二甲双胍联合运动疗法干预妊娠期糖尿病患者的临床研究 *

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摘要 目的：探讨二甲双胍联合运动疗法对妊娠期糖尿病(GDM)患者临床效果的影响。方法：将 2020 年 3 月到 2022 年 3 月北京航天总医院收治的 89 例 GDM 患者，按照抛掷硬币法随机分为组分为观察组(n=45)和对照组(n=44)。对照组口服盐酸二甲双胍片，观察组在对照组基础上加用运动疗法。对比两组患者的临床疗效、血糖指标、氧化应激指标、炎症因子水平、妊娠结局及不良反应。结果：治疗后观察组临床疗效总有效率 93.33 (42/45) 高于对照组 75.00%(33/44)($P<0.05$)。治疗后两组患者空腹血糖(FPG)、餐后 2 h 血糖(2hPG)、糖化血红蛋白(HbAlc)均降低，且观察组显著低于对照组(均 $P<0.05$)。治疗后两组超氧化物歧化酶(SOD)水平均升高且观察组显著高于对照组，丙二醛(MDA)、活性氧(ROS)水平均降低且观察组显著低于对照组(均 $P<0.05$)。治疗后两组超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子(TNF-α、白细胞介素-6(IL-6)水平均降低且观察组水平显著低于对照组(均 $P<0.05$)。观察组剖宫产、早产发生率低于对照组(均 $P<0.05$)。治疗期间两组患者不良反应事件总发生率无差异($P>0.05$)。结论：二甲双胍联合运动疗法能有效控制 GDM 患者血糖水平，优化氧化应激指标，降低炎症因子水平，改善妊娠结局，且具有一定的安全性。

关键词：妊娠期糖尿病；二甲双胍；运动疗法；炎症因子；氧化应激；妊娠结局

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Clinical Study of Metformin Combined with Exercise Therapy in Intervention of Patients with Gestational Diabetes Mellitus*

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ABSTRACT Objective: To explore the influence of metformin combined with exercise therapy on the clinical effect of patients with gestational diabetes mellitus (GDM). Methods: 89 patients with gestational diabetes admitted to Beijing Aerospace General Hospital from March 2020 to March 2022 were were randomly divided into observation group (n=45) and control group (n=44) according to the coin toss method. The control group was given metformin hydrochloride tablets orally, while the observation group was given exercise therapy on the basis of the control group.The clinical efficacy, blood glucose indicators, oxidative stress indicators, inflammatory factor levels, pregnancy outcomes, and adverse reactions of the two groups of patients were compared. Results: After treatment, After treatment, the total effective rate of clinical efficacy in the observation group was 93.33% (42/45), which was higher than 75.00% (33/44) in the control group($P<0.05$). After treatment, fasting blood glucose (FPG), 2 h plasma glucose(2hPG), and glycosylated hemoglobin(HbAlc) in both groups decreased, and the observation group was significantly lower than the control group (all $P<0.05$). After treatment, the levels of superoxide dismutase (SOD) in both groups increased and the observation group was significantly higher than the control group, while the levels of malondialdehyde (MDA) and reactive oxygen species (ROS) decreased and the observation group was significantly lower than the control group (all $P<0.05$). After treatment, the level of hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor (TNF-α), interleukin-6 (IL-6) in both groups decreased and the observation group was significantly lower than that in the control group (all $P<0.05$). The incidence of cesarean section and premature delivery in the observation group was lower than that in the control group (all $P<0.05$). There was no difference in the total incidence of adverse events between the two groups during treatment ($P>0.05$). Conclusion: Metformin combined with exercise therapy can effectively control blood glucose levels in GDM patients,optimize oxidative stress indicators, reduce inflammatory factor levels, and improve pregnancy outcomes, and has certain safety.

Key words: Gestational diabetes mellitus; Metformin; Exercise therapy; Inflammatory factors; Oxidative stress; Pregnancy outcome

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前言

妊娠期糖尿病(GDM)是在妊娠期间首次出现以糖代谢异常为特征的短暂性糖尿病[1,2]。GDM 在全世界的发病率为 14%，被广泛认为是改善母婴健康的主要障碍之一，若未及时得到控制，则会增加短期和长期并发症的发生率，如酮症酸中毒，高血压，分娩并发症等，严重威胁母婴健康[3,4]。GDM 的发病机制尚不明确，多数研究认为该疾病主要是由妊娠期胰岛素抵抗和胰岛β细胞功能障碍引起的，也与氧化应激和炎症反应密切相关[5,6]。目前血糖控制是治疗 GDM 的关键因素，二甲双胍是全球应用最广泛的口服降糖药之一，具有较好的降糖作用，且不良反应较少，国际上已有多个学术组织将其作为 GDM 患者的推荐用药[7]。运动疗法是一种经济有效且较为方便的治疗与预防方案，餐后适当运动可增加组织对血糖的利用，消除肥胖，还有助于细胞对胰岛素敏感性的增加，降低胰岛素抵抗[8]。但目前临床缺少二者联合应用的尝试，因此本研究探讨二甲双胍联合运动疗法 GDM 患者临床效果的影响，现报道如下。

