

2 型糖尿病合并非酒精性脂肪肝病患者 IGF-1 与胰岛素抵抗关系研究 *

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摘要 研究胰岛素样生长因子-1(IGF-1)与 2 型糖尿病(T2DM)胰岛素抵抗关系。有研究证实给予 IGF-1 后,可改善胰岛素抵抗、肝脏脂质代谢,IGF-1 基因缺失的动物会产生胰岛素抵抗和高胰岛素血症,低水平的 IGF-1 还可能与非酒精性脂肪肝病(NAFLD)肝纤维化有关,而 T2DM 和 NAFLD 与胰岛素抵抗共存,T2DM 合并 NAFLD 患者 IGF-1 水平更低。IGF-1 与胰岛素抵抗关系密切,IGF-1 水平能反映胰岛素抵抗的严重程度,为 IGF-1 在今后治疗 T2DM 和 NAFLD 的提供了潜在的临床应用前景。

关键词 2 型糖尿病 非酒精性脂肪性肝病 胰岛素抵抗 生长激素 胰岛素样生长因子-1

中图分类号 R587.2 **文献标识码** A **文章编号** 1673-6273 (2012) 10-1998-03

Relationship between Insulin-Like Growth Factor-1 and Insulin Resistance in Type 2 Diabetic Patients with Nonalcoholic Fatty Liver Disease*

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ABSTRACT: To study the relationship of the insulin resistance between insulin-like growth factor-1 (IGF-1) and type 2 diabetes (T2DM). Researchs have shown that insulin sensitivity and hepatic lipid metabolism could increase when given IGF-1, The animals that IGF-1 gene deletion will produce insulin resistance and hyperinsulinemia, Low levels of IGF-1 also may be associated with non-alcoholic fatty liver disease (NAFLD) liver fibrosis. However, T2DM and NAFLD coexist of insulin resistance, T2DM with NAFLD patients have lower levels of IGF-1. IGF-1 has close relationship with the insulin resistance, the IGF-1 levels can reflect the severity of insulin resistance. This also provides a broad prospect of T2DM and NAFLD.

Key words: Type 2 diabetes mellitus; Nonalcoholic fatty liver disease; Insulin resistance; Insulin-like growth factor-1; Growth hormone

Chinese Library Classification(CLC): R587.2 **Document code:** A

Article ID: 1673-6273(2012)10-1998-03

近年来,随着人们生活水平不断提高、生活方式改变等,2 型糖尿病(T2DM)、非酒精性脂肪性肝病(NAFLD)的发病率逐年上升。T2DM 与 NAFLD 关系密切,流行病学指出 T2DM 患者中 NAFLD 的发生率约 28%~55%,10%~75% 的 NAFLD 存在 T2DM^[1,2],T2DM 患者多存在胰岛素抵抗(IR),IR 与 NAFLD 密切相关。

胰岛素样生长因子-1(IGF-1)和胰岛素原有 50% 的序列相同,血液中的 IGF-1 主要来源于肝脏的生物合成,在代谢方面 IGF-1 具有胰岛素样作用^[3],IGF-1 通过负反馈机制调节生长激素(GH)的分泌,GH 通过肝脏生长激素受体(GHR)促进肝脏 IGF-1 基因表达。本文就 T2DM 合并 NAFLD 患者 IGF-1、GH 与 IR 之间的关系作一综述。

1 NAFLD 和 T2DM 的发病机制与胰岛素抵抗

T2DM 和 NAFLD 的病理特征是胰岛素抵抗(IR)。NAFLD 患者常伴随明显的 IR 特征,表现为超重/肥胖,主要是中心性肥胖(腰围增加)、高胰岛素血症、糖代谢异常、高血压、高三酰甘

油血症和 HDL-C 降低^[4]。这些代谢异常程度与肝酶升高相一致。可通过运动、减重和药物治疗等治疗得到改善,NAFLD 患者 IR 与脂肪肝有关,与糖耐量的关系不大^[5]。除了与糖、脂代谢紊乱密切相关之外,NAFLD 还能预测 2 型糖尿病的发生。在对一组糖代谢正常的印第安人平均随访 7 年的研究表明,ALT 升高预测发生 2 型糖尿病的危险性增加,基线时 ALT 升高的受试者已经存在肝脏胰岛素敏感性下降,表现为肝糖输出增加^[6]。

