·综 述·

# 胰高血糖素样肽 -1 受体激动剂联合基础胰岛素疗效研究进展

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**摘要：**胰高血糖素样肽 -1 受体激动剂（glucagon-like peptide-1 receptor agonist，GLP-1RA）与基础胰岛素的复合制剂是近年来关注的热点，其对 2 型糖尿病（type 2 diabetes mellitus）患者疗效显著且安全性良好，可有效控制血糖水平，减少体质量增加、胃肠道不良反应及心血管疾病的发生风险，降低低血糖（hypoglycemia）发生率及治疗成本，提高患者依从性。现对 GLP-1RA 和基础胰岛素复合制剂研究进展作一综述，旨在阐明其作用机理及疗效，为临床提供一定参考。

**关键词：**胰高血糖素样肽 -1 受体激动剂；胰岛素；复合制剂
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# Research progress on the efficacy of glucagon-like peptide-1 receptor agonists combined with basal insulin

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**Abstract:** In recent years, the complex preparation of glucagon-like peptide-1 receptor agonist（GLP-1RA）and basal insulin has attracted much attention. It has significant efficacy and good safety in patients with type 2 diabetes mellitus, which can effectively control blood glucose level, reduce body mass gain, gastrointestinal adverse reactions and the risk of cardiovascular diseases, reduce the incidence of hypoglycemia and treatment costs, and improve patient compliance. This article reviewed the research progress of GLP-1RA and basic insulin compound preparation, to clarify its mechanism and efficacy, and provide certain reference for clinical practice.

**Key words:** glucagon-like peptide-1 receptor agonist; insulin; compound preparation

近年来，糖尿病（diabetes mellitus，DM）患病率逐年升高，2021 年全球 DM 患者达 5.37 亿例，至 2045 年预计将增加至 7.84 亿例。我国 DM 患病率同样呈持续增长趋势，最新流行病学数据显示我国 DM 患病率为 12.8%，居全球首位[1]。

DM 患者中，糖化血红蛋白（glycosylated hemoglobin，HbA1c）达标（＜ 7%）率仅为 47.7%，若以 HbA1c ＜ 6.5% 为达标，达标率仅有 30.7%[2]。2 型 DM（type 2 diabetes mellitus，T2DM）患者胰岛 β 细胞功能随疾病进展而减退[3]，心血管疾病（cardiovascular disease，CVD）发生风险增高[4]，且肠促胰岛素效应明显减弱[5]。

胰高血糖素样肽 -1 受体激动剂（glucagon-like peptide-1 receptor agonist，GLP-1RA）不仅可部分恢复 T2DM 受损 β 细胞胰岛素反应，增强 GLP-1 活性，保护心血管，且可降低低血糖（hypoglycemia）和体质量增加的发生风险[3]。基础胰岛素可模拟正常人

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体生理性胰岛素分泌作用，帮助有效控制基础血糖水平。因此，GLP-1RA 与基础胰岛素复合制剂可实现“机制互补，靶向调节”[5]。

## 1 GLP-1RA 和基础胰岛素复合制剂概述

GLP-1 是一种由肠道 L 细胞分泌的肠促胰岛素，可促进胰岛β细胞分泌胰岛素，抑制胰高血糖素分泌，控制血糖水平。GLP-1RA 可增加对 GLP-1 受体的持续刺激分泌，模拟天然 GLP-1 作用，起到良好降糖作用。我国上市的 GLP-1RA 依据药代动力学可分为短效的贝那鲁肽（benarutide）、艾塞那肽（exenatide）、利司那肽（lixisenatide），以及相对长效的利拉鲁肽（liraglutide）、艾塞那肽周制剂等[7]。

基础胰岛素指在生理非进食状态下胰岛β细胞持续分泌的胰岛素，约占胰岛素全天分泌总量的 50%。基础胰岛素可通过抑制肝脏中肝糖原分解和糖异生而减少肝糖输出，控制基础血糖水平。DM 患者中，经皮下注射的外源性基础胰岛素药物与内源性基础胰岛素的特性相似。基础胰岛素主要包括中效胰岛素［如精蛋白锌胰岛素（protamine zinc insulin）、长效胰岛素［如地特胰岛素（insulin detemir）、甘精胰岛素（insulin glargine，IGlar）、德谷胰岛素（insulin degu，IDeg）］[6]。

