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肠促胰素类多肽对非酒精性脂肪性肝病的影响

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摘 要

目前，非酒精性脂肪性肝病(NAFLD)是最常见的肝病，影响高达70%的糖尿病患者，尚无特效药可用于治疗。GLP-1受体激动剂(GLP-1 RA)除了其抗高血糖作用和令人惊讶的心肾保护作用外，对NAFLD患者的体重以及脂肪肝和纤维化的临床、生化和组织学标志物具有显著影响。因此，GLP-1 RAs可能是治疗糖尿病和NAFLD的武器。本综述的目的是总结目前可获得的关于GLP-1 RAs在NAFLD治疗中作用的证据，并假设未来的潜在情况。

关键词

非酒精性脂肪性肝病，2型糖尿病，胰高血糖素样肽-1，胰高血糖素样肽-1受体激动剂

Effect of Incretogenic Peptides on Non-Alcoholic Fatty Liver Disease

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Abstract

At present, non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, affecting up to 70% of diabetic patients, and there is no specific drug for treatment. GLP-1 receptor agonists (GLP-1 RA) have significant effects on body weight and clinical, biochemical, and histological markers of fatty liver and fibrosis in patients with NAFLD, in addition to their anti-hyperglycemic effect

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and surprising cardio-renal protection. Therefore, GLP-1 RAs may be a weapon in the treatment of diabetes and NAFLD. The purpose of this review was to summarize the currently available evidence on the role of GLP-1 RAs in the treatment of NAFLD and to hypothesize potential future scenarios.

Keywords

NAFLD, T2DM, GLP-1, GLP-1 RAs

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1. 引言

由于代谢综合征的传播，非酒精性脂肪性肝病(NAFLD)已成为全球最常见的肝病，全球估计患病率为 32.4% [1]。其特征是肝细胞内脂质过度积聚，可因炎症和纤维化的发展而变得复杂，并发展为非酒精性脂肪性肝炎(NASH, non-alcoholic steatohepatitis)和肝硬化[2]。NAFLD 和代谢综合征的基石有共同的发病机制，与胰岛素抵抗密切相关。T2DM 和 NAFLD 的胰岛素抵抗决定了肝脏产量的增加和肌肉葡萄糖摄取的减少，以及脂肪组织中脂解的减少和肝脏脂肪生成的增加，从而提高葡萄糖和循环游离脂肪酸(FFA)水平[3]。高水平的循环 FFA 是通过抑制受体后胰岛素信号导致胰岛素抵抗程度进一步恶化的原因，助长了恶性循环[4]。

胰高血糖素样肽-1 (GLP-1)是一种由肠道内分泌细胞产生的肽类激素，调节餐后葡萄糖稳态[5]。GLP-1 受体激动剂(GLP-1 RAs)能够增加高血糖诱导的胰岛素分泌，减少胰高血糖素分泌，延迟胃排空，减少食欲和热量摄入，强烈推荐用于 T2DM 治疗[6]。与钠－葡萄糖转运蛋白 2 (SGLT2)抑制剂类似，GLP-1 RA 表现出令人惊讶的心脏和肾脏保护作用，因为它们显著降低了 T2DM 患者的主要不良心血管事件(MACE)发生率和肾脏疾病进展风险[7]。由于它们促进体重减轻，最近被批准用于治疗患有或不患有 T2DM 的患者的肥胖[8] [9]。它们可以改善肝脏损伤，有利于降低脂肪变性、炎症的程度，并有望降低肝纤维化。这些影响的程度和长期临床影响仍在评估中，但现有数据表明 GLP-1 RAs 在 NAFLD 的治疗中发挥着主要作用。本篇综述旨在收集目前关于 GLP-1 RAs 在 NAFLD 中作用的证据，并描述其对肝脏疾病及其并发症的潜在影响，评估未来的临床使用场景。

2. GLP-1 受体激动剂：作用机制和当前适应症

GLP-1 是一种由 30 个氨基酸组成的肠道激素，其作用由位于肠道(远端回肠和结肠)、胰腺 α 和 β 细胞以及中枢神经系统(CNS)的特异性受体(GLP-1 受体，GLP-1R)介导[10]。尽管水平较低，但它也在心脏、肺、肾脏、血管和外周神经系统中表达[10] [11]。GLP-1 的主要作用是增强 β 细胞对高血糖的胰岛素分泌，并抑制 α 细胞释放胰高血糖素[12]。此外，GLP-1 减缓胃排空和胃肠动力，以减少葡萄糖吸收，从而控制餐后葡萄糖和甘油三酯的转运。除了肠道机制外，GLP-1 还能够通过直接刺激中枢神经系统来诱导饱腹感[11]。通过这些作用机制，GLP-1 RAs 增强了内源性 GLP-1 的生理作用。GLP-1 RAs 诱导的良好代谢特征(体重减轻和热量摄入减少，血糖改善)使人们能够假设其在治疗非酒精性脂肪肝、T2DM 和肥胖方面的潜在有效性。

