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新进展综述

妊娠期糖尿病与肠道菌群改变的研究进展

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[**摘要**]　妊娠期糖尿病(GDM)是妊娠常见并发症之一,表现为妊娠期糖代谢异常,对母儿造成长久的影响。妊娠期孕妇肠道菌群数量和种类出现生理性改变。研究表明,肠道菌群多样性及丰富度的改变是造成GDM发生发展的潜在因素。该文对GDM女性菌群改变的研究文献作一综述。

[**关键词**]　妊娠期糖尿病;　肠道菌群;　内毒素;　胰岛素抵抗;　短链脂肪酸
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Advances in the study on gestational diabetes mellitus and changes in intestinal flora　*CAO Yu-zhi, WANG Qian, MENG Yu-jun, et al. Second Clinical Medical College of Jinan University, Shenzhen* 518000, *China*

[**Abstract**]　Gestational diabetes mellitus(GDM) is one of the common complications of pregnancy, which manifests as abnormal glucose metabolism during pregnancy and causes profound effects on pregnant women and their fetuses. Physiological changes in the number and type of intestinal flora occur during pregnancy, and numerous studies have showed that changes in the diversity and abundance of intestinal flora are potential contributing factors to the development of GDM. In this paper, we review the literature on the changes in intestinal flora of women with GDM.

[**Key words**]　Gestational diabetes mellitus(GDM);　Intestinal flora;　Endotoxin;　Insulin resistance;　Short chain fatty acid

妊娠期糖尿病(gestational diabetes mellitus,GDM)是妊娠常见并发症之一,GDM 的发病率国外报道为 1% ~14%[1],我国发病率为 5% ~10%,近年来呈上升趋势[2]。GDM 对母儿健康造成严重影响,增加妊娠期高血压、巨大胎、早产、难产等其他妊娠并发症风险[3]。GDM 患者子代在出生后发生 2 型糖尿病、心血管疾病、自闭症等风险较生理妊娠者子代明显增高[4]。GDM 的发病机制较为复杂,目前尚不完全明了。除遗传背景因素外,同时也受后天生活方式因素影响。妊娠期孕妇肠道菌群会发生生理性变化,这与妊娠期激素水平改变、饮食习惯、炎症反应、免疫状态等有密切的关系。近年来,有研究证明,肠道菌群失调与代谢性疾病密切相关,其在糖尿病及 GDM 的发病中的作用及其机制探究成为一大热点。人体胃肠道、呼吸道、生殖道及泌尿道均存在大量微生物群,其中益生菌占据主导地位[5]。肠道微生物群构成了一个错综复杂的生态系统,参与人体的多项重要生命活动(包括消化吸收、内环境稳态的维持、免疫调节等)[6-7]。当胃肠道微生物群的种类或数量改变时,将导致许多疾病的发生,如胃肠道炎症、肿瘤、免疫相关疾病及代谢相关疾病[8]。既往研究表明,胰岛素抵抗患者及糖尿病患者的肠道菌群多样性降低[9],厚壁菌门/拟杆菌门比例升高,增加食物能量在肠道中的获取[10]。该比率被认为是肥胖和胰岛素抵抗中低度全身炎症的标志[11]。Sililas 等[12]观察到 GDM 患者妊娠晚期的厚壁菌门/拟杆菌门比值高于对照组。2012 年 Koren 等[13]首次报道妊娠晚期孕妇肠道中微生物的数量、比例、种类发生明显改变,肠道菌群的失调与胰岛素抵抗、炎症反应、体重增加有着直接的联系。此后,多项研究中均证实了肠道菌群与 GDM 之间具有密切关联。本文对肠道菌群的改变导致 GDM 的发生发展相关研究作一综述,为其发病机制及治疗提供新思路。

