

·综述·

胆胰分流术与胃旁路术治疗 2 型糖尿病的机制比较

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【摘要】 临床研究发现，减重手术可以改善甚至治愈糖尿病。采用不同术式其效果不一，其中胆胰分流术(BPD)对糖尿病治愈率最高，达 98%以上；其次为 Roux-en-Y 胃旁路术(RGBP)，可达 80%。但这两种手术对于治疗糖尿病的具体作用机制尚不明确，且争议较多。BPD 与 RGBP 术后患者体内多种激素水平、尤其是肠道激素 GLP-1 和 GIP 的变化并不一致，很难用前肠及后肠假说完全解释。本综述根据国内外最新研究成果，比较了 BPD 及 RGBP 两种术式的解剖结构及术后 GLP-1 和 GIP 的变化，并对两种术式在治疗糖尿病上可能存在的不同机制进行了探讨。

【关键词】 胆胰分流术；胃旁路术；2 型糖尿病；类胰高血糖素肽 1；糖依赖性促胰岛素肽

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【Abstract】 A large number of clinical studies indicate that bariatric surgery leads to improvement or resolution of type 2 diabetes. The outcomes vary depending on procedure adopted. Biliopancreatic diversion (BPD) is associated with the highest cure rate (98%), followed by Roux-en-Y gastric bypass (RGBP) (80%). However, the mechanism is still unclear and controversial. The changes of many hormones after surgery are different between BPD and RGBP, especially some gastrointestinal hormones such as GLP-1 and GIP, however it cannot be fully explained by the widely known hindgut hypothesis and the foregut hypothesis. This review is intended to compare the anatomical structures and postoperative gastrointestinal hormones GLP-1 and GIP changes between the two procedures according to the latest researches in the world, and discuss different mechanisms which may take effect in improving diabetes.

【Key word】 Biliopancreatic diversion; Roux-en-Y gastric bypass; Type 2 diabetes; Gastrointestinal hormones; GLP-1, GIP

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随着生活水平的提高，肥胖和糖尿病的发病率逐年增长。糖尿病已是严重威胁人类健康的慢性代谢病。目前，对于 2 型糖尿病的主要治疗是通过饮食控制、运动、减肥及药物治疗，但效果不佳。随着减重手术后 2 型糖尿病显著改善的意外发现，为糖尿病的根治带来了希望。人们越来越关注外科手术对于糖尿病的治疗，甚至有人提出了“代谢疾病手术”的新概念。在比较多种手术方式之后发现，胆胰分流术(biliopancreatic diversion, BPD)和 Roux-en-Y 胃旁路术(Roux-en-Y gastric bypass, RGBP)对于糖尿病的治愈率均达 80%以上。此外，研究发现，血糖在术后第 2 天即出现改善，此疗效明显地早于体质量下降。这些观察结果表明，除体质量减轻的因素外，应该还有其他的重要因素改善了胰岛细胞功能，血糖的改善可能是术后解剖结构改变所致的肠道激素水平改变引起。

一、BPD 与 RGBP 手术解剖的差异

1. BPD 方式：先将远端胃切除，保留上端功能胃，使其容量为 200~500 ml，然后将上端残余胃与小肠末端 250 cm 处吻合，胆胰支则与距离回盲瓣 50 cm 处的回肠吻合。此术式旷置了大部分胃、十二指肠、空肠和部分近端回肠^[1]。

2. RGBP 方式：是将远端胃切除仅保留一小于 30 ml 的胃囊，将上端残余胃囊与距离 Treitz 韧带 30~75 cm 处的空肠吻合，Roux 肠祥的长度为 75~100 cm，在 BMI 大于 50 kg/cm² 的患者保留 Roux 肠祥的长度为 100~250 cm^[1]。此术式人为地旷置了 95% 的胃和全部十二指肠及部分空肠。

3. BPD 与 RGBP 的异同点：此两种术式都旷置了十二指肠和空肠，未消化的食物可以提早到达回肠。但 BPD 术后的共同通路在回肠末端；而 RGBP 术后的共同通道在空肠。且 BPD 术后，大部分胃被切除，前肠内基本没有胃液；而 RGBP 术后，虽然大部分胃被旷置，但仍未与前肠分离。

二、BPD 与 RGBP 两种术式治疗糖尿病疗效的比较

在治疗糖尿病方面，很多研究发现，RGBP 与 BPD 都能显著改善糖尿病，但前者疗效不如后者。在一项包括 237 例患者的研究中发现，BPD 术后 10 年，98% 的患者糖尿病完全治愈(血糖正常，无需用药，自由饮食)^[2]。同样，Buchwald 等^[3-4]通过 Meta 分析发现，在重度肥胖的 2 型糖尿病患者中，BPD 组的糖尿病缓解率为 98.9%。而多数报道，RGBP 术后糖尿病治愈率为 74%~89%^[3,5-8]。另有多项研究表明，在 BMI 小于 35 kg/cm² 的非严重肥胖伴 2 型糖尿病患者中，不管早期还是长期疗效，BPD 的糖尿病治疗效果优于 RGBP^[9-12]。