3. GLP-1 受体激动剂对 NAFLD 的影响

3.1. GLP-1 RA 对体重的影响

迄今为止，唯一有效的治疗 NAFLD 的方法是减肥，通常通过改变生活方式(饮食、体育活动)或减肥手术来实现。然而，很难实现显著和持久的体重减轻。除了生活方式的改变外，GLP-1 RA 还被证明可以通过早期饱腹感和食欲下降来降低 2~7 公斤的体重，从而降低热量摄入[13] [14] [15]。此外，这些药物的治疗可以减少对食物的渴望，增加用餐带来的乐趣[16]。参与这一进程的机制既有核心机制，也有外围机制。在中枢神经系统中，血清素是食欲调节的关键因素。通过刺激其在中枢神经系统中的受体，GLP-1 降低了下丘脑中 5-羟色胺 5-HT2A 受体的表达，导致食欲下降[17]。这种作用独立于血清素分泌，血清素分泌不受影响[18]。同时，GLP-1 RAs 能够延迟胃排空并减缓胃肠道的肠道运动，从而在中枢水平增强早期饱腹感[19]。然而，由于快速反应的机制，GLP-1 随着时间的推移对受体的长期刺激减少了对胃排空的影响[20]。体重减轻的程度取决于所使用的 GLP-1 RA 和剂量。到目前为止，还没有确定对减肥的长期反应的具体预测因素。

3.2. GLP-1 RAs 对肝细胞裂解的影响

肝细胞裂解标志物(天冬氨酸氨基转移酶，AST，最重要的是丙氨酸氨基转移酶，ALT)代表了 NAFLD 患者潜在肝脏炎症。事实上，患有 NAFLD 和肝细胞裂解酶升高的患者患 NASH 和进展为肝硬化的风险增加[21]。同时，降低 NAFLD 进展风险的治疗都与肝细胞溶解的显著减少有关[21] [22] [23]。在患有 NAFLD 的超重或肥胖患者中，体重减轻 ≥7%~10%可改善肝脏酶以及疾病的组织学分级[24]。值得注意的是，大约 40%的基线肝酶升高的患者在治疗后达到了正常的 ALT。Fan 等人[25]比较了艾塞那肽和二甲双胍对患有 NAFLD 的糖尿病患者的治疗。作者表明，与二甲双胍治疗相比，艾塞那肽治疗 12 周可显著降低肝脏酶。

NAFLD 治疗的另一个目标是减少甘油三酯在肝脏中的积聚。在这方面，GLP-1 RAs 已被证明可显著改善肝脏脂肪变性。与其他降血糖药物相比，艾塞那肽显著降低了与减肥相关的肝脏甘油三酯含量和心外膜脂肪组织[26]。Braslov 等人[27]强调，其他口服降糖药无法检测到艾塞那肽诱导的肝脏脂肪积聚的改善(使用脂肪肝指数 FLI 评估)。Vanderheiden [28]、Petit [29]等人通过磁共振成像证明，利拉鲁肽治疗患者的肝脏和皮下脂肪显著减少。

3.3. GLP-1 RAs 对肝纤维化的影响

肝纤维化是 NASH 患者临床结果的主要决定因素[30]。特别是，约 15%的糖尿病患者可检测到临床相关的纤维化[31]。NAFLD 的治疗必须能够影响肝纤维化，旨在降低死亡率、肝移植和肝脏相关事件。到目前为止，很少有研究评估 GLP-1 RAs 对 NAFLD 相关肝纤维化的疗效[32]。此外，大多数数据是从纤维化的间接标志物中获得的，如 APRI (AST 与血小板计数比指数)、NFS (NAFLD 纤维化评分)、FIB-4 (基于 4 个因素的纤维化指数)或肝硬度评估(LSM)。Tan 等人[33]发现，与使用其他降糖药物治疗的患者相比，使用利拉鲁肽治疗的糖尿病患者在 12 个月的随访后，NFS、FIB-4 和 LSM 显著降低。

4. GLP-1 RAs 在 NAFLD 中的潜在作用机制

首先，内源性 GLP-1 和 GLP-1 受体激动剂可以改善肝脏胰岛素抵抗[34]。在肝脂肪变性的情况下，胰岛素信号通路在很大程度上是缺乏的。特别是，胰岛素信号传导的关键效应器 AKT 的磷酸化似乎显著降低，阻碍了胰岛素受体底物-2 (IRS-2)下游的受体后信号级联[35]。GLP-1 配体能够促进 AKT 和 IRS-2

