

## 雌激素在糖尿病胃轻瘫中的作用

姜亚, 吴高珏, 汤玉蓉, 林琳

### ■背景资料

糖尿病胃轻瘫(diabetic gastroparesis, DGP)是糖尿病(diabetes mellitus, DM)的重要并发症之一, 损害患者的生活质量, 并且不利于血糖的控制。胃排空延迟是诊断胃轻瘫的客观指标, 具有重要意义。DGP患者中女性居多, 且患者症状随体内雌激素水平波动而变化, 本文旨在探讨雌激素对DGP患者胃排空的作用。

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### Role of estrogen in diabetic gastroparesis

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### Abstract

Gastroparesis is a highly prevalent chronic disorder of the stomach, which is characterized by delayed gastric emptying and accompanied by a series of upper gastrointestinal symptoms. Diabetic gastroparesis (DGP) is one of the severe complications of diabetes, seriously affecting the patient's quality of life. At present, the pathogenesis of DGP is still unclear. The majority of DGP patients are women, and women's symptoms change with the fluctuation of the level of estrogen.

Therefore, we speculate that estrogen may play an vital role in the stomach motility. Gastric emptying is an objective index for the diagnosis of gastroparesis. This article reviews the role of estrogen in DGP and the possible mechanisms.

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Key Words: Estrogen; Diabetic gastroparesis; Gastric emptying; Nitric oxide

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### 摘要

胃轻瘫是临床常见的胃动力障碍性疾病, 以非梗阻因素导致的胃排空延迟为特点, 伴有一系列上消化道症状。糖尿病胃轻瘫(diabetic gastroparesis, DGP)是糖尿病的重要并发症之一, 严重损害患者的生活质量。目前, DGP的发病机制尚不明确。DGP患者中女性居多, 并且女性患者的症状随体内雌激素水平的波动而变化, 推测雌激素可影响胃运动。胃排空是诊断胃轻瘫的客观指标, 本文就DGP以及雌激素对胃排空的可能作用机制就现有文献进行综述。

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关键词: 雌激素; 糖尿病胃轻瘫; 胃排空; 一氧化氮

核心提示: 雌激素参与糖尿病胃轻瘫(diabetic

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gastroparesis, DGP)的发病机制, 既往研究认为雌激素减缓胃肠运动, 抑制胃排空. 但在DGP中, 研究者们发现雌激素可以通过抗氧化保护自主神经功能, 直接或通过Cajal间质细胞(interstitial cell of Cajal)间接维护一氧化氮(nitric oxide)信号通路协调胃十二指肠运动, 从而改善患者的胃排空.

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## 0 引言

胃轻瘫是临床常见的胃动力障碍性疾病, 以非梗阻因素导致的胃排空延迟为特点, 伴有上消化道症状, 如: 餐后饱胀、早饱、胀气、恶心、呕吐等<sup>[1-3]</sup>. 常见病因: 特发性、糖尿病(diabetes mellitus, DM)、手术后以及风湿免疫性疾病等<sup>[4,5]</sup>. 糖尿病胃轻瘫(diabetic gastroparesis, DGP)是DM的重要并发症之一, 影响患者的进食、消化与吸收, 导致营养不良, 并且干扰食物及药物代谢, 不利于血糖的控制<sup>[6,7]</sup>, 严重损害患者的生活质量.

胃轻瘫患者中女性居多, Jones等<sup>[8]</sup>发现, DM患者中DGP男女发病率比为1:4, 机制不明. 女性患者的症状可随体内雌激素水平的波动而变化<sup>[9]</sup>, 推测雌激素可影响胃运动. 本文就DGP以及雌激素对胃排空的作用综述如下.

## 1 胃排空与DGP

**1.1 胃排空的生理特点及影响因素** 胃排空由胃底、胃体、胃窦及幽门的协调运动共同完成: 胃底容受性舒张来储存食物, 胃体蠕动将食物向胃远端输送, 胃窦强力收缩、胃内压升高以及幽门括约肌舒张将食物传送至十二指肠, 完成胃排空<sup>[10]</sup>.

胃排空受自主神经、肠神经系统(enteric nervous system, ENS)、Cajal间质细胞(interstitial cell of Cajal, ICC)、平滑肌细胞(smooth muscle cell, SMC)共同调节<sup>[11,12]</sup>. 以上某一环节出现障碍, 正常胃排空过程即被打破<sup>[13]</sup>. 此外, 胃运动还受到多种胃肠激素的调控, 如胃泌素、5-羟色胺等加快胃排空, 而抑胃肽、促胰液素、胆囊收缩素等则延迟胃排空<sup>[14]</sup>.