1 资料与方法

1.1 一般资料

收集 2020 年 3 月到 2022 年 3 月北京航天总医院治疗的 89 例患者，均符合 GDM 的诊断标准[9]。纳入标准如下：(1)血糖指标符合要求且需要药物控制；(2) 患者年龄 22~40 岁；(3)单胎妊娠，临床病历资料齐全；(4)无糖尿病史、家族糖尿病史。排除标准：(1)心肝肾等重要器官功能严重异常者；(2)对本次治疗药物过敏者；(3)合并高血压者；(4)患有甲状腺疾病等其他内分泌疾病者；(5)精神、智力存在障碍者。按照抛掷硬币法随机分为观察组和对照组，其中观察组 45 例，年龄为 26~39 岁，平均(28.40± 3.80)岁，孕周 18~29 周，平均孕周(23.40± 4.50)周；孕次 1~5 次，平均孕次(3.10± 1.30)次；产次 1~3 次，平均产次(2.21± 0.62)次。对照组 44 例，年龄为 26~40 岁，平均为(29.32± 3.60)岁；孕周为 20~28 周，平均孕周(23.80± 4.11)周；孕次为 2~5 次，平均孕次(3.21± 1.50)次；产次为 1~3 次，平均产次(2.1± 0.6)次。两组一般资料比较无差异(均 $P>0.05$)。本次研究经过伦理委员会批准，所有患者及家属均知情同意。

1.2 方法

对照组口服盐酸二甲双胍片(中美上海施贵宝制药有限公司，0.5 g / 片，国药准字 H20023370)，每次 0.5 g，每天 2 次，随早晚用。观察组在对照组的基础上进行运动治疗，指导每日餐后进行 60 min 的运动锻炼，主要运动方式为上肢运动与体操运动。上肢运动：患者坐于靠背椅上，左右手各一个重为 1 kg 的哑铃，伸直胳膊向上举起，与地面呈垂直角度，一组 5 min，共运动 6 组，每做一组可暂停休息 2 min。体操运动：脚腕运动，左右摇摆脚腕，十次一组，左右各两组；骨盆运动，单膝曲起，膝盖慢慢向外侧最大角度打开，然后慢慢收回，十次一组，左右各两组；盘腿运动：盘腿坐下，背部挺直，双手轻放于两膝上，呼气时按压两膝向下，吸气时放松双手，十次一组，一共两组。以上运动可根据孕妇个人具体情况进行调整，也可自行增加散步、瑜伽等基础运动。时刻注意孕妇的身体情况，若有轻微不适立即停止运动。每周运动至少 4 次。两组均持续治疗直至胎儿出生。

1.3 观察指标

(1)疗效评价：参考《临床疾病诊断与疗效判断标准》[10]：治愈：患者各时段血糖水平恢复至正常值水平，妊娠正常，胎儿发育正常，症状体征明显改善；好转：血糖达到控制目标，胎儿发育、妊娠正常，症状体征得到改善；无效：没有达到以上标准者。总有效率 = 治愈率 + 好转率。(2)血糖指标：治疗前和治疗后分别采集两组患者的空腹、餐后 2 h 的外周静脉血，使用迈瑞 BS-280 全自动生化分析仪（深圳迈瑞生物医疗电子股份有限公司)检测血清空腹血糖(FPG)，餐后 2 h 血糖(2hPG)水平，使用 SK68 糖化血红蛋白分析测定仪(潍坊华盛医疗器械有限公司)测定糖化血红蛋白(HbAlc)水平。(3)氧化应激指标：采用酶联免疫吸附法(ELISA)检测治疗前后两组患者超氧化物歧化酶(SOD)、丙二醛(MDA)、活性氧(ROS)指标，检测试剂盒购自北京华越洋生物科技有限公司。(4)炎症因子指标：采用免疫比浊法检测治疗前后两组患者超敏 C 反应蛋白（hs-CRP)水平，用酶联免疫吸附法检测肿瘤坏死因子(TNF-α)、白细胞介素 -6(IL-6)水平。所有检测试剂盒均购自上海科艾博生物技术有限公司。(5)妊娠结局：随访至分娩或终止妊娠，记录两组患者所出现的羊水过多、剖宫产、早产、流产、新生儿呼吸窘迫、新生儿低血糖等事件发生情况。(6)不良反应：记录治疗期间两组患者的不良反应。