下游其他关键分子(PDK-1 和 PKC-ζ)的磷酸化[36]。GLP-1 和 GLP-1 受体激动剂诱导的受体后信号级联的激活以及由此产生的胰岛素信号通路的调节将减少肝细胞甘油三酯的储存，从而改善肝脂肪变性[36]。关于胰岛素抵抗的机制，脂肪因子起着重要作用。其中，脂联素是一种激素，能够通过与受体结合发挥胰岛素增敏作用，并激活主要由腺苷单磷酸依赖性激酶(AMPK)和过氧化物酶体增殖物激活受体(PPAR)-α介导的受体后信号通路[37]。肥胖和脂肪肝患者的脂联素水平显著降低。据推测，GLP-1 RAs 可增加脂联素水平，改善胰岛素抵抗程度，从而减少肝脏脂肪积聚[38]，并对纤维化的发展具有保护作用[39]。事实上，GLP-1 增加了肝细胞中的环磷酸腺苷(cAMP)，导致 AMPK 的磷酸化和脂肪生成的抑制[40]。然而，这些假设还需要进一步研究。事实上，无论涉及何种机制，GLP-1 RAs 治疗后检测到的脂联素水平升高可能与体重减轻和炎症有关，与血糖控制改善有关[38]。

法尼素 X 受体(FXR)可能在 GLP-1 RAs 的抗脂肪变性机制中发挥非边缘作用。这是一种多功能受体，在进食状态反应中发挥关键作用，能够调节葡萄糖和脂质代谢、胆汁酸稳态和肝脏再生[41]。最近，Errafii 等人[42]在体外脂肪变性模型(HepG2 细胞)上表明，GLP-1 RAs 诱导的脂肪变性的改善可以部分解释为通过直接刺激 GLP-1R 激活法尼素 X 受体/维甲酸 X 受体(FXR/RXR)途径，从而抑制新生脂肪生成。此外，FXR 激活似乎通过增加脂肪酸氧化[43]和抑制 PPAR-γ 表达[44]来降低脂肪肝疾病的程度[45]。后者在非酒精性脂肪肝中过度表达，与肝脏脂肪变性的发展和进展直接相关[46]。在这方面，利拉鲁肽已被证明可减少 PPAR-γ 的肝脏表达，从而减少肝细胞内脂肪酸的积累，恢复生理脂质稳态[47] [48]。

另一种可以解释 GLP-1 RAs 在 NAFLD 中作用的保护机制是预防肝细胞凋亡的潜在作用[49]。事实上，肝细胞脂肪积累能够诱导内质网(ER)应激，从而导致肝细胞凋亡和肝损伤的进展。溶酶体降解和自噬的机制对于去除潜在的毒性和保护性脂肪酸以对抗内质网应激诱导的细胞死亡至关重要[50]。Sharma 等人[49]证明 GLP-1R 刺激能够激活自噬机制，减轻内质网应激介导的细胞凋亡，减少肝细胞内脂肪酸的积累。这可能潜在地防止 NAFLD 中肝损伤的进展。

除了 GLP-1 RAs 在肝细胞中潜在的直接作用机制外，一些证据证实了这些药物在降低低级别慢性和全身炎症(代谢综合征的一个特征)方面的作用。事实上，炎症标志物，如血清 C 反应蛋白(CRP)、白细胞介素(IL)-6 和肿瘤坏死因子(TNF)-α，在胰岛素抵抗患者中显著升高。除了改善代谢状况外，GLP-1 RA 已被证明可显著降低血清 CRP [51]、IL-6 [52]和 TNF-α [51]的水平。GLP-1 RAs 治疗还能够减少脂肪组织的巨噬细胞浸润，抑制脂肪细胞中的炎症途径，同时改善胰岛素敏感性[53]。全身炎症状态的改善可能是降低 NAFLD 进展和 HCC 发展风险的重要辅助因子，也是 GLP-1 RAs 发挥心血管保护作用的关键决定因素[54]。此外，GLP-1 RA 最近被证明可以通过影响骨骼肌代谢来改善肥胖小鼠的肌肉减少性肥胖[55] [56] [57]。在这些小鼠模型中，除了减肥外，索马鲁肽还可以降低肌肉内脂肪的积累，促进蛋白质的合成，增加质量和肌肉功能[55]。GLP-1 RAs 已被证明可以通过抑制肌肉生长抑制素的表达和促进肌生成因子的表达，以及通过抗炎和抗凋亡作用来改善肌肉萎缩[56] [57]。GLP-1 RAs 可以保证独立于体重减轻和血糖控制的额外直接益处。