1 生理妊娠孕妇的肠道菌群

2012 年 Koren 等[13]认为妊娠前 3 个月孕妇的肠道菌群与正常健康人群无显著差异,进入妊娠晚期后肠道菌群中的放线菌门和变形菌门丰富度增加,而具有抗炎作用的粪杆菌属含量明显降低。妊娠早期和晚期粪便中的主要门群为拟杆菌门(56.9% 和 57.6%),其次为厚壁菌门(37.9% 和 36.5%)、变形菌门(2.5% 和 2.7%)、放线菌门(1.7% 和 2.1%)和绿弧菌门[14]。妊娠早期至妊娠后期,双歧杆菌、变形杆菌和产乳酸菌增加,产丁酸菌减少。妊娠晚期孕妇肠道菌群相较于妊娠早期 α 多样性下降(即个体内菌群多样性下降),而 β 多样性增高(即个体间菌群多样性差别增加)。认为妊娠期肠道黏膜上皮发生低度炎性改变,致使微生物群失调,宿主产生相应炎性反应形成正反馈。将孕妇体内的低多样性微生物群移植到无菌小鼠体内,可诱导炎症反应。菌群失调主要表现为变形菌纲水平升高,细菌负荷加重。生理妊娠的女性肠道微生物群是易通过饮食及生活习惯随之改变的,而患有 GDM 的女性的肠道菌群则不易受到饮食、生活的改变而改变[14]。孕期体重超重女性肠道内双歧杆菌和拟杆菌数量明显下降,而葡萄球菌、肠杆菌科和大肠杆菌的数量则呈上升趋势[15]。Jost 等[16]则发现妊娠晚期及哺乳期肠道菌群以厚壁菌门、拟杆菌门和双歧杆菌门占主要优势。

2 GDM 孕妇的肠道菌群

2.1 GDM 孕妇明显增加的肠道菌群物种 与正常妊娠期间发生的肠道菌群的广泛变化相比,GDM 妇女从妊娠早期到妊娠中期,肠道菌群的分类和功能变化较少,差异性平衡变化较小[17]。妊娠期高血糖孕妇的肠道微生物群丰富度和多样性较生理妊娠显著减少。一项研究表明,拟杆菌门在 GDM 患者中显著增加,其中拟杆菌属、柠檬酸杆菌属、副拟杆菌属、脱硫弧菌属的丰富度增加,副拟杆菌丰富度明显高于生理妊娠孕妇[18]。上述菌群的改变也在 Kuang 等[19]的研究中得到了进一步的证实。肠道中部分种类菌群可产生内毒素,在糖尿病中起重要的致病作用,而内毒素正是起源于拟杆菌属,拟杆菌被认为是导致胰岛素抵抗和葡萄糖不耐受的原因。另一项研究表示 GDM 孕妇产后仍存在胰岛素抵抗,肠道菌群异常可持续存在,表现为可降解黏液蛋白的普雷沃氏菌科比例增高,而厚壁菌门丰富度降低[20]。与妊娠血糖正常的孕妇相比,GDM 妇女产后仍持续胰岛素抵抗则将该风险进一步增加,在 10 年内患 2 型糖尿病的风险增高 10 倍。该研究认为富含普雷沃氏菌科的微生物群是 GDM 产后转变为 2 型糖尿病的高危因素之一。Chen 等[21]研究认为在厚壁菌门中,肠球菌科的 2 个属(小类杆菌属)和一个未分配属是 GDM 的生物标志物。一项关于日本 GDM 孕妇的研究再次证实罗姆布茨菌属丰富度增加,罗姆布茨菌属在妊娠期相关的胰岛素抵抗疾病中发挥着重要作用[22]。

2.2 GDM 孕妇明显减少的肠道菌群物种 GDM 孕妇的变形菌门、厚壁菌门、放线菌门、疣微菌门、科氏杆菌科、瘤胃球菌科阿克曼氏菌属、大肠志贺氏菌属、双歧杆菌、梭状芽胞杆菌罗氏菌属和棒状杆菌属的丰富度下降[23-24]。梭状芽胞杆菌、棒状杆菌属及罗氏菌