1.4 统计学分析

所有数据经 SPSS 25.0 完成分析，符合正态分布且具备方差齐性计量资料以均数± 标准差($\bar{x}± s$)表示，采用独立样本 t 检验或校正 t 检验；计数资料以例或百分比表示，采用卡方检验或校正卡方检验，检验水准 α=0.05，$P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗后观察组治愈 36 例；好转 6 例；无效 3 例，对照组治愈 20 例；好转 13 例；无效 11 例。观察组临床疗效总有效率 93.33(42/45)高于对照组 75.00%(33/44)(x^2=5.641，P=0.018)。

2.2 两组治疗前后血糖指标比较

治疗前两组 FPG、2hPG、HbAlc 水平比较无差异(均 $P>0.05$)，治疗后两组 FPG、2hPG、HbAlc 水平均降低，且观察组显著低于对照组(均 $P<0.05$)，见表 1。

2.3 两组治疗前后氧化应激指标比较

治疗前两组 SOD、MDA、ROS 水平比较均无统计学差异(均 $P>0.05$)，治疗后两组 SOD 水平均升高且观察组显著高于对照组，MDA、ROS 水平均降低且观察组显著低于对照组（均 $P<0.05$)，见表 2。

2.4 两组治疗前后炎症因子指标比较

治疗前 hs-CRP、TNF-α、IL-6 水平比较均无统计学差异(均 $P>0.05$)，治疗后两组 hs-CRP、TNF-α、IL-6 水平均降低且观察组显著低于对照组(均 $P<0.05$)，见表 3。

2.5 两组妊娠结局比较

观察组剖宫产、早产发生率低于对照组(均 $P<0.05$)，羊水过多、流产、新生儿呼吸窘迫及新生儿低血糖发生率与对照组比较无差异(均 $P>0.05$)。见表 4。

表 1 两组治疗前后血糖指标比较($\bar{x}\pm s$)

Table 1 Comparison of blood glucose indicators between the two groups before and after treatment($\bar{x}\pm s$)

Groups	FPG(mmol/L)		2hPG(mmol/L)		HbAlc(%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group(n=45)	9.11± 1.41	3.94± 0.91*#	12.11± 2.35*#	5.87± 0.79*#	7.93± 1.41*#	5.20± 0.63*#
Control group(n=44)	9.13 ± 1.39	6.09± 1.06*	11.92± 2.34*	8.98± 0.83*	8.05± 1.40*	6.02± 0.87*
t	0.067	10.275	0.382	18.109	0.403	5.101
P	0.946	0.000	0.703	0.000	0.688	0.000

Note: Comparison with before treatment, *$P<0.05$; Compared with the control group during the same period, #$P<0.05$.

表 2 两组治疗前后氧化应激指标比较($\bar{x}\pm s$)

Table 2 Comparison of oxidative stress indicators between the two groups before and after treatment($\bar{x}\pm s$)

Groups	SOD(μ/mL)		MDA(nmol/L)		ROS(μ/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group(n=45)	111.29± 11.03	229.12± 22.75*#	64.57± 6.34	40.43± 4.08*#	353.26± 35.42	201.03± 19.87*#
Control group(n=44)	110.01± 10.57	171.13± 17.23*	64.28± 6.31	52.34± 5.12*	352.32± 35.38	273.25± 27.31*
t	0.559	13.533	0.216	18.109	0.125	14.289
P	0.578	0.000	0.829	0.000	0.901	0.000

Note: Comparison with before treatment, *$P<0.05$; Compared with the control group during the same period, #$P<0.05$.

表 3 两组治疗前后炎症因子指标比较($\bar{x}\pm s$)

Table 3 Comparison of inflammatory factor indicators between the two groups before and after treatment($\bar{x}\pm s$)

Groups	hs-CRP(mg/L)		TNF-α(pg/mL)		IL-6(mmol/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group(n=45)	5.89± 1.13	3.35± 0.76*#	27.45± 2.13	19.37± 1.64*#	34.56± 3.80	24.43± 2.51*#
Control group(n=44)	5.73± 1.42	4.12± 0.92*	28.08± 2.19	22.48± 2.05*	35.21± 3.76	30.66± 2.74*
t	0.589	4.309	1.320	7.912	0.811	11.189
P	0.558	0.000	0.190	0.000	0.420	0.000

Note: Comparison with before treatment *$P<0.05$; Compared with the control group during the same period, #$P<0.05$.