5. 未来展望

GLP-1 RA 已被证明可促进 NASH 患者的显著减肥，降低肝损伤指数和脂肪变性，诱导脂肪性肝炎的消退，并减缓纤维化的进展。然而，GLP-1 受体激动剂在 NASH 中的潜力尚未得到充分探索。事实上，目前还没有旨在评估 GLP-1 RA 在减少肝纤维化方面的疗效的长期试验。目前缺乏关于 GLP-1 RAs 治疗对 HCC 发病率或复发风险的影响的具体试验。然而，目前关于 GLP-1 Ras 益处的现有证据使我们能够假设这类药物在 NASH 患者中实现纤维化的长期消退和 HCC 的发病率/复发率降低方面的潜在疗效。这些假设需要在专门的试验中得到验证。

由于 NASH 的复杂和异质的病理生理学，有人假设对不同途径的同时作用可以发挥协同作用，优化治疗结果。从这个角度来看，双重(GLP-1 和 GIP 或 GLP1 和胰高血糖素)或三重(GLP-1、GIP 和胰高胰素)受体激动剂[58] [59]的可能性是最近研究的问题。葡萄糖依赖性促胰岛素肽(GIP)通过增加脂肪组织中的胰岛素分泌、肝脏葡萄糖和甘油三酯摄取发挥作用。胰高血糖素还参与葡萄糖和脂质稳态，以及能量消耗和食物摄入的调节。特别是，它抑制肝脏合成，促进脂肪酸的 β 氧化[60]，并可能促进脂肪组织的脂解[61]。它还通过诱导棕色脂肪组织产热来增加能量消耗[62]，并减少热量摄入[63]。然而，胰高血糖素会抵消胰岛素的作用，促进糖异生和肝脏糖原分解[59]。由于这些途径的激活有时会产生相反的效果，对其中两种或多种途径的同时作用可能会产生互补和协同效应[64]。

越来越多的证据表明 GLP-1 和胰高血糖素具有双重激动作用[65]。胰高血糖素和 GLP-1 都能降低食欲，促进体重减轻；此外，胰高血糖素还会增加能量消耗。此外，在双重激动剂中，GLP-1 可能对胰高血糖素的高血糖作用具有保护作用。

与 GLP-1/GCG 双重激动剂类似，GLP-1 受体和 GIP 的共同激活在治疗 T2DM 和肥胖方面具有迷人的前景。事实上，如果 GIP 受体激动剂(GIP-RA)在刺激胰岛素分泌和促进外周葡萄糖摄取方面有效，单独使用它们就不会影响体重。GIP-RA 能够增强 GLP-1 RA 作用的机制尚不清楚。双受体激动剂可以比选择性单受体激动剂更有效地抵消 T2DM 的两种发病机制(肥胖诱导的胰岛素抵抗和胰腺胰岛素缺乏) [66]。

如果双受体激动剂 GLP-1/GCG 和 GLP-1/GIP 在血糖控制和减肥方面表现出协同作用，那么三重 GLP-1/GCG/GIP 激动剂可能会导致结果的进一步最大化。事实上，对三种关键代谢途径的协同作用可能更有效地减轻体重和治疗肥胖，促进食物摄入量(GLP-1，胰高血糖素)的减少、能量消耗(胰高血糖蛋白)的增加和外周葡萄糖摄取，并增强 GLP-1 诱导的体重减轻(GIP)，减轻胰高血糖肽的高血糖作用。然而，到目前为止，还没有在人类身上进行的研究。

双重和三重激动剂可能在治疗 T2DM 和肥胖方面具有潜在疗效，但目前很少有数据表明它们在 NAFLD 中的作用。在这方面，Finan 等人[67]在小鼠模型中初步显示了三重激动剂在逆转脂肪肝方面的优异疗效。这种作用明显优于单激动剂和双激动剂。迄今为止，只有一项关于多种激动剂联合治疗人类 NAFLD 疗效的试验可用。Nara 等人[68]研究表明，与单一疗法相比，联合疗法显著减轻了体重，尤其是肝脏脂肪变性、炎症和纤维化，证实了 GLP-1 和 FXR 激动剂在 NASH 治疗中的互补或协同作用。

6. 结论

GLP-1 受体激动剂已被证明能有效降低体重、肝损伤指数和肝脏脂肪含量。一些证据还表明，这些药物能够在不可忽视的 NASH 患者中促进脂肪性肝炎的消退，并减少肝纤维化的进展。目前没有证据表明 GLP-1 RAs 在改善 NAFLD 患者先前存在的肝纤维化方面的疗效。然而，GLP-1 RA 长期治疗后的数据尚不可用。双重和三重激动剂有望带来额外的益处，但还需要具体的人体临床试验。

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