属的丰富度的下降程度被证实与空腹血糖、餐后 1 h 和 2 h 的血糖水平呈正相关。阿克曼氏菌属丰富度也被证实与 1 h 血糖呈负相关,与胰岛素敏感性呈正相关[18]。梭状芽胞杆菌科、瘤胃菌属、罗姆布茨菌属、毛螺菌属和韦荣氏球菌属被认为是妊娠期正常葡萄糖的生物标记。非肥胖的 GDM 患者中阿克曼氏菌属丰富度显著提高,阿克曼氏菌丰富度易受饮食影响。患者饮食中增加富含粗膳食纤维食物的摄入量,肠道菌群中阿克曼氏菌丰富度便会显著提高[22]。在一项动物实验中添加阿克曼氏菌益生菌可明显改善胰岛素敏感性[25]。GDM 孕妇孕中期及孕晚期产生短链脂肪酸(short-chain fatty acid,SCFA)的粪杆菌属、粪球菌属、瘤胃菌群属、考拉杆菌属和真杆菌属相对丰富度下降[26]。

3 GDM 孕妇肠道菌群改变与代谢异常潜在机制

3.1 内毒素学说 细菌脂多糖(lipopolysaccharide,LPS),又称内毒素,来源于由脂质和多糖构成的革兰阴性细菌细胞壁的外壁,通过与宿主细胞的细胞膜表面的 Toll 样受体 4(Toll-like receptor 4,TLR4)结合,激活 TLR4-NF-κB 信号转导通路,使靶细胞分泌多种炎性因子[如白细胞介素 6(interleukin-6,IL-6)、IL-8、肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)等],从而损伤 β 细胞,降低胰岛素分泌[27]。既往研究认为 GDM 患者血清中 IL-6 和 CRP 水平显著升高[28],认为胰岛素抵抗的启动因素可能是慢性炎症。有推测认为 IL-6 可能参与了 GDM 的发生[29-30]。IL-6 参与炎症的免疫反应,在局部组织损伤和全身免疫反应之间起到桥梁作用。同时促进细胞凋亡,损伤胰岛细胞,从而加重 GDM[31-32]。TNF-α 则主要分布在血管内皮细胞表面,可直接影响胰岛细胞,导致胰岛素抵抗。TNF-α 和 IL-6 相互作用干扰胰岛素信号转导,导致胰岛素抵抗,最终发生 GDM[33-34]。研究显示 GDM 模型小鼠血浆中 TNFα 和 IL-6 的表达高于健康妊娠小鼠组[35]。有研究表明,GDM 的发生与妊娠晚期孕妇肠道中游离的 LPS 的增加和血清内 LPS 的升高为特征的肠黏膜损伤有关[36]。在 GDM 患者肠道菌群研究中革兰阴性菌,如脱硫弧菌属、拟杆菌属、柠檬酸杆菌属、副拟杆菌属及纺锤链杆属的丰富度增加。脱硫弧菌属可通过内毒素,将硫酸盐还原成硫化氢,破坏肠道屏障,导致宿主体内持续产生低级别炎性反应,使 CD36 表达上调增加宿主细胞对肠道内脂质的吸收,进而导致胰岛素抵抗和肥胖[37]。分泌型免疫球蛋白 A(SIgA)与肠道表面黏液一同分泌至黏膜层,覆盖于肠黏膜外层,SIgA 包裹肠道内特定共生菌群,促进菌群定植,消除致病菌群的过度繁殖。当 SIgA 与人体免疫蛋白 A Fc 段受体 1 结合激活后招募大量炎症相关细胞,如中性粒细胞、单核细胞和巨噬细胞,诱导炎症反应的形成。GDM 孕妇 SIgA 结合菌群较生理妊娠孕妇更具有多样性。双歧杆菌、乳酸菌及阿克曼氏菌均是 SIgA 包裹菌群[38]。双歧杆菌和乳酸杆菌数量下降导致 SIgA 减少,肠道通透性增加,LPS 通过肠壁血管进入血液循环。实验证明 SIgA 包裹的罗伊氏乳杆菌 QS01 可降低 LPS,进一步降低血糖和糖化血红蛋白水平[36-39]。双歧杆菌也被证实与妊娠早期葡萄糖浓度呈负相关[14]。