**1.2 DGP的可能机制** 一项针对227例1型糖尿

病(type 1 diabetes mellitus, T1DM)患者、360例2型糖尿病(type 2 diabetes mellitus, T2DM)患者及639例非DM人群, 为期10年的前瞻性研究中, Choung等<sup>[15]</sup>发现T1DM胃轻瘫发病率为5.2%, T2DM为1.0%, 非DM人群为0.2%. 胃轻瘫具有2个重要的诊断条件: (1)胃排空延迟; (2)上消化道症状. 胃轻瘫症状与胃排空有时呈不平行关系, 因为症状不仅与胃排空速率相关, 还受自主神经的传入神经、胃感觉、分泌等影响<sup>[10,16]</sup>, 但胃排空延迟是诊断胃轻瘫的客观指标, 具有重要价值.

DGP的可能机制: (1)自主神经损伤<sup>[17]</sup>; (2)ENS受损<sup>[18]</sup>; (3)ICC缺失<sup>[19,20]</sup>; (4)SMC异常<sup>[20]</sup>; (5)DM与其他激素的相互作用<sup>[21,22]</sup>. 上述损伤因素可导致胃底的容受性异常、胃体运动节律紊乱、胃窦收缩力减弱、幽门痉挛、胃窦十二指肠运动失调<sup>[11]</sup>等, 影响正常的胃排空.

## 2 雌激素在DGP中的作用

**2.1 雌激素与胃排空** 正常人群中, 女性的胃窦十二指肠运动弱于男性, 胃排空时间较长<sup>[23,24]</sup>. 动物研究<sup>[25]</sup>也发现, 雌性大鼠较雄鼠胃窦收缩力弱并且胃内压低.

雌激素对DM患者胃排空的影响尚有争议. Showkat Ali等<sup>[26]</sup>在一项动物实验中发现, DM大鼠血浆雌激素水平较对照组高, 伴胃排空延迟. 与此同时, Dickman等<sup>[27]</sup>与Esfahlan等<sup>[28]</sup>研究发现, 肥胖合并难以控制的T2DM女性更易患胃轻瘫, 此类患者血浆雌激素水平与雌激素受体(estrogen receptor, ER)表达均较对照组高, 过多的脂肪组织可以促使体内雄激素转化为雌激素, 减质量可能会改善此类患者的症状, 认为雌激素对延迟的胃排空有一定作用. 但尚不能排除糖脂代谢异常对胃排空的干扰作用.

有部分学者<sup>[29,30]</sup>持相反意见, 他们认为, DM可导致人和动物血清雌激素水平降低, 而雌激素的缺乏会延迟胃排空; Kim<sup>[31]</sup>与Gangula等<sup>[32]</sup>研究也表明: DM的长期高血糖可降低血浆雌激素水平及其受体表达. 雌激素的缺乏可能干扰胃十二指肠的协调运动, 从而导致胃轻瘫.

Rao<sup>[33]</sup>综合多项临床研究、基础研究认为: 上述结论的分歧可能与胃排空、激素水平测量方法、DM类型、病程、严重程度的差异, 以及进食的食物是否含有植物雌激素等因素相关.

## ■ 研究前沿

DGP是一类内分泌疾病引发的消化系统并发症, 需要两个学科相互协作控制病情. 女性患者在DGP中占有相当大的比重, 既往关于雌激素影响胃肠运动的研究有很多, 因此有必要探讨雌激素在DM状态下对胃排空的影响. 目前关于雌激素对DGP胃排空的作用有较多争议, 但从一氧化氮(nitric oxide, NO)通路上解释, 雌激素对胃十二指肠的协调运动有保护作用. 雌激素对DGP胃排空的具体作用机制仍不明确, 以下问题有待进一步研究: (1)雌激素对DGP作用的性别差异及具体机制; (2)雌激素与DM在DGP发病及病程发展中的相互作用.

## ■ 相关报道

NO通路是雌激素影响胃排空的公认机制: 雌激素可以增加胃神经型一氧化氮合酶(neuronal nitric oxide synthase, nNOS)表达, 促进NO的释放、经过NO信号通路, 最后松弛肌肉. 在生理状态下, 雌激素可增加NO释放、减弱胃窦收缩力、减慢胃排空. 但是, 在DM状态下, 研究者们发现DM小鼠/大鼠胃底、幽门的nNOS密度较对照组减低, nNOS蛋白表达下降, 活性降低, 导致NO合成障碍, 胃底张力增大、容受性舒张障碍, 幽门松弛受阻、胃内压升高、胃排空延迟. 推测女性DM状态体内雌激素减低、胃NO信号通路受损是DGP的发病机制.

