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度拉糖肽对 2 型糖尿病合并代谢相关脂肪性肝病的影响

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[摘　要]　**目的：**探讨度拉糖肽对2型糖尿病合并代谢相关性脂肪性肝病患者肝脂肪变和肝纤维化相关指标的影响。**方法：**选取2020年4月至2020年8月就诊于吉林大学第二医院内分泌科的2型糖尿病合并代谢相关性脂肪性肝病患者100例，随机分为对照组(甘精胰岛素组)与观察组(度拉糖肽组)，每组50例。比较两组治疗24周前后的临床生化指标。**结果：**治疗24周时，观察组体重、BMI较基线显著下降，对照组较基线无显著变化(P<0.05)。丙氨酸氨基转移酶(alanine aminotransferase，ALT)、天门冬氨酸氨基转移酶(aspartate amino transferase，AST)、肝硬度值(liver stiffness measurement，LSM)和脂肪受控衰减参数(controlled attenuation parameter，CAP)水平较治疗前均下降，其中观察组下降水平更明显(P<0.05)。空腹血糖(fasting blood-glucose，FPG)、HbA1c、空腹胰岛素(fasting insulin，FINS)、胰岛素抵抗指数(homeostasis model assessment of insul in resistance index，HOMAIR)、三酰甘油(triglyc-erides，TG)、总胆固醇(total cholesterol，TC)及低密度脂蛋白胆固醇(low density lipoproteincholesterol，LDL-C)水平较治疗前均下降(P<0.05)，其中观察组HOMA-IR下降水平更明显(P<0.05)；高密度脂蛋白胆固醇(high density lipoprotein-cholesterol，HDL-C)和TIR水平均升高(P<0.05)，且观察组范围内时间(time in range，TIR)升高水平更明显(P<0.05)。**结论：**度拉糖肽在治疗合并MAFLD的T2DM患者中可能是一种有效的药物，可以改善肝脂肪变、肝脏炎症及肝纤维化。

[关键词]　2型糖尿病；代谢相关脂肪性肝病；度拉糖肽

Effect of dulaglutide on type 2 diabetes mellitus with metabolic-associated fatty liver disease

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Abstract　**Objective:** To investigate the effect of dulaglutide on hepatic adipoosis and liver fibrosis in type 2 diabetes combined with metabolic-related fatty liver disease. **Methods:** A total of 100 patients with type 2 diabetes and metabolic-related fatty liver disease in the Department of Endocrinology of the Second Hospital of Jilin University from April 2020 to August 2020, randomly divided into a control group (insulin glargine group) and an observation group (dulaglutide group), 50 cases in each group. Clinical biochemical measures were compared

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between the two groups around 24 weeks of treatment. **Results:** At 24 weeks of treatment, significant decreases in weight and body mass index (BMI) were observed in the observed group and no significant change from baseline in the control group (all $P<0.05$). Both alanine aminotransferase (ALT), aspartate amino transferase (AST), liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) levels decreased compared with before the treatment, and more pronounced decreased levels in the observed group (all $P<0.05$). Both fasting blood-glucose (FPG), HbA1c, fasting insulin (FINS), homeostasis model assessment of insul in resistance index (HOMA-IR), triglyc-erides (TG), total cholesterol (TC) and low density lipoproteincholesterol (LDL-C) levels decreased compared to before the treatment (all $P<0.05$), and the levels of HOMA-IR decreased more obviously in the observation group ($P<0.05$); higher high density lipoprotein-cholesterol (HDL-C) levels ($P<0.05$) and higher time in range (TIR) in the observed group ($P<0.05$). **Conclusion:** Dulaglutide may be an effective drug in treating type 2 diabetes patients with metabolic-associated fatty liver disease to improve liver adiatosis, liver inflammation and liver fibrosis.