3.2 胰岛素抵抗学说 人类肠道微生物主要由两个优势菌门组成:厚壁菌门和拟杆菌门,占肠道菌群的 90%。研究表明,体重超重的 GDM 妇女在妊娠中期及晚期的饮食消耗和肠道微生物对葡萄糖代谢有直接影响。厚壁菌门/拟杆菌门比值的增高虽仍具争议,但多数人认为是肥胖和代谢综合征的生物学标志,并认为随着体重的减少而比例随之下降[40-42]。厚壁菌门和拟杆菌门通过产生丁酸调节胰高血糖素样肽-1(glucagon-like peptide-1,GLP-1)和肽酪氨酸的分泌来介导胰岛素抵抗[43]。GLP-1 在体重减轻、葡萄糖稳态和营养代谢中发挥重要作用[44]。GLP-1 的缺乏加剧高脂食物诱导的内啡肽和肝胰岛素信号通路的抑制,出现肝脏胰岛素抵抗。GLP-1 是一种因营养摄入而分泌的肠促胰岛素,I 细胞主要在营养状态下释放 GLP-1。GLP-1 的活性形式调节大脑的饱腹感,降低对高脂食物的偏好,刺激高血糖状态下的胰岛素释放和肌肉中的葡萄糖吸收,以维持系统能量稳态,并且产生对食欲的抑制作用[45-46]。另一项研究表明疣微菌门和毛螺菌门菌群的丰富度影响妊娠期的糖代谢和脂代谢,与瘦素水平呈正相关[47]。疣微菌门与肥胖女性妊娠诱导的胰岛素抵抗相关,该细菌可能改变了胰岛素信号通路,导致葡萄糖稳态和炎症受损[48]。

3.3 SCFA 的合成与代谢学说 通过细菌发酵难以消化的多糖(即膳食纤维)分解产生 SCFA,为结肠细胞提供能量底物,缓解炎症,调节饱腹感[49],包括乙酸、丙酸和丁酸。丁酸被认为是第二信使和能量来源,能增加胰岛素的敏感性,发挥抗炎活性,调节能量和增加瘦素的基因表达[41]。GDM 患者中产 SCFA 的瘤胃球菌属、罗氏菌属、粪杆菌属、粪球菌属、考拉杆菌属、阿克曼氏菌属和真杆菌属的相对丰度降低[26]。GDM 女性妊娠早期及妊娠中期,产丁酸菌球菌和产乳酸菌链球菌的相对丰度下降。实验结果表明,产生 SCFA 的微生物水平与葡萄糖不耐受的早期发展呈负

相关[50]。SCFA 通过抑制组蛋白去乙酰化酶和内源性 G 蛋白偶联受体(GPR)41 和 GPR43 的长链结合,GPR43 信号通路调节胰岛素刺激脂肪细胞的脂质积累和炎症反应[51],促进肠内分泌细胞分泌肽酪氨酸和 GLP-1,从而减少肠道运动,增加食物通过肠道时间和 SCFA 的吸收率,参与调节胰岛素释放和促进葡萄糖代谢[52]。抑胃肽的水平与粪球菌属的丰富度呈正相关[34]。SCFA 还通过激活过氧化物酶体增殖物激活受体通路,在加强肠道屏障、减少炎症和氧化应激方面发挥重要作用[53-54]。在糖尿病患者中 SCFA 的作用也得到证实,在糖尿病个体中产生丁酸的细菌水平降低,动物实验研究中在肥胖、糖尿病前期小鼠中补充丁酸显著改善胰岛素抵抗、高胰岛素血症[55]。