### ■ 创新盘点

本文从胃运动的生理、胃轻瘫的发病机制、雌激素对DGP的作用及其相关机制方面做了系统详尽的阐述。结合相关文献, 本文归纳出雌激素如何通过氧化应激、NO信号通路及Cajal间质细胞(interstitial cell of Cajal)介导胃轻瘫的病理生理机制, 为雌激素在DGP中的保护作用提供了依据; 并提出了今后探讨雌激素对DGP的具体作用机制的研究方向。

**2.2 雌激素的生理性波动与胃排空** 女性雌激素水平随月经周期、妊娠、绝经、口服避孕药、雌激素替代治疗等变化而波动, 从而影响胃肠道运动。研究<sup>[34-36]</sup>表明, 约80%的DGP患者为女性, 并且胃轻瘫与绝经、月经周期等相关。

正常女性胃肠动力在排卵期和妊娠时明显减弱<sup>[8,37]</sup>。绝经前女性、妊娠妇女、绝经后接受激素替代治疗的女性均比同龄男性的胃排空时间延长<sup>[25]</sup>, 可能与特定时期雌激素水平升高、胃动力下降相关, 但不排除孕激素的干扰作用<sup>[37]</sup>。

Verrengia等<sup>[9]</sup>发现, 女性胃轻瘫患者症状随月经周期而变化: 黄体期恶心、早饱加重, 而口服避孕药患者体内雌激素维持在稳定水平, 因此未发现她们胃轻瘫症状的周期性变化, 但该研究中未检测胃排空时间, 仅以胃轻瘫症状衡量雌激素的作用, 难以评估雌激素对胃排空速率的客观影响。

但是Brenna等<sup>[38]</sup>发现, 健康女性卵泡期的“葡萄糖胃排空速率(单位时间内葡萄糖经胃排至小肠的量)”小于黄体期, 而此时体内雌激素水平相对较低, 胃排空减慢可能与胃内容物的性质相关。

Camilleri等<sup>[11]</sup>在小鼠实验中发现, 雌激素缺乏可导致糖脂代谢障碍、增加肥胖、T2DM的发生, 而DM导致的“下丘脑-垂体-卵巢轴”功能障碍又加重了雌性体内的雌激素减少, 形成恶性循环, 导致胃轻瘫。

总之, 生理状态下, 雌激素对胃动力有抑制作用, 但在DGP中, 雌激素缺乏似乎更多参与到DGP的病理过程, 那么雌激素对于胃排空的作用是否直接抑或间接? 可能与疾病状态、雌激素绝对量等相关, 还需要多中心、分层、控制变量的大样本研究提供证据。

## 3 雌激素影响DGP胃排空的机制

雌激素影响胃排空的机制尚不明确, 与既往观点不同的是, 目前大多学者认为雌激素的缺乏诱发DGP的胃排空延迟, 可能机制如下:

**3.1 雌激素的抗氧化作用** DM状态下, 高血糖诱发氧化应激, 通过以下机制引发DGP: (1)自主神经发生渐进性病变, 如神经细胞(尤其是迷走神经)凋亡等<sup>[39]</sup>, 损伤迷走神经调控的胃运动、致胃排空异常; (2)降低一氧化氮(nitric oxide, NO)的生物利用度<sup>[40]</sup>, 使NO信号传导障

碍, 胃十二指肠协调运动受损; (3)使L型Ca<sup>2+</sup>通道失活从而减弱Ca<sup>2+</sup>依赖的肌收缩: 胃窦SMC L型Ca<sup>2+</sup>电流减弱、胃窦收缩受抑可能与胃排空延迟有关<sup>[41]</sup>。而雌激素具有重要的抗氧化作用, 保护细胞(包括SMC、神经元等)免遭氧化损伤<sup>[42-44]</sup>, 但其在DGP中的作用还需进一步证实。

**3.2 雌激素与NO信号通路** NO有抑制肌肉(如: 平滑肌、括约肌等)收缩的作用, ENS中神经型一氧化氮合酶(neuronal nitric oxide synthase, nNOS)表达减少或活性减低可降低幽门顺应性、幽门舒张障碍、延迟胃排空<sup>[16,32]</sup>。雌激素通过NO调节胃窦、幽门的协调运动、影响胃排空。但是, 雌激素增加或抑制nNOS表达及活性仍有争议。

NO信号通路受损是公认的DGP机制之一: 雌激素可以增加胃nNOS表达, 促进NO的释放<sup>[45,46]</sup>、经过NO信号通路, 最后松弛肌肉<sup>[40]</sup>。在生理状态下, 雌激素可增加NO释放、减弱胃窦收缩力、减慢胃排空。正常女性胃窦的nNOS二聚体、NO水平、NO对肌肉的松弛作用均比同龄男性高, 胃排空时间延长<sup>[25]</sup>。动物实验还证实, 在发情期(雌激素升高)时, 胃窦收缩减弱、胃排空减慢。

