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利拉鲁肽联合二甲双胍对肥胖 2 型糖尿病患者糖脂代谢、血管内皮功能及微炎症状态的影响 *

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摘要 目的：探讨利拉鲁肽联合二甲双胍对肥胖 2 型糖尿病（T2DM）患者糖脂代谢、血管内皮功能及微炎症状态的影响。**方法：**选取 2016 年 7 月 ~2019 年 4 月期间我院收治的 117 例 T2DM 肥胖患者。根据随机数字表法分为对照组（n=58，二甲双胍治疗）和研究组（n=59，利拉鲁肽联合二甲双胍治疗），比较两组患者体质量指数（BMI）、糖脂代谢指标[高密度脂蛋白胆固醇（HDL-C）、空腹血糖（FPG）、甘油三酯（TG）、糖化血红蛋白（HbA1c）、低密度脂蛋白胆固醇（LDL-C）、总胆固醇（TC）]、血管内皮功能指标[内皮素（ET）、一氧化氮（NO）]及微炎症状态指标[C 反应蛋白（CRP）、白介素 -6（IL-6）以及肿瘤坏死因子 -α（TNF-α）]，记录两组治疗期间不良反应情况。**结果：**治疗 12 周后，两组 BMI、FPG 及 HbA1c、TG、TC、LDL-C、ET、CRP、TNF-α 及 IL-6 均低于治疗前，且研究组低于对照组（$P<0.05$）。治疗 12 周后，两组 HDL-C、NO 高于治疗前，且研究组高于对照组（$P<0.05$）。两组不良反应发生率比较无差异（$P>0.05$）。**结论：**利拉鲁肽联合二甲双胍治疗肥胖 T2DM 患者，可有效控制其体内糖脂代谢紊乱，改善血管内皮功能及微炎症状态，且用药安全性较好。

关键词：利拉鲁肽；二甲双胍；肥胖 2 型糖尿病；糖脂代谢；内皮功能；微炎症状态

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The Effect of Lilaluptide Combined with Metformin on Glucose and Lipid Metabolism, Vascular Endothelial Function and Microinflammation in Obese Type 2 Diabetic Patients*

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ABSTRACT Objective: To investigate the effect of lilaluptide combined with metformin on glucose and lipid metabolism, endothelial function and microinflammation in obese type 2 diabetes mellitus (T2DM). **Methods:** 117 obese T2DM patients who were admitted to our hospital from July 2016 to April 2019 were selected. According to the random number table method, the patients were divided into the control group (n=58, metformin treatment) and study group (n=59, lilalutide combined with metformin treatment). The body mass index (BMI), glucose and lipid metabolism indexes [high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), triglycerides (TG), glycosylated hemoglobin (HbA1c), low density lipoprotein cholesterol (LDL-C), total cholesterol (TC)], endothelial function indexes [endothelin (ET), nitric oxide (NO)] and micro inflammation state indexes [C-reactive protein (CRP) and interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α)] were compared between the two groups, the adverse reactions during the treatment were recorded. **Results:** 12 weeks after treatment, the BMI, FPG, HbA1c, TG, TC, LDL-C, ET, CRP, TNF-α and IL-6 of the two groups were lower than those before treatment, and those of the study group were lower than those of the control group ($P<0.05$). 12 weeks after treatment, HDL-C and NO of the two groups were higher than those before treatment, and those of the study group were higher than those of the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Lilaluptide combined with metformin in the treatment of obese T2DM patients can effectively control the glucose and lipid metabolism, improve the vascular endothelial function and micro inflammatory state, and the drug safety is good.

Key words: Lilalutide; Metformin; Obesity Type 2 diabetes; Glucose and lipid metabolism; Endothelial function; Microinflammatory state