4 结语

肠道菌群的丰富度和多样性在 GDM 的发病中起到了重要的作用,肠道菌群可作为 GDM 早期检测的生物标志物,对 GDM 的早期预防与治疗提供了新的方向。目前,肠道菌群在妊娠糖代谢领域的研究及临床应用仍处于起步阶段。GDM 孕妇肠道菌群较生理妊娠孕妇改变,α 多样性下降,而 β 多样性增高,厚壁菌门/拟杆菌门比值增高,产 SCFA 的菌群减少,与 SIgA 结合的菌群种类增多,而双歧杆菌、乳酸杆菌减少等。肠道菌群失调参与妊娠期糖代谢异常的潜在发病机制,包括内毒素入血导致的低级别炎性反应、菌群失调导致 GLP-1 失调胰岛素抵抗、SCFA 合成和代谢改变等。关于妊娠孕妇肠道菌群改变与 GDM 关系的研究,结果尚存在不一致性,可能与种族、样本量、纳入标准、饮食习惯、测序方法等不同有关。随着高通量测序等研究技术手段的进步及更多研究数据的产生,将进一步确定我国 GDM 孕妇肠道菌群特有的变化,为 GDM 的防治提供更准确的指向。

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新进展综述

液体活检在乳腺癌诊疗中的研究进展

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[**摘要**] 液体活检作为乳腺癌诊疗的新兴技术,主要通过无创或微创的方式对患者的血液、尿液、唾液等体液取样,检测癌性标志物用以诊断、预后评估及随访。液体活检技术对于乳腺癌的早期诊断、个体化治疗、改善预后具有重要的临床意义。该文从循环肿瘤细胞、循环肿瘤 DNA、微小 RNA 等方面对液体活检在乳腺癌中的研究进展作一综述。

[**关键词**] 液体活检; 乳腺癌; 循环肿瘤细胞; 循环肿瘤 DNA; 微小 RNA

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Research progress of liquid biopsy in diagnosis and treatment of breast cancer *SHEN Jia-yue, TANG Xiao-qi, ZHOU Tao-sheng, et al. Department of Gastrointestinal and Glandular Surgery, the First Affiliated Hospital of Guangxi Medical University, Nanning* 530021, *China*

[**Abstract**] As an emerging detection technology, liquid biopsy is mainly used to take samples of patients' blood, urine, saliva and other body fluids by a non-invasive or minimally invasive way to detect cancer markers in them for diagnosis, prognosis assessment and follow-up. Liquid biopsy technique has important clinical significance for the early diagnosis, individualized treatment and improvement of prognosis of breast cancer. This paper introduces the research progress of liquid biopsy in breast cancer from the aspects of circulating tumor cells(CTCs), circulating tumor deoxyribonucleic acid(ctDNA) and micro ribonucleic acid(microRNA, miRNA).

[**Key words**] Liquid biopsy; Breast cancer; Circulating tumor cells(CTCs); Circulating tumor deoxyribonucleic acid(ctDNA); Micro ribonucleic acid(microRNA, miRNA)

乳腺癌是严重损害我国女性健康的恶性肿瘤[1]。如何在超早期诊断乳腺癌、动态评估乳腺癌治疗疗效及精准监测乳腺癌的复发转移是临床实践中的难点及热点。目前乳腺癌诊疗依赖宏观的临床资料,包括影像学检查、活检病理结果等,难以超早期评估和诊断病变。传统的组织活检方法受限于肿瘤的大小、取材部位的定位等条件。对于微小的肿瘤病灶发现不及时,导致病情延误甚至肿瘤转移,而侵入式的取材方式也给患者带来一定的风险(如出血和感染等)。液体活检作为一种新兴的肿瘤检测方法,主要通过无创或微创的方式对患者的血液、尿液、唾液等体液取样,检测所取体液中的肿瘤生物标志物,如循