目前，临床上 GLP-1RA 和基础胰岛素的组合有两种固定比例复方制剂[8—9]：IDeg 利拉鲁肽注射液（IDegLira）和 IGlar 利司那肽复方制剂（IGlarLixi）。

## 2 药动学与药效学特性及作用机制

GLP-1RA 和基础胰岛素复合制剂药效学特性稳定。中国药物代谢动力学（pharmacokinetic，PK）试验显示，IDegLira 与单独给药相比，IDeg 和利拉鲁肽单独给药除峰值浓度略低，其他方面 PK 模式相似[10]，这与全球 PK 试验及 DUAL I 中国的结论一致。与 IGlar 相比，IGlarLixi 血浆葡萄糖浓度依赖性降低，较安慰剂具有剂量依赖性延迟。IGlarLixi 5 U/5 μg 还能显著降低餐后 2 小时血糖（2-hour postprandial blood glucose，2hPG）曲线下面积[11]。

GLP-1RA 主要作用于胰腺和肝脏，促进葡萄糖依赖性胰岛素释放，并抑制胰高血糖素分泌。GLP-1RA 可通过促进体质量减轻，降低肌肉脂质水平，改善肌肉胰岛素敏感性，还作用于脑和胃肠道，增强饱腹感，结合并激活全身 GLP-1R 以补充肠道中缺乏的肠促胰岛素效应并延缓胃排空[12]。基础胰岛素模拟胰岛素生理持续释放，调节空腹血糖（fasting blood glucose，FBG），主要作用于脂肪细胞和肝脏，减少脂肪分解，同时抑制肝脏葡萄糖产生[13]。GLP-1RA 和基础胰岛素复合制剂不涉及肾脏对葡萄糖的重吸收，亦覆盖大部分 T2DM 发病机制[13]。GLP-1RA 和基础胰岛素复合制剂结合了 GLP-1RA 和基础胰岛素各自作用特征，控制血糖水平。

## 3 GLP-1RA 和基础胰岛素复合制剂疗效

### 3.1 降糖作用

#### 3.1.1 一般人群降糖效果

GLP-1RA 和基础胰岛素复合制剂可有效降低血糖并延长有效治疗时间，且 HbA1c 降低幅度更大[14—25]。IDegLira 可帮助 89.9% 的 DM 患者控制 HbA1c 水平[20]；IGlarLixi 可同时控制 FBG 和 2hPG[26]。在基础胰岛素和口服降糖药（oral antidiabetic drug，OAD）无法控制的 T2DM 中，IDegLira 治疗 26 周较 IDeg 的 HbA1c、FBG 水平降幅大，自我血糖监测（self-monitoring of blood glucose，SMBG）较基线亦显著降低[23,27]。在 OAD 无法控制的 T2DM 患者中，使用 IDegLira 者 HbA1c ＜ 7.0% 和≤ 6.5% 占比显著高于使用 IDeg 者[28]。IDegLira 对 HbA1c 的改善效果较 IDeg 或甘精胰岛素更佳[29]。此外，较 IGlar U100 组，IDegLira 组需强化治疗的时间显著延长，需强化治疗的患者例数亦更少[30]。

GLP-1RA 和基础胰岛素复合制剂还可有效改善血糖波动。研究显示，IDegLira 组 2hPG 水平在餐后 60、90 和 120 分钟均显著低于 IDegAsp 组，较 IDegAsp 作用时间更长、范围更大[31]。IDegLira 还可改善血糖波动平均振幅、血糖变异性指数和 24 小时平均血糖浓度[32]。与 IDeg、利拉鲁肽组相比，IDegLira 组 SMBG 值在目标范围内（3.9～9.0 mmol/L）

受试者比例更高；与 IDeg 相比，IDegLira 治疗 24 小时内 SMBG 值变化范围更小，间质葡萄糖（interstitial glucose，IG）波动和餐后 IG 增量更少；与利拉鲁肽相比，血糖波动于 IG 目标外的时间明显缩短[33]。