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前言

2 型糖尿病(T2DM)主要是由于患者胰岛β细胞功能受损致使胰岛素分泌不足引起机体糖代谢紊乱[1,2]。T2DM 除可引起机体糖代谢紊乱外,还可导致脂质代谢紊乱,肥胖诱发[3]。据以往报道统计[4],约有 80%左右的 T2DM 患者超重或者肥胖。近年来,随着人们生活水平的改善,饮食结构的改变,T2DM 肥胖患者发病率呈逐年递增趋势,给人们的日常工作和生活带来严重影响[5,6]。故临床在对 T2DM 患者进行对症降糖治疗的同时,亦需要患者控制体质量来进行辅助治疗。二甲双胍是临床治疗 T2DM 的一线药物,具有控制血糖效果佳、保护心血管、不良反应少等特点,虽可获得一定治疗效果,但整体疗效仍有待提升[7]。利拉鲁肽是一种新型的治疗 T2DM 和肥胖的药物,具有减轻患者体质量、降低血糖水平及促进胰岛 β 细胞再生的优点[8]。本研究通过对我院收治的部分 T2DM 患者给予利拉鲁肽联合二甲双胍治疗,疗效满意,整理如下。

1 资料与方法

1.1 基线资料

选取 2016 年 7 月 ~2019 年 4 月期间我院收治的 117 例 T2DM 肥胖患者。纳入标准:(1)T2DM 诊断标准参考《中国 2 型糖尿病防治指南(2013 年版)》[9];(2)体质量指数(BMI)≥ 30 kg/m^2;(3) 入组时降糖药物服用 <1 个月且停药超过 3 个月或未服用降糖药物;(4)患者及其家属知情本研究且签署同意书。排除标准:(1)长期服用糖皮质激素患者;(2)合并糖尿病急性并发症;(3)伴有甲减、甲亢等内分泌系统疾病患者;(4)合并心肝肾等脏器功能障碍者;(5)精神意识障碍患者;(6)对本次研究用药存在禁忌者;(7)妊娠及哺乳期妇女。此次研究已获取我院伦理学委员会批准进行。根据数字表法分为对照组(n=58)和研究组(n=59),其中对照组女 24 例,男 24 例;年龄 40-74 岁,平均(55.38± 9.27)岁;BMI 为 30~35 kg/m^2,平均(32.15± 0.86) kg/m^2;病程 4-16 年,平均(7.39± 2.18)年。研究组男 33 例,女 26 例;年龄 40-72 岁,平均(54.92± 10.27)岁;BMI 为 31~37 kg/m^2,平均(32.46± 0.81)kg/m^2;病程 3-17 年,平均(7.18± 2.06)年。两组一般资料比较无差异(P>0.05),具有可比性。

1.2 方法

两组患者入院后均给予疾病知识讲解、指导患者合理饮食计划、健康教育、适量运动等常规干预,在此基础上,对照组患者给予二甲双胍片(上海上药信谊药厂有限公司,国药准字:H20123035,规格:0.5 g)口服治疗,1g/ 次,2 次 /d。研究组则在对照组的基础上联合利拉鲁肽注射液(Novo Nordisk A/S,注册证号:J20160037,规格:3 mL:18 mg)治疗,于每日早餐前皮下注射,0.6 mg/ 次,1 次 /d。两组患者均连续治疗 12 周,治疗期间若出现低血糖者,则适当降低剂量以减轻不良反应。

1.3 观察指标

1.3.1 糖代谢指标、BMI 测量 于治疗前、治疗 12 周后测量两组患者的身高和体重,计算 BMI,BMI= 体重(kg)/ 身高(m^2)。于治疗前、治疗 12 周后抽取两组患者空腹静脉血,采用美国贝克曼 DXC800 全自动生化分析仪测量空腹血糖(FPG)、糖化血红蛋白(HbA1c)。

1.3.2 内皮功能、血脂、微炎症指标测量 于治疗前、治疗 12 周后抽取患者 6 mL 空腹静脉血,离心半径设置为 10 cm,经 3800 r/min 离心 12 min,分离血清待测。采用全自动生化分析仪检测血脂指标:甘油三酯(TG)、高密度脂蛋白胆固醇(HDL-C)、总胆固醇(TC)、低密度脂蛋白胆固醇(LDL-C);采用放射免疫法检测内皮素(ET),采用硝酸还原比色法检测一氧化氮(NO),采用酶联免疫吸附法检测 C 反应蛋白(CRP)、白介素 -6(IL-6)以及肿瘤坏死因子 -α(TNF-α)水平,严格遵守试剂盒(武汉明德生物科技股份有限公司)说明书进行操作。

1.3.3 安全性评价 记录不良反应情况。

1.4 统计学方法

本研究结果的处理软件为 SPSS21.0,以($\bar{x}\pm s$)表示计量资料,采用 t 检验,计数资料以率表示,采用 x^2 检验,α=0.05 为检验水准。