Keywords type 2 diabetes mellitus; metabolic-associated fatty liver disease; dulaglutide

代谢相关性脂肪肝(metabolic-associated fatty liver disease，MAFLD)这一概念是在2020年初由国际知名肝病专家小组为突出代谢因素在此类疾病中的核心地位[1]，将非酒精性脂肪肝病更名而来。MAFLD的诊断是以肝脂肪变性为基础，同时必须符合以下诊断标准中的一项，包括超重、肥胖、2型糖尿病(type 2 diabetes mellitus，T2DM)或代谢功能异常的临床证据，如血脂、血糖异常或腰围增加等。可与病毒性肝炎、酒精性肝病同时存在[2]。T2DM和MAFLD均存在胰岛素抵抗，两者互为因果，40%~50%的T2DM患者合并有MAFLD[3]。大部分MAFLD患者长期无症状，肝功能检查轻度异常或者无异常，但每年MAFLD病死率可达0.0117‰[4]。降糖药胰高糖素样肽-1(glucagon-like peptide-1，GLP1-1)受体激动剂能有效改善肝脂质沉积和炎症反应[5-7]。这也表明GLP-1及其衍生物可能成为治疗肝脏炎症的衍生药物，尤其是T2DM合并MAFLD[8-9]。度拉糖肽是GLP-1受体激动剂周制剂，本研究主要观察其对T2DM合并 MAFLD患者肝脂肪变和肝纤维化的影响，为临床治疗提供依据。

1 对象与方法

1.1 对象

选取2020年4月至8月就诊于吉林大学第二医院内分泌科的T2DM合并MAFLD患者100例，其中男51例，女49例。所有患者自愿签署知情同意书，本研究已获得吉林大学第二医院医学伦理委员会审批。入组标准：依据《中国2型糖尿病防治指南(2017年版)》诊断为T2DM及《2018版中国非酒精性脂肪性肝病防治指南》诊断为MAFLD的患者；年龄18~65岁；糖化血红蛋白7.5%~15%(包括界值)。排除标准：合并急性感染性疾病及半年内有过急性代谢并发症者；既往有急慢性胰腺炎，或血淀粉酶≥3倍正常值以上；合并有严重肝肾心肺功能不全者，包括肝功能明显异常(谷丙转氨酶和/或谷草转氨酶>3倍正常上限和/或总胆红素>34.2 μmol/L)，肌酐清除率<60 mL/h；合并有甲肝、乙肝、丙肝、戊肝、自身免疫性肝炎、遗传性肝病等患者；有甲状腺髓样癌(medullary thyroid carcinoma，MTC)个人既往病史或2型多发性内分泌腺瘤综合征(multiple endocrine adenoma syndrome 2，MEN2)的患者；妊娠者。根据随机数字表法将其分为对照组($n=50$)与观察组($n=50$)。

1.2 方法

所有患者给予糖尿病健康教育，监测血糖，每周中等强度有氧运动至少2 h，对照组采用甘精胰岛素进行治疗，所有患者于晚20:00给予甘精胰岛素注射液(赛诺菲安万特北京制药有限公司，来得时，300 U/3 mL)皮下注射，入组患者按照0.2 U/kg剂量，此后根据患者每日空腹及睡前血糖变化调整剂量。观察组给予度拉糖肽注射液(美国礼来公司，度易达，1.5 mg/0.5 mL)1.5 mg，每周1次皮下注射。对照组及观察组均治疗24周。

1.3 观察指标

收集患者的一般临床资料，包括身高、体重、体重指数(body mass index，BMI)，并于清晨6点抽取患者治疗前的空腹外周静脉血，采用美国BECKMAN CX8型全自动生化分析仪测定空腹血糖(fasting blood-glucose，FPG)、三酰甘油

(triglyc-erides，TG)、总胆固醇(total cholesterol，TC)、低密度脂蛋白胆固醇(low density lipoprotein-cholesterol，LDL-C)、高密度脂蛋白胆固醇(high density lipoprotein-cholesterol，HDL-C)；丙氨酸氨基转移酶(alanine aminotransferase，ALT)、天门冬氨酸氨基转移酶(aspartate amino transferase，AST)。采用美国伯乐(BIO-RAD)糖化血红蛋白检测仪测定HbA1c，采用美国AXSYM全自动免疫分析仪测得空腹胰岛素(fasting insulin，FINS)，并计算胰岛素抵抗指数(homeostasis model assessment of insulin resistance index，HOMA-IR)=FINS×FPG/22.5。通过9点指尖末梢血糖(三餐前、三餐后2 h、睡前、0点、3点)数值是否在3.9~10.0 mmol/L间计算葡萄糖目标范围内时间(time in range，TIR)，TIR=9个点血糖中落在3.9~10.0 mmol/L中的次数/9×100%。所有患者在基线及治疗后均应用瞬时弹性成像技术检测肝硬度值(liver stiffness measurement，LSM)和脂肪受控衰减参数(controlled attenuation parameter，CAP)，由一名操作经验在500次以上的操作者进行操作，一般选用M型探头，在BMI≥28.0 kg/m^{2}使用XL型探头。同一检测点至少成功检测10次，检测值的四分位间距与中位数的比值<0.3有效。