IR 时糖代谢产生异常,使脂肪动员增加,血中游离脂肪酸含量增加;高胰岛素血症能激活羟甲基戊二酰辅酶 A (HMG-CoA)还原酶,使胆固醇(CH)合成增加,胰岛素和胰岛素样因子通过改变能量代谢从而激发脂肪肝形成。而 IR 是 T2DM 发病的基础,前瞻性研究显示胰岛素抵抗在 T2DM 出现前 10~20 年就存在,而且是日后发生 T2DM 的最好的临床预测指标^[7]。T2DM 合并 NAFLD 的患者其 IR 更显著。除了 IR,2 型糖尿病和 NAFLD 还共同存在慢性低水平的炎症、氧化应激增加和肝毒性细胞因子的上调^[8]。

2 IGF-1 和 GH 与 T2DM 及 NAFLD 关系

* 基金项目 江苏省淮安市科技局资助项目(HAS2010027)

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(收稿日期 2011-09-09 接受日期 2011-09-30)

2.1 IGF-1、GH 的结构及生理作用

IGF-I 是 70 个氨基酸的单链多肽,相对分子质量为 7500,和胰岛素原有 50%的序列相同。IGF-1 可在全身各处表达。血液中的 IGF-1 主要来源于肝脏的生物合成。肾、结缔组织、肺、胸腺、脾、心、骨骼肌、睾丸以及大肠中也能检测到 IGF-1 的存在^[9],IGF 只有 1%左右是游离形式,其余都与 IGF 结合蛋白(IGFBP)结合。IGFBP 是 IGF-1 的主要运输载体,依靠抑制 IGF-1 释放入循环中调节 IGF-1 的生物学作用,以减少血中游离的 IGF-1 的生物活性^[10]。80%IGF-1 与 IGFBP-3 结合,随着年龄的增加,IGF-1 和 IGFBP-3 的比例下降,导致游离 IGF-1 的水平和活性降低。除了在生长和发育方面的作用,IGF-1 也有胰岛素样作用^[11]。体外实验证明,增加 IGF-1 可增加脂肪肝脏线粒体的保护,阻止与再灌注损伤有关的活性氧(ROS)的产生^[12]。生长激素(GH)是腺垂体细胞分泌的蛋白质,正常情况下呈脉冲式分泌,其分泌除受下丘脑产生的生长激素释放素(GHRH)的调节外,还受性别、年龄和昼夜节律的影响。GH 有促进组织生长、机体合成代谢和蛋白质合成、脂肪分解以及对胰岛素有拮抗等作用。IGF-1 水平主要受 GH 调节,而 IGF-1 又可通过负反馈调节 GH 水平,即 GH/IGF-1 轴^[13]。在正常情况下,GH 通过肝脏生长激素受体,促进肝脏 IGF-1 基因表达,从而促进 IGF-1 的合成和释放,IGF-1 反馈抑制垂体 GH 的释放,血清 IGF-I 浓度和 GH 水平在体内处于大致平衡。

2.2 IGF-1 和 GH 与 NAFLD 肝纤维化

研究表明,GH、IGF-1 和 IGFBP-3 是 NAFLD 肝脂肪变和肝纤维化发展的预测因子,低水平的 IGF-1 及 IGF-1/IGFBP-3 可能与 NAFLD 肝纤维化有关^[14]。NAFLD 肝纤维化是由肝星状细胞(HSC)激活转化的,在四氯化碳(CCL4)诱导的小鼠肝损伤模型中,HSC 中 IGF-1 的过量表达可以促进肝细胞的再生^[15]。这可能与部分上调肝细胞生长因子(HGF)、下调转化因子(TGF-1B)有关。尽管 GH 是刺激肝细胞合成 IGF-1 的主要刺激因子,一些炎症细胞因子如 IL-1B、TNF- α 等抑制肝细胞 IGF-1 的分泌,而这些炎症因子在发展 NAFLD 中起主要作用^[16]。这也是解释早期 NASH 低水平的 IGF-1 及 IGF-1/IGFBP-3 原因。IGF-1 替代治疗可以改善肝硬化、保护肝脏受损、增加白蛋白浓度和减少能量消耗。肝纤维化与肥胖、胰岛素抵抗和糖尿病紧密相关^[17],低水平的 IGF-1 与胰岛素敏感性相关的不同程度的糖耐量异常有关^[18]。因此,IGF-1 也是治疗 1 型和 2 型糖尿病胰岛素治疗的辅助性药物^[19],IR 也是代谢综合症包括 NAFLD、T2DM 的最重要的因素,低水平 IGF-1 可能会导致胰岛素抵抗^[19]。