2 结果

2.1 血糖相关指标、BMI 比较

治疗前,两组 BMI、FPG 及 HbA1c 比较无统计学差异(P>0.05);治疗 12 周后,两组 BMI、FPG 及 HbA1c 均低于治疗前,且研究组低于对照组(P<0.05)。见表 1。

表 1 血糖相关指标、BMI 比较($\bar{x}\pm s$)

Table 1 Comparison of blood glucose related indexes and BMI($\bar{x}\pm s$)

Groups	BMI(kg/m^2)		FPG(mmol/L)		HbA1c(%)	
	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment
Control group(n=58)	32.15± 0.86	27.75± 0.93*	10.48± 1.18	7.26± 0.91*	9.15± 0.73	7.39± 0.74*
Study group(n=59)	32.66± 0.81	24.36± 0.74*	10.36± 1.03	5.95± 0.92*	9.08± 0.86	6.01± 0.68*
t	1.360	21.837	0.586	7.742	0.474	10.506
P	0.177	0.000	0.559	0.000	0.636	0.000

Note: compared with before treatment, *P<0.05.

2.2 血脂指标比较

治疗前,两组 TG、TC、LDL-C 及 HDL-C 比较无差异(P>0.05);治疗 12 周后,两组 HDL-C 高于治疗前,TG、TC、LDL-C 均低于治疗前,且研究组 HDL-C 较对照组高,TG、TC、LDL-C 较对照组低(P<0.05)。见表 2。

表 2 两组血脂指标比较($\bar{x}\pm s$)

Table 2 Comparison of blood lipid indexes between the two groups($\bar{x}\pm s$)

Groups	TG(mmol/L)		TC(mmol/L)		HDL-C(mmol/L)		LDL-C(mmol/L)	
	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment
Control group (n=58)	2.84± 0.61	1.97± 0.58*	6.34± 0.54	4.18± 0.65*	0.94± 0.13	1.46± 0.26*	5.02± 0.41	3.93± 0.35*
Study group (n=59)	2.78± 0.73	1.24± 0.46*	6.28± 0.43	2.35± 0.53*	0.99± 0.18	1.79± 0.23*	5.09± 0.38	2.56± 0.31*
t	0.482	7.550	0.665	16.703	1.720	7.275	0.958	22.423
P	0.631	0.000	0.507	0.000	0.088	0.000	0.340	0.000

Note: compared with before treatment, *P<0.05.

2.3 内皮功能指标比较

治疗前,两组血清 ET、NO 水平比较无统计学差异(P>0.05);两组治疗 12 周后血清 ET 水平较治疗前降低,NO 水平较治疗前升高(P<0.05);研究组治疗 12 周后血清 ET 水平低于对照组,NO 水平高于对照组(P<0.05)。见表 3。

表 3 两组内皮功能指标比较($\bar{x}\pm s$)

Table 3 Comparison of endothelial function indexes between the two groups($\bar{x}\pm s$)

Groups	ET(ng/L)		NO(μmol/L)	
	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment
Control group(n=58)	71.53± 8.54	62.77± 9.94*	58.92± 6.40	66.14± 7.82*
Study group(n=59)	72.13± 9.27	50.79± 9.62*	59.77± 6.36	78.95± 6.97*
t	0.364	6.625	0.721	9.357
P	0.717	0.000	0.473	0.000

Note: compared with before treatment, *P<0.05.

2.4 微炎症状态指标比较

治疗前,两组 CRP、TNF-α 及 IL-6 比较无差异(P>0.05);治疗 12 周后两组 CRP、TNF-α 及 IL-6 降低,且研究组较对照组低(P<0.05)。见表 4。

表 4 两组微炎症状态指标比较($\bar{x}\pm s$)

Table 4 Comparison of microinflammatory state indexes between the two groups($\bar{x}\pm s$)

Groups	IL-6(pg/mL)		CRP(mg/L)		TNF-α(ng/L)	
	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment
Control group (n=58)	20.27± 3.17	14.90± 3.02*	3.62± 0.94	2.16± 0.39*	37.26± 2.42	24.36± 3.34*
Study group(n=59)	19.52± 2.46	9.86± 2.28*	3.66± 0.85	1.29± 0.32*	37.54± 3.92	15.26± 3.64*
t	1.431	10.199	0.242	13.201	0.464	13.505
P	0.155	0.000	0.810	0.000	0.644	0.000

Note: compared with before treatment, *P<0.05.