但是, 在DM状态下, Lu等<sup>[6]</sup>发现DM小鼠胃底、幽门的nNOS密度较对照组减低, nNOS蛋白表达也下降, 胃底张力增大、容受性舒张障碍, 幽门松弛受阻、胃排空延迟。Gangula等<sup>[47]</sup>也发现, 雌性大鼠胃部nNOS表达减少、活性降低导致NO合成障碍、幽门肥厚、松弛障碍、胃内压升高、胃排空延迟, 而雄鼠胃部NO介导的松弛作用仍在, 推测女性DM状态体内雌激素减低、胃NO信号通路受损是胃轻瘫的发病机制。

四氢生物蝶呤(tetrahydrobiopterin, BH4)是nNOSα二聚化的辅助因子, 三磷酸鸟苷环水解酶抗体(GTP cyclohydrolase 1, GCH-1)和二氢叶酸还原酶(dihydrofolate reductase, DHFR)将二氢生物蝶呤(dihydrobiopterin, BH2)合成BH4。研究<sup>[29,47]</sup>发现, 卵泡刺激素受体敲除小鼠由于缺乏雌激素, 胃GCH-1和DHFR表达均降低, BH4合成减少, nNOS二聚物表达降低, NO生成减少, 幽门括约肌松弛障碍、胃出口功能性梗阻致小鼠胃排空延迟。雌激素可通过与ER结合, 上调GCH-1, 增加BH4的表达, 恢复



nNOS活性, 增加NO释放、缓解胃轻瘫<sup>[25,32]</sup>. 由此可见, 雌激素绝对水平的降低可导致NO信号通路受损、胃窦收缩正常但幽门痉挛、胃内压增高, 导致胃排空障碍.

然而, Showkat Ali等<sup>[26]</sup>却发现: DGP大鼠血浆雌激素及ER $\alpha$ 表达上升, 而胃窦、幽门nNOS表达下降、活性减弱, 胃排空延迟. 本研究提示雌激素可降低nNOS表达及活性. 但该研究只检测了大鼠处死前的一次雌激素浓度, 没有提示雌激素浓度变化与nNOS表达的相关性, 其结论有一定的局限性.

3.3 雌激素与ICC 有文献报道, ICC上表达蛋白激酶G(protein kinase G, PKG)和鸟苷酸环化酶, 作为NO的作用靶点, 介导抑制性神经传导通路<sup>[48,49]</sup>, 调控胃排空. Micci等<sup>[45]</sup>在动物实验中发现: 胃轻瘫雄鼠多有ICC缺失. Oh等<sup>[50]</sup>提出nNOS表达下降与ICC的缺失相关, 当补充NO供体时, ICC表达也会相应增加. 通过以上研究, 我们推测雌激素可通过影响NO的生成而改变ICC的表达, 从而实现对胃排空的调节. 研究者们<sup>[51,52]</sup>发现, 胃轻瘫患者存在胃ICC缺失, 同时伴有胃电图(electrogastrogram, EGG)异常, 产生无效蠕动, 其中DGP患者居多, 但胃ICC缺失的具体原因尚不清楚.

## 4 结论

DGP是DM的重要并发症之一, 常见于女性患者, 雌激素可以调节患者的胃排空速率. 在DGP中, 雌激素可通过抗氧化应激保护自主神经、直接或通过ICC间接维持NO通路正常等协调胃运动, 从而改善患者的胃排空. 但雌激素对DGP胃排空的具体作用机制仍不明确, 以下问题有待进一步研究: (1)雌激素对DGP作用的性别差异及具体机制; (2)雌激素与DM在DPG发病及病程发展中的相互作用; (3)有研究<sup>[45]</sup>提出, 雌激素可以通过调节NO通路的上游或下游物质改善胃排空, 为治疗DGP提供了新思路, 不过, 还需要更多的循证学依据作支撑.

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## ■应用要点

目前, DGP的治疗主要依赖促动力药物、胃肠起搏、针灸等方法, 本文结合相关文献综述了雌激素对DGP的作用, 发现雌激素可以通过调节NO通路的上游或下游物质协调胃十二指肠运动、改善胃排空, 为治疗DGP提供了新思路.

## ■名词解释

糖尿病胃轻瘫 (DGP): 是DM胃肠植物神经病变常见的症状。以非梗阻因素导致的胃排空延迟为特点, 典型症状为腹胀、早饱、厌食、嗝气、恶心、呕吐、体质量减轻, 症状通常在餐后较为严重; 胃排空延迟: 指胃内容物积贮而未及时排空。凡呕吐出4-6 h以前摄入的食物, 或空腹8 h以上, 胃内残留量>200 mL者, 表示有胃排空延迟。

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# 同行评价

本文内容新颖, 有一定的科学性, 较全面地综述了“雌激素在糖尿病胃轻瘫中的作用”, 探讨雌激素在DM状态下对胃排空的影响, 对于防治DGP和进一步明确DGP的发病机制有一定的指导意义。题目确切, 内容叙述较清晰, 逻辑性较好, 具有一定的可读性。

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