2.3 IGF-1 和 GH 与胰岛素抵抗

2.3.1 IGF-1 与胰岛素抵抗 IGF-1 在包括肝脏^[20]的多种组织中^[21-22],对胰岛素抵抗有保护作用。IGF-1 基因缺失的动物会产生胰岛素抵抗和高胰岛素血症^[23]。外源性的给予低剂量的 IGF-1 增加循环中 IGF-1 的水平,在改善胰岛素抵抗、肝脏和脑的脂质代谢、氧化应激损伤等方面发挥作用。IGF-1 剂量及其分布在血液中的浓度共同决定胰岛素敏感恢复的程度^[24],这可能也是 IGF-1 维持正常糖耐量的一个补充机制^[25-26]。Lam 等对 3977 名一项大型样本研究证实,循环中 IGF-1 的水平还与胰岛素抵抗成负相关,代谢综合症成分越多,IGF-1 水平越低^[27]。也有学者认为 IGF-1 与代谢综合症成分之间是反 U 型关系

-IGF-1 活性高峰出现在代谢综合症 3 个诊断标准,当达五个标准时显著下降^[28]。

2.3.2 GH 与胰岛素抵抗 GH 与 IGF-1 通过 GH/IGF-1 轴互为调节。GH 与胰岛素抵抗可能的机制为:低水平的 IGF-1 在下丘脑或垂体抑制 GH 的负反馈调节,引起生长激素过度分泌,而生长激素的过度分泌可能是导致胰岛素抵抗的一个因素,从而造成机体对胰岛素的敏感性下降;GH 能通过增加脂肪组织中 P85 亚基表达和磷脂酰肌醇-3 激酶(PI-3K)活性,降解脂肪组织,使游离脂肪酸(FFA)释放增加^[29];GH 还通过增加血浆胰岛素浓度,抵抗胰岛素介导的低血糖和糖耐量异常^[30]。循环中增加的 FFA 能通过产生直接或间接的代谢产物改变各种组织中胰岛素级联反应对胰岛素抵抗做出贡献^[31]。Yong Fan 等通过建立组织特异性敲除生长激素受体(GHR)模型试验证实,敲除 GHR 的肝脏显示胰岛素抵抗、糖耐量异常、循环中游离脂肪酸增加、肝脏明显的脂肪变。这是三酰甘油合成增加、分解减少的结果,同时说明 GH 的信号转导是调节肝内脂质代谢的关键^[30]。也有学者认为低于生理水平的 GH 与 NAFLD 的脂肪变密切相关^[32],GH 替代能够改善脂肪肝^[33],且药理剂量的 GH 能克服慢性肝病患者肝脏 GH 的抵抗,增加血清 IGF-1、改善蛋白分解状态^[34]。尽管如此,由于 GH 的脂肪分解作用,长期慢性服用 GH 可造成血糖代谢的持续性恶化,结果增加脂质氧化和胰岛素抵抗^[35]。

综上所述,IGF-1 通过负反馈机制调节 GH 的分泌,对胰岛素抵抗有保护作用,GH 通过 GHR 促进肝脏 IGF-1 基因表达,可诱导胰岛素抵抗,而 T2DM 和 NAFLD 常与胰岛素抵抗、血脂紊乱、肥胖相并存,故 IGF-1、GH 又有潜在的治疗 T2DM 和 NAFLD 的临床应用前景。

参考文献(References)