2.5 不良反应比较

治疗期间,对照组发生低血糖 1 例、恶心呕吐、头疼各 2 例,不良反应发生率为 8.62%(5/58);研究组发生低血糖、头疼各 3 例、恶心呕吐 2 例,不良反应发生率为 13.56%(8/59);两组不良反应发生率比较无差异(x^2=0.723,P=0.394)。

3 讨论

T2DM 在我国 20 岁以上人群的发病率约为 9.7%,其中肥胖人群的发病率尤高[10]。现已有不少研究证实了肥胖与胰岛素抵抗关系密切[11,12]。T2DM 患者胰岛素抵抗可引起脂质代谢紊乱,血管弹性降低,进而导致内皮功能损伤,肥胖加重,提高 T2DM 并发症发生率[13,14]。同时胰岛素抵抗还可促进动脉粥样硬化的形成,增加心血管事件发生率,而心血管病变也是导致 T2DM 患者死亡的主要原因之一[15,16]。基础的胰岛素治疗可在短期内将 T2DM 患者血糖控制在正常范围,但胰岛素长期大量使用易引起胰岛β 细胞功能不全,导致低血糖、中心性肥胖

加重等并发症的风险增加[17,18]。因此,对于本身即存在肥胖的T2DM患者，口服降糖药物是其首选方案。二甲双胍是治疗T2DM的常用药物,可控制胰岛素抵抗,控制血糖并减轻体重[19]。然而T2DM作为由遗传因素和环境因素共同作用形成的多基因遗传性疾病,发病机制及其复杂,单一的降糖药物治疗并不能达到理想的治疗效果。利拉鲁肽在控制T2DM伴肥胖患者的血糖及整体状态方面均有积极意义,已得到了临床的广泛认可[20]。

本次研究中，两组治疗12周后BMI、糖脂代谢均有所改善,且研究组效果更佳,可见利拉鲁肽联合二甲双胍治疗肥胖T2DM患者，可有效控制其体内糖脂代谢紊乱及体重增长,究其原因,甲双弧的主要作用机制体现为以下几点:通过作用于肝脏,抑制糖异生,降低肝糖输出量;通过作用于肠道,抑制肠壁细胞摄取葡萄糖,提高胰升糖素样肽1水平;通过作用于脂肪、肌肉,增加其对葡萄糖的摄取及利用率[21-23]。利拉鲁肽的主要作用机制则体现为以下几点：通过促进机体胰岛素分泌,提高机体组织细胞对胰岛素的敏感性；减少胰高血糖素的分泌,抑制患者食欲从而减轻体重;利拉鲁肽经皮下注射,半衰期较长,可延长其药效作用时间,使患者在一定时间内有饱腹感,持续控制血糖水平;利拉鲁肽可抑制胰岛β细胞凋亡,促进并恢复胰岛β细胞的功能[24-26]。既往研究表明[27],利拉鲁肽可促使白色脂肪棕色化,增加棕色脂肪产热,利于减少内脏脂肪、减轻体重。上述两种药物从不同作用机制出发,发挥协同作用,共同提高治疗效果。此外本次研究结果还显示,两组血管内皮功能及微炎症状态均有所改善,且利拉鲁肽联合二甲双胍治疗者改善效果更佳。NO主要由血管内皮细胞分泌,可扩张血管,防止动脉粥样硬化的形成;ET则是一种缩血管物质,在维持血管张力中发挥重要作用；而微炎症反应可通过氧化应激、NF-κB等作用,引起T2DM患者各脏器结构和功能的改变,加重其病情程度,其中CRP、TNF-α及IL-6均是临床常见的炎症因子[28]。这可能是因为胰升糖素样肽1本身即具有能改善内皮功能以及合理控制炎症的发生,而利拉鲁肽是一种与胰升糖素样肽1序列相似度达97%的衍生物,控制病情效果较佳[29,30]。另两组不良反应发生率比较差异无统计学意义,可见两药用药安全性较好。

综上所述,利拉鲁肽联合二甲双胍治疗肥胖T2DM患者,可有效控制其体内糖脂代谢紊乱,改善血管内皮功能及微炎症状态,且用药安全性较好。

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