BPD 改善糖尿病的疗效独立于体质量的下降。

Scopinaro 等^[9]报道了一组非重度肥胖患者(BMI 中位数为 33.2 kg/cm²)在 BPD 术后糖尿病得到显著改善,而体质量没有明显减轻。说明 BPD 有独立于体质量改变之外的其他特异性因素给糖尿病的治疗带来了益处,而这些已经通过胰岛素反应的早期正常化(体质量尚无明显减轻时)得到了证实^[13]。

三、BPD 与 RGBP 的降糖机制

手术改善糖尿病的机制已成为研究的热点,但具体机制尚不明确。目前,多数学者认为,BPD 与 RGBP 改善糖尿病的机制主要基于后肠假说和前肠假说。

1. 后肠假说:是指胃肠绕道后,未消化或不完全消化的食物快速到达远端小肠,刺激远端小肠产生类胰高血糖素肽 1(GLP-1)等肠促胰岛素促进胰岛素分泌,改善胰岛素敏感性^[14]。在动物及人体的回肠转位术的多项研究结果是该假说有力的证据^[15-18]。

2. 前肠假说:是指阻断十二指肠和空肠黏膜与营养素的接触,从而可能阻止了一种能促进胰岛素抵抗的激素分泌^[19]。这种抗肠促胰岛素与肠促胰岛素之间的平衡影响着糖代谢。有研究,通过比较十二指肠空肠绕道手术的大鼠和胃空肠吻合术的大鼠以及比较大鼠十二指肠绕道术和回肠转位术的实验得出结论:前肠旷置和早期刺激后肠提高糖耐量的效果类似,都能改善糖尿病,且都提高 GLP-1 的水平,但前者较后者低,并认为可能是由于不同机制所致,后者主要是提高 GLP-1 等肠促胰岛素水平从而改善 2 型糖尿病,而前者可能存在别的因素^[20-21]。另有研究,通过大鼠腔内十二指肠空肠袖带术(endoluminal duodenal-jejunal sleeve, ELS)同样验证了前肠假说^[22-26]。

3. 其他可能的机制:BPD 手术治疗糖尿病疗效优于 RGBP,BPD 及 RGBP 手术后患者糖尿病的改善及肠道激素 GLP-1 和糖依赖性促胰岛素肽(GIP)的改变无法用后肠假说和前肠假说完全解释,且存有较多矛盾之处。提示,除上面两种假说外可能还存在其他的机制,并且两者可能通过不同的机制改善糖尿病。

四、BPD 与 RGBP 术后激素水平的改变

1.BPD 术后:关于 BPD 术后 GLP-1 及胰岛素水平改变的报道不尽相同。大部分研究发现,GLP-1 分泌增加,但胰岛素分泌率降低,并认为胰岛素分泌降低是由于胰岛素敏感性增高所继发而来的,显然,BPD 术式改善糖尿病的主要机制是迅速提高了胰岛素的敏感性^[10,27-38]。但 GLP-1 的分泌增加不能完全解释胰岛素敏感性的增加^[36]。Mingrone 等^[39]在一项比较糖耐量正常患者和糖尿病患者 BPD 术后 GLP-1 和 GIP 激素水平改变的研究中发现,术后在糖耐量正常组 GLP-1 明显升高,而在糖尿病组没有显著升高,GIP 在糖尿病组降低,而在糖耐量正常组没有改变,胰岛素分泌减少,胰岛素敏感性明显增加($P<0.01$),双因素方差分析显示,GIP 对于 BPD 术后糖尿病的影响比 GLP-1 更主要。其他研究也发现,BPD 术后 GIP 水平下降^[36]。有研究表明,胰岛素抵抗的糖尿病与 GIP 水平增高有关^[40-41]。另有研究发现,小鼠

GIP 受体基因的敲除与糖尿病的改善和胰岛素抵抗改善密切相关^[42-43]。GIP 受体抗体改善节食患者的糖耐量和胰岛素分泌反应也支持 GIP 对于改善胰岛素抵抗的重要作用^[44]。因此目前认为,BPD 手术治疗糖尿病主要是通过提高胰岛素敏感性来实现的,而 GIP 减少是胰岛素敏感性提高的一个重要因素。

2. RGBP 术后:RGBP 术后空腹 GLP-1 水平在不同研究报告不一^[36,45-50]。但有关术后患者餐后 GLP-1 的研究报告基本一致,都是升高的,既高于手术前,也高于非手术组^[49,51-59]。Pournaras 等^[60]在一项研究中报道,RGBP 术后 2 d 内,糖尿病患者的餐后 GLP-1 和胰岛素分泌及 δ 胰岛素(餐后 15 min 与餐前胰岛素水平的差值)分泌均有明显的增加,胰岛素抵抗在术后 7 d 降低 44%。推测胰岛素分泌增加与 GLP-1 分泌增加有关,尤其是 δ 胰岛素分泌的提高是由 GLP-1 的反应性增加引起^[46]。