- [1] Angulo P. GI epidemiology: nonalcoholic fatty liver disease [J]. *Aliment Pharmacol Ther*, 2007, 25(8): 883-889
- [2] Neuschwander-Tetri BA. Nonalcoholic steatohepatitis and the metabolic syndrome [J]. *Am J Med Sci*, 2005, 330(6): 326-335
- [3] Pennisi, O Gavrilo, J Setser-Portas, et al. Recombinant human insulinlike growth factor-I treatment inhibits gluconeogenesis in a transgenic mouse model of type 2 diabetes mellitus [J]. *Endocrinology* 2006, 147(6): 2619-2630
- [4] Nannipieri M, Gonzales C, Baldi S, et al. Liver Enzymes, the Metabolic Syndrome, and Incident Diabetes: the Mexico City diabetes study [J]. *Diabet Care*, 2005, 28(7): 1757-1762
- [5] 李芳萍, 张四青, 王斐, 等. 2 型糖尿病和非酒精性脂肪肝病的胰岛素抵抗研究 [J]. *新医学*, 2009, 40(7): 427-429
- [6] Li Fang-ping, Zhang Si-qing, Wang Fei, et al. Study on insulin resistance in type 2 diabetes mellitus and non-alcoholic fatty liver disease [J]. *New Medicine*, 2009, 40(7): 427-429
- [7] Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and pre-diets the development of type 2 diabetes [J]. *Diabet*, 2002, 51(6): 1889-1895
- [8] Tassone F, Procopio M, Gianotti L, et al. Insulin resistance is not coupled with defective insulin secretion in primary hyperparathyroidism [J]. *Diabet Med*, 2009, 26(10): 968-973