表 4 两组妊娠结局比较[n(%)]

Table 4 Comparison of pregnancy outcomes between the two groups[n(%)]

Groups	n	Polyhydramnios	Cesarean section	Premature delivery	Abortion	Neonatal respiratory distress	Neonatal hypoglycemia
Observation group	45	4(8.89)	6(13.33)	3(6.67)	1(2.22)	2(4.44)	2(4.44)
Control group	44	8(18.18)	16(36.36)	11(25.00)	6(13.64)	4(9.09)	2(4.55)
x^2		1.647	6.341	5.641	1.681	0.204	0.239
P		0.199	0.012	0.018	0.195	0.652	0.625

2.6 两组不良反应发生情况比较

治疗期间,两组患者均出现胃肠道反应、皮疹、肝功能异常、低血糖等不良反应事件,但总发生率组间无差异($P>0.05$)。见表5。

3 讨论

GDM 是目前最常见的妊娠并发症,会增加孕妇和婴儿长期并发症的风险,包括过度肥胖、葡萄糖代谢障碍、高血压等疾病[11,12]。二甲双胍是较为常用的一种双胍类降糖药物,能有效改善 GDM 患者血糖水平,且经济实惠、安全性高[13,14]。但单一药物治疗存在起效慢,疗效欠佳等缺点,因此临床医师开始采用其他疗法进行辅助治疗[15,16]。运动疗法是治疗 GDM 患者的首选方法之一,能有效降低孕妇 GDM 发生率[17,18]。鉴于此,本研究对二甲双胍联合运动疗法治疗 GDM 患者并对其临床效果进行观察,旨在为相关研究提供理论依据。

有研究表明,GDM 患者的氧化应激指标水平明显高于正常孕妇,是反应血糖水平的重要指标[19,20]。本研究结果显示,治疗后两组的 SOD 水平均升高,MDA、ROS 水平均降低,且观察

表 5 两组不良反应发生情况比较[n(%)]

Table 5 Comparison of adverse reactions between the two groups[n(%)]

Groups	n	Gastrointestinal reactions	Erythra	Abnormal liver function	Hypoglycemia	Total occurrence rate
Observation group	45	3(6.67)	2(4.44)	1(2.22)	1(2.22)	7(15.56)
Control group	44	4(9.09)	2(4.55)	1(2.27)	3(6.82)	10(22.73)
x^2						0.741
P						0.390

组的指标水平变化幅度明显高于对照组,提示二甲双胍联合运动疗法能有效改善患者的氧化应激指标。分析其原因可能为患者体内血糖水平降低,使得氧化/抗氧化作用相对平衡。炎症反应参与了 GDM 的发生和进展, 其可使胰岛素敏感性降低,调节机体激素分泌,增加胰岛素抵抗[21,22]。本研究治疗后两组患者的 hs-CRP、TNF-α、IL-6 水平均下降,且观察组的降低程度显著优于对照组,提示二甲双胍联合运动疗法能有效改善患者的hs-CRP、TNF-α、IL-6 水平,控制炎症反应。

　　本研究结果显示,观察组的总有效率为 93.35%,高于对照组的 75.00%;治疗后两组血糖指标 FPG、2hPG、HbAlc 水平均降低,且观察组显著低于对照组。分析其原因可能为二甲双胍能抑制糖异生,增加机体组织对葡萄糖的摄取和再利用,提高机体对胰岛素的增敏性[23,24],结合运动疗法,加大机体对葡萄糖的消耗,使血糖水平降低[25,26]。孕妇血糖过高会使胎儿长期处于高血糖环境中,影响胎儿的胰岛素分泌水平,胎儿出生后胰岛素的过多释放会导致低血糖、呼吸窘迫等一系列并发症出现[27,28]。在本研究结果中,观察组剖宫产、早产发生率显著低于对照组,提示二甲双胍联合运动疗法不仅可降低患者血糖水平,还可改善妊娠结局。两组不良反应较少,且总发生率组间差异无统计学意义($P>0.05$),提示二甲双胍联合运动疗法不增加不良反应,安全性高。

　　综上所述, 二甲双胍联合运动疗法治疗可显著降低 GDM 患者血糖水平, 降低体内氧化应激指标水平及炎症因子水平,改善患者的妊娠结局,且具有一定的安全性。

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