RGBP 术后糖耐量试验中发现,GIP 水平升高^[46,48]。也有研究报道了胃旁路术后 6 个月至 20 年,餐后 GIP 水平的升高^[61]。目前认为,RGBP 术后胰岛功能的改善主要是通过肠促胰岛素(包括 GLP-1 和 GIP)分泌增加致胰岛素分泌增加起作用的。因此,有学者认为,胰岛素的过度分泌和摄入糖和碳水化合物的吸收过快,可以解释一些术后低血糖的现象^[61]。

五、目前的主要争议

我们知道,GLP-1 是由位于回肠的 L 细胞分泌的。根据后肠假说机制,与 RGBP 术式相比,BPD 术后,更多的未完全消化的营养素快速地到达远端小肠并刺激 L 细胞,应该有更多的 GLP-1 释放,有更多胰岛素分泌。而实际观察中却并非如此,推测可能是由于 BPD 术后胰岛素敏感性显著提高致胰岛素分泌代偿性减少,但这仍不能完全解释 BPD 术后 GLP-1 未有显著增加的原因,而糖耐量正常组的患者 BPD 术后 GLP-1 明显增加,是否有可能糖尿病患者 L 细胞分布较正常者不同? 目前尚未有相关研究报道。

另一方面,动物实验已经发现,十二指肠及空肠的旷置可导致胰岛素敏感性显著增加,但同样旷置了十二指肠和空肠的 RGBP 术后,胰岛素敏感性的提高不如 BPD 术后明显。胰岛素的敏感性与 GIP 水平关系密切,GIP 主要由十二指肠和空肠近端的 K 细胞分泌。虽然 RGBP 术后十二指肠及空肠也被旷置,但 GIP 的水平未见明显减低,甚至分泌增加,其机制尚不确定,可能还有其他手术所致的未知因素调节胰岛素的敏感性^[36,62-63]。另外,Mingrone 等^[39]发现,BPD 术后在糖耐量正常组中也未发现 GIP 水平改变。Rubino 等^[45]也发现,RGBP 术后,在非糖尿病肥胖患者中也未发现 GIP 的减少。这可能由于糖耐量正常者与糖尿病患者 K 细胞分布不同有关。BPD 术后,胰岛素敏感性较 RGBP 术后明显增高可能还与这两种术式的解剖结构的不同有关。

RGBP 术后,只保留了约 30 ml 的小胃囊,95% 的残胃仍与胆胰支相连通,虽然旷置的前肠没有食物的刺激,但仍会有胃酸与胆胰液的混合。而 BPD 术后,没有胃液和胆胰液的接触,推测前肠分泌成分不确定的抗肠促胰岛素可能不

只是由营养物质刺激前肠黏膜产生，胃液或胃液及胆胰液的混合物也可能刺激前肠分泌抗肠促胰岛素。

与RGBP手术相比,BPD术式的胆胰液及营养液混合的共同通道为回肠末端50 cm,脂肪和淀粉在此段吸收,BPD术后,脂肪吸收受限,细胞内脂肪消耗增加,尤其是肌细胞,恢复葡萄糖作为能量源的利用,从而减少胰岛素抵抗^[27,64]。Briatore等^[65]也认为,BPD术后,脂肪吸收减少,脂毒性的下降可能是改善胰岛素抵抗的机制。Scopinaro等^[66]研究发现,在共同通道延长的BPD手术有20%的患者在术后8~14年有糖尿病反弹的现象,推测可能是由于脂肪吸收增加而影响了胰岛素的敏感性。但目前尚缺乏大样本的研究。

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·医学信息·

新辅助治疗是否会改变 K-ras 和微卫星不稳定基因在直肠腺癌中的检测结果

新辅助放化疗已经越来越多地应用于治疗晚期直肠癌,同时,分子检测也已成为结直肠癌患者诊断和治疗的组成部分。微卫星不稳定(MSI)和K-ras基因检测可预测肿瘤对表皮生长因子受体抑制剂化疗的反应。而新辅助放化疗后的遗传毒性作用对分子诊断测试结果的影响是未知的,如果新辅助治疗改变了分子检测的结果,就可能误导临床决策。这就提出了新辅助放化疗后的肿瘤组织进行DNA分子检测是否恰当的问题。本研究旨在探讨新辅助治疗前后,直肠腺癌的K-ras和MSI基因检测结果是否发生改变。

本研究比较了17例直肠腺癌患者新辅助治疗前后MSI和K-ras的检测情况。结果,17例直肠癌组织新辅助放化疗前后,MSI和K-ras检测结果未改变($P=1.000, 95\% CI: 0.3969 \sim 2.520$)。其中17例(100%)肿瘤灶均微卫星稳定;12例(72%)K-ras基因为野生型,5例(28%)K-ras基因12和13位点突变。

结论:新辅助放化疗不会改变K-ras基因12或13位点密码子以及MSI在直肠腺癌的检测结果,这为新辅助治疗前后进行分子检测的确定性提供了证据。

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