1.4 统计学处理

采用SPSS 21.0统计软件进行数据分析。对于服从正态分布的计量资料，以均数±标准差($\bar{x}\pm s$)描述，组间比较采用t检验及配对t检验；计数资料以构成比(%)表示，组间比较采用χ^2检验。P<0.05为差异有统计学意义。

2 结果

2.1 两组治疗前后一般资料比较

两组性别、年龄、病程、体重及BMI差异有统计学意义(P<0.05)。经治疗后，观察组患者体重及BMI均较治疗前下降，且差异有统计学意义(P<0.05，表1)。

2.2 两组治疗前后肝功能指标的比较

两组AST、ALT、LSM和CAP水平差异无统计学意义(P>0.05)。两组治疗后ALT、AST、LSM和CAP水平较治疗前均下降，且均以观察组下降水平更明显，差异有统计学意义(P<0.05，表2)。

2.3 两组治疗前后糖脂代谢指标的比较

两组治疗后FPG、HbA1c、FINS、HOMA-IR、TG、TC及LDL-C水平较治疗前均下降，差异有统计学意义(P<0.05)；其中观察组HOMA-IR下降更明显，差异有统计学意义(P<0.05)；两组治疗后HDL-C和TIR水平均升高(P<0.05)，且观察组TIR升高水平更明显(P<0.05，表3)。

表1 两组治疗前后一般资料的比较(n=50)

Table 1 Comparison of general data before and after the treatment between the 2 groups (n=50)

组别	性别/[例(%)]		年龄/岁	病程/年
	男	女		
对照组组	23 (46.0)	27 (54.0)	52.50 ± 14.22	8.48 ± 6.52
观察组	28 (56.0)	22 (44.0)	54.92 ± 12.07	9.67 ± 7.05
χ^2/t	1.000		−0.917	−0.873
P	0.317		0.361	0.385

组别	体重/kg		BMI/(kg·m^{-2})	
	治疗前	治疗后	治疗前	治疗后
对照组	74.32 ± 9.43	75.50 ± 9.13	25.90 ± 2.79	26.28 ± 2.91
观察组	74.80 ± 9.29	71.76 ± 9.28*	25.36 ± 2.25	22.98 ± 1.51*
t	−0.256	2.015	1.067	10.001
P	0.798	0.047	0.288	<0.001

与治疗前相比，*P<0.05。

Compared with before the treatment, *P<0.05.

表2 两组治疗前后肝功能指标的比较 (n=50)

Table 2 Comparison of liver function indicators before and after the treatment between the 2 groups (n=50)

组别	ALT/(U·L^{-1})		AST /(U·L^{-1})	
	治疗前	治疗后	治疗前	治疗后
对照组	37.29 ± 23.82	30.36 ± 14.39*	26.06 ± 12.25	17.98 ± 11.55*
观察组	43.33 ± 23.89	29.90 ± 13.33*	22.51 ± 7.65	12.58 ± 6.07*
t	−1.267	2.204	1.737	2.177
P	0.208	0.030	0.085	0.032

组别	LSM/kPa		CAP/(dB·m^{-1})	
	治疗前	治疗后	治疗前	治疗后
对照组	7.91 ± 3.22	6.53 ± 2.44*	262.64 ± 19.28	248.50 ± 17.92*
观察组	7.98 ± 3.99	5.97 ± 2.99*	256.52 ± 15.28	228.44 ± 15.27*
t	−0.086	2.343	1.759	5.527
P	0.932	0.021	0.082	<0.001

与治疗前相比，*P<0.05。

Compared with before the treatment, *P<0.05.

