间质内少量慢性炎性细胞, 12周后出现胰腺组织内超氧化物歧化酶及丙二醛含量升高, 由此说明吸烟可通过氧化应激诱导胰腺炎的发生. 后续Lugea等[22]的研究发现香烟烟雾可以加重酒精和脂多糖诱导的小鼠胰腺炎症及纤维化; 同时用香烟烟雾提取物作用于胰腺腺泡细胞, 发现香烟烟雾和酒精联合可以显著降低腺泡细胞中内质网和酶原颗粒的数量, 通过诱导胰腺腺泡细胞内质网应激促进胰腺

腺泡细胞死亡.

需要强调的是, 吸烟与CP的发生及进展更为相关[23,24]. CP是一种进行性的疾病, 长期吸烟可能导致炎症持续存在, 加重胰腺损伤, 最终发展为CP. 吸烟可以通过多个靶点及相关机制通路来影响CP的发生发展[25,26]. 细胞靶点包括胰腺星状细胞(pancreatic stellate cells, PSCs)、胰腺腺泡细胞、胰腺导管细胞、免疫细胞等[16], 而通路则包括内质网应激、细胞内钙超载、线粒体损伤和氧化应激损伤等. 其中, PSCs是CP的主要效应细胞, 而尼古丁又是烟草的主要成分之一. 因此, 围绕尼古丁促进PSCs活化, 加重CP胰腺纤维化也有着一系列的研究. 研究发现[27], 尼古丁可加重CP动物模型胰腺纤维化, 并可通过α7亚型nAChR促进CP动物模型PSCs活化; 同时, 尼古丁可加重CP动物模型的氧化应激, 且应用抗氧化剂可以抑制PSCs活化[27,28]; 更进一步的, 研究还发现尼古丁可通过线粒体氧化应激促进PSCs中线粒体分裂相关蛋白Drp1相关的线粒体动力学改变[29], 更深入地明确了尼古丁在CP进展中的作用机制.

除了尼古丁, 香烟烟雾中的其他有害物质对CP及胰腺纤维化的影响也有着一定的研究. Lee等[30]的研究表明, 香烟烟雾中的亚硝胺酮也可通过细胞上nAChR介导促进PSCs活化, 进而促进CP的进展. 2022年的一项新研究[17]发现, 长期暴露于香烟烟雾的小鼠和有吸烟史的CP患者的胰腺中蛋白质组发生了独特的变化, 细胞外基质蛋白检测到丙二醛-乙醛加合物, 而这显著抑制了X-box结合蛋白-1的表达, 增加胰腺腺泡细胞内质网应激, 导致腺泡细胞死亡. 另外也有研究发现[31]香烟烟雾中苯并芘及四氯二苯-p-二恶英可作用于T细胞的相关受体, 诱导产生白细胞介素(interleukin, IL)-22, 与PSCs的IL-22受体结合, 磷酸化STAT3, 促进细胞外基质基因表达及纤维化形成. 这也说明了吸烟可以通过调节免疫信号来影响胰腺纤维化的进展.

综上所述, 吸烟与胰腺炎密切相关. 吸烟增加了胰腺炎的患病风险, 并促进胰腺炎症反应的发生和进展. 此外, 吸烟还影响胰腺的血液供应, 加重疾病的严重程度和复发率. 因此, 戒烟对于预防和管理胰腺炎非常重要.

3 吸烟与胰腺癌的关联

胰腺癌是一种恶性程度较高的肿瘤, 早期发现困难且治疗效果较差, 病死率较高. 吸烟是胰腺癌的主要危险因素之一, 且吸烟时间越长, 吸烟量越大, 患病风险也越高[32-34]. 香烟烟雾中的多种致癌物质如尼古丁、亚硝胺和多环芳烃等可以通过吸入进入人体内, 与胰腺组织接触并引发一系列致癌事件, 最终促进癌症的发生和进展[35]. 吸烟引起的胰腺的长期慢性炎症状态会导致胰腺组织的持续损伤和纤维化, 这也与胰腺癌的发生相关.

近年来, 多项研究聚焦吸烟与胰腺癌的相关机制研究. 早期的研究就发现, 香烟烟雾可使大鼠的酶活性增加, 基因改变, 导致其对胰腺癌的易感性增加[18]. 此外, 多项研究发现吸烟可以通过多种途径来触发胰腺癌, 如IL-6、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等炎症反应及免疫抑制; miRNA表达异常; α7AChR、细胞外信号调节激酶等信号通路改变; KRAS、TP53等致癌基因突变或抑癌蛋白失活; 以及胰腺内微环境改变等[36,37]. 也有研究表明, 香烟烟雾长期暴露下的人类和小鼠胰腺组织可以通过聚合酶相关因子1表达升高来激活其干细胞特征, 从而促进胰腺癌的发生[38].

此外, 吸烟还与胰腺癌的治疗效果及预后不良、肿瘤转移扩散和复发率增加相关[39,40]. 研究发现, 烟草中的尼古丁和亚硝胺酮可以通过α7nAChR介导的钙信号和黏蛋白4上调等调节炎症细胞和免疫反应, 促进胰腺癌的发生和转移[41]. 而Zhang等[42]的研究发现, 香烟烟雾可使吸烟者的胰腺导管上皮细胞中的致癌原代miR-25过度成熟形成过多的miR-25-3p, 进而激活AKT-p70S6K信号通路来触发胰腺癌, 同时这也与胰腺癌患者预后不良相关. 也有研究发现, 香烟烟雾提取物可以上调染色质结合蛋白3, 通过染色质修饰调节下游靶标的表达, 促进胰腺癌的进展[43]. 这些结果表明, 香烟烟雾可以在表观遗传学的水平促进胰腺癌的发生和进展, 并影响其预后.

综上所述, 吸烟可以通过多种途径来增加胰腺癌的患病风险. 需要指出的是, 吸烟不仅与胰腺癌的发生相关, 还会促进疾病的进展和恶化, 与疾病的预后不良相关. 了解并采取积极的措施来减少吸烟行为对于预防胰腺癌的发生及进展具有重要意义.

4 戒烟对胰腺损伤的影响

戒烟被认为是降低胰腺损伤风险的重要措施, 对于改善整体健康和降低患病风险非常重要. 戒烟可以显著降低胰腺炎和胰腺癌的患病风险, 即使是对既往有吸烟史的人群. 日本的一项研究就表明, 吸烟男性在戒烟5年后患胰腺癌的风险与非吸烟者相当[33].

同时, 通过强化吸烟控制措施和促进健康生活方式, 也有助于提高治疗效果, 并改善预后. 研究显示, 戒烟后胰腺炎和胰腺癌的复发率和死亡风险显著降低[1].

因此, 积极宣传戒烟的重要性, 并提供戒烟支持和干预措施, 对于保护胰腺健康具有重要意义. 但也需要注意到吸烟对身体的损害是累积的, 戒烟仅可以逆转一部分损害.

5 结论

吸烟与胰腺损伤之间存在明确的关联. 吸烟不仅对胰腺功能产生不利影响, 还与胰腺炎和胰腺癌的发生及进展密切相关. 然而, 戒烟可以明显减少胰腺损伤及相关疾病发生的风险. 因此, 教育公众认识吸烟对胰腺健康的危害, 并积极推广戒烟措施, 对于预防和管理胰腺相关疾病具有重要意义. 未来的研究应进一步探索吸烟与胰腺损伤的机制, 并寻求更有效的预防和治疗策略, 以降低相关疾病的发生率和提高患者的生存质量.

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