- [8] Leite NC, Salles GF, Araujo AL, et al. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus[J]. *Liver Int*, 2009, 29(1): 113-119
- [9] Murugasu E. Recent advances in the treatment of sensorineural deafness [J]. *Ann Acad Med Singapore*, 2005, 34(4): 313-321
- [10] Delafontaine P, Song YH, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels [J]. *Arterioscler Thromb Vasc Biol*, 2004, 24(3): 435-444
- [11] Pennisi P, Gavrilova J, Setser-Portas, et al. Recombinant human insulin-like growth factor-I treatment inhibits gluconeogenesis in a transgenic mouse model of type 2 diabetes mellitus [J]. *Endocrinology*, 2006, 147(6): 2619-2630
- [12] Mohamed Amine Zaouali, Susagna Padrisa-Alt  s, Ismail Ben, et al. Mosbah Insulin like growth factor-1 increases fatty liver preservation in IGL-1 solution[J]. *World J Gastroenterol*, 2010, 16(45): 5693-5700
- [13] Grotto S, Gasco V, Mainolfi A, et al. Growth hormone/insulin-like growth factor I axis, glucose metabolism, and lipolysis but not leptin show some degree of refractoriness to short-term fasting in acromegaly[J]. *Endocrinol Invest*, 2008, 31(12): 1103-1109
- [14] Tatsuki Ichikawa, Kazuhiko Nakao, Keisuke Hamasaki, et al. Role of growth hormone, insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 in development of non-alcoholic fatty liver disease[J]. *Hep Intl*, 2007, 1(2): 287-294
- [15] Sanz S, Pucilowska JB, Liu S, et al. Expression of insulin-like growth factor I by activated hepatic stellate cells reduces fibrogenesis and enhances regeneration after liver injury[J]. *Gut*, 2005, 54(1): 134-141
- [16] Larter CZ, Farrell GC. Insulin resistance, adiponectin, cytokines in NASH: which is the best target to treat [J]. *Hepatol*, 2006, 44(2): 253-261
- [17] Harrison S, Oliver D, Arnold H, et al. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease[J]. *Gut*, 2008, 57(10): 1441-1447
- [18] Sesti G, Sciacqua A, Cardellini M, et al. Plasma concentration of IGF-I is independently associated with insulin sensitivity in subjects with different degrees of glucose tolerance [J]. *Diabet Care*, 2005, 28(1): 120-125
- [19] Dominici FP, Argentino DP, Munoz MC, et al. Influence of the crosstalk between growth hormone and insulin signalling on the modulation of insulin sensitivity[J]. *Growth Horm IGF Res*, 2005, 15(5): 324-336
- [20] Casillas-Ram  rez A, Zaouali A, Padrisa-Alt  s S, et al. I Insulin-like growth factor and epidermal growth factor treatment: new approaches to protecting steatotic livers against ischemia-reperfusion injury[J]. *Endocrinology*, 2009, 150(7): 3153-3161
- [21] Pi Y, Goldenthal MJ, Mar  n-Garc  a J. Mitochondrial involvement in IGF-1 induced protection of cardiomyocytes against hypoxia/reoxygenation injury[J]. *Mol Cell Biochem*, 2007, 301(1-2): 181-189
- [22] Davani EY, Brumme Z, Singhera GK, et al. Insulin-like growth factor-1 protects ischemic murine myocardium from ischemia/reperfusion associated injury [J]. *Critical care (London, England)*, 2003, (6): R176-183
- [23] Yakar S, Liu JL, Fernandez AM, et al. Liver-specific IGF-1 gene deletion leads to muscle insulin insensitivity [J]. *Diabetes*, 2001, 50(5): 1110-1118
- [24] Clemmons DR, Sleeve M, Allan G, et al. Effects of combined recombinant insulin-like growth factor (IGF)-1 and IGF binding protein-3 in type 2 diabetic patients on glycemic control and distribution of IGF-1 and IGF-2 among serum binding protein complexes [J]. *J Clin Endocrinol Metab*, 2007, 92(7): 2652-2658
- [25] Mar  a Garc  a-Fern  ndez, Gloria Delgado, Juan Enrique Puche, et al. Low Doses of Insulin-Like Growth Factor I Improve Insulin Resistance, Lipid Metabolism, and Oxidative Damage in Aging Rats [J]. *Endocrinology*, 2007, 149(5): 2433-2442
- [26] Clemmons DR. Involvement of insulin-like growth factor-1 in the control of glucose homeostasis [J]. *Curr Opin Pharmacol*, 2006, 6(6): 620-625
- [27] Lam Carolyn S P, Chen Ming-Huei, Lacey, et al. Circulating Insulin-Like Growth Factor-1 and Its Binding Protein-3: Metabolic and Genetic Correlates in the Community [J]. *Arterioscler Thromb Vasc Biol*, 2010, 30(7): 1479-1484
- [28] Michael P Bruggs, Cornelia M van Duijn, Leo J Hofland, et al. IGF-I bioactivity in an Elderly Population: Relation to Insulin Sensitivity, Insulin levels, and the Metabolic Syndrome[J]. *Diabetes*, 2010, 59(2): 505-508
- [29] Del Rincon, J. P, Iida K, Gaylinn, B. D, et al. Growth hormone regulation of p85   expression and phosphoinositide 3-kinase activity in adipose tissue: Mechanism for growth hormone-mediated insulin resistance[J]. *Diabetes*, 2007, 56(6): 1638-1646
- [30] Yong Fan, Ram K. Menon, Pinchas Cohen, et al. Liver-specific Deletion of the Growth Hormone Receptor Reveals Essential Role of Growth Hormone Signaling in Hepatic Lipid Metabolism [J]. *Chem*, 2009, 284(30): 19937-19944
- [31] Delarue J, and Magnan C. Free fatty acids and insulin resistance[J]. *Curr Opin Clin Nutr Metab Care*, 2007, 10(2): 142-148
- [32] Ichikawa T, Nakao K, Hamasaki K, et al. Role of growth hormone, insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 in development of non-alcoholic fatty liver disease [J]. *Hepatol Int*, 2007, 1(2): 287-294
- [33] Takahashi Y, Iida K, Takahashi K, et al. Growth hormone reverses nonalcoholic steatohepatitis in a patient with adult growth hormone deficiency[J]. *Gastroenterol*, 2007, 132(3): 938-943
- [34] Ying Qin, Ya-ping Tian. Preventive effects of chronic exogenous growth hormone levels on diet-induced hepatic steatosis in rats [J]. *Lipid Health Dis*, 2010, 9(1): 78-90
- [35] Wallace DJ, Abbott-johnson WJ, Crawford DHG, et al. GH treatment in adults with chronic liver disease: A randomized, double-blind, placebo-controlled, cross-over study [J]. *Endocrinol Metab*, 2002, 87(6): 2751-2759