表3 两组治疗前后糖脂代谢指标的比较 (n=50)

Table 3 Comparison of glycolipid metabolism indicators before and after the treatment between the 2 groups (n=50)

指标	对照组	观察组	t	P
TG/(mmol·L^{-1})				
治疗前	2.04 ± 0.74	2.14 ± 1.23	−0.495	0.622
治疗后	1.75 ± 0.93*	1.69 ± 0.82*	1.286	0.201
TC/(mmol·L^{-1})				
治疗前	5.76 ± 1.33	5.45 ± 1.38	1.119	0.266
治疗后	4.03 ± 1.12*	3.40 ± 1.21*	1.908	0.059
LDL-C/(mmol·L^{-1})				
治疗前	3.15 ± 0.99	3.06 ± 1.00	0.458	0.648
治疗后	1.55 ± 0.98*	1.32 ± 0.90*	1.778	0.078
FINS/(μIU·mL^{-1})				
治疗前	23.41 ± 6.80	25.16 ± 10.83	−0.965	0.337
治疗后	15.13 ± 8.76*	16.76 ± 10.42*	0.058	0.954
HbA1c/%				
治疗前	8.49 ± 1.96	8.58 ± 1.75	−0.264	0.792
治疗后	7.64 ± 1.53*	7.50 ± 1.21*	1.457	0.148
HOMA-IR				
治疗前	6.73 ± 4.07	6.97 ± 5.16	−0.259	0.796
治疗后	5.45 ± 3.52*	4.84 ± 2.93*	2.162	0.033

续表3

指标	对照组	观察组	*t*	*P*
HDL-C/(mmol·L^{-1})				
治疗前	1.07 ± 1.14	1.14 ± 0.30	−1.339	0.184
治疗后	1.13 ± 0.13*	1.20 ± 0.31*	−0.143	0.887
FPG/(mmol·L^{-1})				
治疗前	9.83 ± 3.26	9.37 ± 2.84	0.756	0.452
治疗后	7.69 ± 1.91*	7.71 ± 1.70*	−1.458	0.148
TIR/%				
治疗前	68.00 ± 17.87	63.94 ± 16.00	1.197	0.234
治疗后	75.84 ± 16.60*	74.90 ± 16.46*	−2.197	0.030

与治疗前相比，*P<0.05。

Compared with before the treatment, *P<0.05.

2.4 安全性

研究过程中所有患者未出现严重低血糖。观察组不良反应主要以胃肠道症状为主，程度较轻，3例腹泻，4例恶心，2例呕吐，均发生在用药前2周，给予对症处理后均好转。所有患者完成随访。

3 讨论

MAFLD已经成为一个世界性的健康问题，全世界约有10亿人口患有此病，大大增加了人群的全因死亡率，包括心血管疾病及肝病相关的病死率[4]。NAFLD的定义中没有区分以代谢因素和以其他脂肪肝危险因素所致的脂肪肝，这导致NAFLD在临床诊疗中存在一定的异质性问题[10]。而新定义MAFLD更强调了代谢因素在此类疾病发生发展中的重要意义，能将诊断的患者分层分类，这对于疾病的进一步治疗有指导意义。MAFLD常与T2DM共存，两种疾病的发生互相促进，糖-肝共病模式，代谢异常导致肝中TG过量进而发生肝脂肪变性，同时导致胰岛素抵抗，这也是T2DM发生的重要因素[11]。对于MAFLD的治疗，目前主要得益于生活方式的干预和减肥[12]，以及针对代谢异常的其他治疗。这种治疗方法虽有效，但患者难以长期坚持，治疗效果不理想，治疗难度增加。因此，对于合并MAFLD的T2DM患者，在选择降糖药物的同时，应优先选择肝安全性高，能降低体重及改善血脂异常的药物。GLP-1受体激动剂在NASH动物模型中已被证明能降低肝脂肪和改善肝组织学[13-16]。对肝纤维化的效果也十分明显[17-20]，这对治疗T2DM合并MAFLD有重要意义。