**3.1.2** 老年人群降糖效果

研究显示，对于年龄≥ 65 岁的患者，使用 IDegLira 可改善血糖控制，且总体耐受性良好。对于年龄≥ 75 岁且服用≥ 2 种抗糖药物的 T2DM 患者，以单剂量 IDegLira 代替其他降糖治疗，患者认知功能、体质量指数、FBG、HbA1c、肿瘤坏死因子 -α 水平均有明显改善[34]，但还需更大规模的研究证实这一结论。

**3.2** 降糖外作用

**3.2.1** 减少体质量增加

IDegLira 可为 T2DM 患者带来体质量获益。DUAL 系列研究中，IDegLira 组多有体质量减轻[18—19,21,23—24,35]，LixiLan 系列研究亦证实 IGlarLixi 不增加体质量[36—37]。对基础胰岛素和 OAD 无法控制的 T2DM，IDegLira 组体质量变化优于 IDeg 组[27]。对 OAD 未能控制的 T2DM，IDegLira 组较 IDeg 组体质量减少效果更优[28]。与 IDeg、IGlar U100 相比，IDegLira 在体质量减少方面的结果更佳[29]。一项真实世界研究显示，由其他治疗转为 IDegLira 治疗 6 个月后，T2DM 体质量平均减轻了 0.7 kg[38]。

**3.2.2** 改善心血管风险标志物

GLP-1RA 和基础胰岛素复合制剂与血压、血脂等心血管风险标志物的改善相关。DUAL Ⅱ研究中，除年龄≥ 65 岁者，IDegLira 组脑钠肽水平显著低于 IDeg 组[23]。与基础胰岛素和基础 - 餐时胰岛素治疗相比，IDegLira 治疗 26 周时收缩压均降低，且总胆固醇、低密度脂蛋白胆固醇和游离脂肪酸水平均降低[25]。DUAL Ⅱ、Ⅴ和Ⅶ试验事后分析证实，IDegLira 组心血管风险标志物普遍改善[39—40]，这与 LEAD-6、LEADER 的结论一致[41—42]。长期使用 GLP-1RA 和基础胰岛素复合制剂还可显著降低 CVD 风险升高的 T2DM 患者的并发症的发生率[43—44]。

## 4 安全性

GLP-1RA 和基础胰岛素复合制剂可不良反应发生率，安全性较佳。IDegLira 较 IDeg、IGlar U100 低血糖发生率均较低[18,21—22,45]。IGlarLixi 组达到复合终点 HbA1c ＜ 7% 且无症状性低血糖的患者比例均分别高于 IGlar、利司那肽、GLP-1RA 组[36,46—47]。与 DUAL Ⅰ中的利拉鲁肽组和 DUAL Ⅲ中的 GLP-1RA 组相比，IDegLira 组胃肠道不良事件较少[17,48—49]。IGlarLixi 组恶心、呕吐发生率均分别低于利司那肽、GLP-1RA 组[50]。此外，GLP-1RA 和基础胰岛素复合制剂过敏反应和心血管事件发生率较低，且极少有与服用复合制剂相关的胰腺炎（pancreatitis）、甲状腺髓样癌（medullary thyroid carcinoma）发生[46]。

## 5 成本与患者依从性

GLP-1RA 和基础胰岛素复合制剂可降低 DM 相关并发症发生率，降低治疗成本，提高患者依从性。与其他治疗方案相比，IDegLira、IGlarLixi 能以更低的成本改善临床结果[51—52]。DUAL Ⅶ显示，IDegLira 较 IGlar U100 联合门冬胰岛素的平均费用降低了 3 571 美元[53]。真实世界研究显示，胰岛素更换为 IDegLira 后，患者平均费用差异为（-0.41±0.59）欧元，且多数患者对 IDegLira 满意度更高，包括达到 HbA1c 目标、注射次数和避免体质量增加[54]。事后分析显示，与 IGlar U100 联合门冬胰岛素相比，接受 IDegLira 治疗的患者心理健康领域评分显著提高[55]。IDegLira 可提高 DM 患者治疗满意度和依从性，并改善与 DM 管理、治疗负担和心理健康相关结局。

## 6 结语

GLP-1RA 与基础胰岛素复合制剂可有效控制血糖水平，降低血糖波动和 CVD 发生风险，还能降低低血糖和不良反应发生率，安全性较高，同时还能降低治疗成本，提高患者依从性，为 T2DM 患者血糖管理带来了更安全、有效和方便的新选择，亦为临床提供了新的治疗策略。

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