本研究中，与对照组相比，观察组体重以及BMI明显降低。体重减轻是所有GLP-1受体激动剂的常见临床治疗反应。通过改善生活方式减轻体重会使肝脂肪变性情况有所改变[21]，且改善程度与体重减轻情况呈正相关。另一项研究[22]发现肥胖患者通过手术减轻体重后，肝脂肪变性、炎症等情况明显改善。此外，GLP-1受体激动剂也被证实可减轻肝及脂肪细胞中的胰岛素抵抗情况。GLP-1受体激动剂可抑制内源性葡萄糖生成，增加肝葡萄糖的摄取，改善肝和脂肪组织的胰岛素抵抗，降低游离脂肪酸水平[23]。一项随机前瞻性实验[24]发现：GLP-1受体激动剂可降低BMI、HbAlc、LDL-C、ALT，增加肝和脂肪组织的胰岛素敏感性，抑制肝脂肪酸合成，促进胰岛素的脂肪分解，降低脂肪对肝的毒性作用。GLP-1受体激动剂还可以通过减少胃肠蠕动，减少乳糜微粒的合成和分泌，降低胃肠道对脂肪的吸收，最终降低血脂水平[24]。本研究中，两组患者治疗后FPG、HbA1c、FINS、HOMA-IR、TG、TC及LDL-C水平较治疗前均下降；其中HOMA-IR观察组下降水平更明显；与以上研究结果基本一致。一项关于TIR与T2DM合并MAFLD患者肝纤维化的相关性研究[25]发现：TIR与肝纤维化呈负相关，TIR的时间越长，肝纤维化的风险越小。本研究中两组治疗后TIR水平均升高，且观察组TIR升高水平更明显，符合既往研究[25]得出的结论。GLP-1受体激动剂还可改善肝炎症反应以及减少氧化应激对肝细胞的损伤。最近的一项研究[26]表明，GLP-1受体激动剂通过减少巨噬细胞的募集和激活来减轻肝脏的炎症。在一项关

于高脂饮食(high-fat diet，HFD)的雄性C57BL/6J小鼠进行腹腔注射GLP-1受体激动剂或生理盐水治疗4周的实验中发现，GLP-1受体激动剂显著降低了HFD引起的肝重量和肝脂肪变性。SIRT1是一种依赖NAD的蛋白脱乙酰酶，已被认为是肝脂质稳态的重要调节因子。SREBP-1c是肝新生脂肪发生的主要脂肪转录因子之一[7]。目前研究[27]表明SIRT1介导GLP-1受体激动剂对肝脂肪变性有缓解作用。GLP-1受体激动剂主要通过激活AMPK通路及抑制SREBP-1c来改善SIRT1介导的脂肪生成。此外，GLP-1受体激动剂还需要SIRT1来减轻肝脏炎症。有研究[27]首次表明SIRT1是GLP-1受体激动剂减少小鼠肝脂肪变性所必需的，提示GLP-1受体激动剂可以作为MAFLD的潜在药物，特别是在T2DM联合MAFLD中SIRT1可能是NAFLD的治疗靶点。GLP-1受体激动剂可增加患者体内脂联素水平，降低瘦素和抵抗素等促炎症因子的水平[28-29]。而脂联素本身具有改善胰岛素抵抗，抗炎/改善氧化应激，抑制肝纤维化等多种作用。这些作用对于改善肝炎症反应及纤维化的发生均有明显作用。现被临床广泛应用的瞬时弹性成像技术(transient elastography，TE)可以用来检测LSM，进而判断肝纤维化的严重程度，是一种无创诊断技术[30-31]。瞬时弹性记录仪FibroScan实施受控衰减参数也被广泛应用于无创定量检测肝脂肪变性程度，其影响因素少，灵敏度、特异度及可重复性较好[32-36]。研究[37]发现CAP值与代谢综合征组分个数呈正相关，CAP值可在一定程度上反映MAFLD的严重程度。且CAP值越高，肝脂肪变性的程度越严重。本研究两组治疗后ALT、AST、LSM和CAP水平均较治疗前下降，且均以观察组下降更明显，进一步证实度拉糖肽对MAFLD的治疗效果。

综上所述，度拉糖肽在治疗合并MAFLD的T2DM患者中兼顾了有效性和安全性，由于药物作用时间长，患者依从性高，在降糖的同时可以减轻体重，减轻胰岛素抵抗，改善肝功能，降低肝纤维化程度，改善脂代谢紊乱，无低血糖风险。因此，度拉糖肽可能是一种可有效改善肝脂肪变、肝炎症及肝纤维化的药物。本研究观察时间短，肝酶指标仅间接反映肝病情，未进行肝活检，需进一步完善。

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