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## 双歧杆菌四联活菌片对初诊超重2型糖尿病患者 糖脂代谢和 Toll 样受体 4 的影响

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**[摘要]** 目的: 探讨双歧杆菌四联活菌片对初诊超重2型糖尿病(type 2 diabetes mellitus, T2DM)患者血糖、血脂、Toll样受体4(Toll-like receptor 4, TLR4)的影响。方法: 选取2019年1月至6月就诊的初诊T2DM患者, 符合 $24.0 \text{ kg/m}^2 \leq \text{体重指数}(\text{body mass index, BMI}) < 28.0 \text{ kg/m}^2$ , 将入选患者按照1:1随机分为对照组(50例)和观察组(50例)。两组均给予饮食指导及适量运动等建议, 对照组给予盐酸二甲双胍片(1 500 mg/d)治疗, 观察组在对照组的基础上予以双歧杆菌四联活菌片(3片/次, 3次/日)治疗, 两组均治疗3个月。统计两组患者最终纳入数。比较两组治疗前后空腹血糖(fasting plasma glucose, FPG)、餐后2 h血糖(2-hour postprandial blood glucose, 2hPG)、糖化血红蛋白(glycosylated hemoglobin, HbA1c)、总胆固醇(total cholesterol, TC)、三酰甘油(triglyceride, TG)、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)、空腹胰岛素(fasting insulin, FINS)、稳态胰岛素评价指数(homeostasis model assessment-insulin resistance, HOMA-IR)、TLR4等指标的差异。结果: 在治疗研究过程中, 对照组退出7例, 观察组退出5例, 最终对照组纳入43例, 观察组纳入45例。治疗3个月后, 两组患者FPG, 2hPG, HbA1c, TG, FINS, HOMA-IR, TLR4较前下降, HDL-C较前升高, 且观察组下降/升高更明显(均 $P < 0.05$ ); 两组患者TC, LDL-C均较前下降, 但两组治疗后差异无统计学意义(均 $P > 0.05$ )。结论: 双歧杆菌四联活菌片辅助口服降糖药在超重T2DM患者中应用效果良好, 能够改善患者的血糖、血脂水平, 降低TLR4水平, 有一定的临床意义。

**[关键词]** 双歧杆菌四联活菌片; 超重糖尿病; Toll样受体4; 胰岛素抵抗

## Effect of bifidobacterium tetragenous viable bacteria tablets on newly diagnosed overweight type 2 diabetes on glucose and lipid metabolism and Toll-like receptor 4

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**Abstract** **Objective:** To investigate the effect of bifidobacterium tetragenous viable bacteria tablets on newly diagnosed

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overweight type 2 diabetes on blood glucose, blood lipid and Toll-like receptor 4 (TLR4). **Methods:** Newly diagnosed type 2 diabetic patients who were diagnosed from January 2019 to June 2019 were selected, which met  $24.0 \text{ kg/m}^2 \leq \text{body mass index (BMI)} < 28.0 \text{ kg/m}^2$ . The selected patients were randomly divided into two groups according to 1:1, and the control group was 50 cases, observation group of 50 cases. Both groups were given basic treatments such as dietary guidance and proper exercise. The control group was given metformin hydrochloride tablets (1 500 mg/day). The observation group was treated with bifidobacterium tetragenous viable bacteria tablets (3 tablets/time, 3 times/day) on the basis of the control group. Both groups were treated for 3 months. The number of patients included in the 2 groups was counted. Fasting plasma glucose (FPG), 2-hour postprandial blood glucose (2hPG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), fasting insulin (FINS), homeostasis model assessment-insulin resistance (HOMA-IR), and TLR4 were compared before and after treatment in the 2 groups. **Results:** During the study, 7 patients were withdrawn from the control group, 5 patients were withdrawn from the observation group, 43 patients were eventually included in the control group, and 45 patients were included in the observation group. After 3 months of treatment, FPG, 2hPG, HbA1c, TG, FINS, HOMA-IR, and TLR4 decreased in the 2 groups, HDL-C was higher than before, and the observation group decreased/increased significantly (all  $P < 0.05$ ). The TC and LDL-C of the 2 groups were lower than before, but there was no significant difference between the 2 groups after treatment (all  $P > 0.05$ ). **Conclusion:** The bifidobacterium tetragenous viable bacteria tablets supplemented oral hypoglycemic agent is good for the overweight type 2 diabetes patients, and can improve blood sugar and blood lipid levels, as well as reduce TLR4 levels, which has a certain clinical significance.

**Keywords** bifidobacterium tetragenous viable bacteria tablets; overweight diabetes; Toll-like receptor 4; insulin resistance

2型糖尿病(type 2 diabetes mellitus, T2DM)是一种常见的代谢紊乱综合征,主要表现为胰岛素抵抗和相对胰岛素缺乏所致的高血糖<sup>[1]</sup>。T2DM常伴有超重或肥胖,超重及肥胖又可加重胰岛素抵抗和糖尿病。新近研究<sup>[2-3]</sup>表明肠道菌群在糖尿病的发生、发展中扮演着重要角色,肠道双歧杆菌数量的减少与超重及肥胖糖尿病有密切关系,并导致低度炎症状态。Toll样受体4(Toll-like receptor 4, TLR4)是天然免疫反应的典型模式受体,可辨别革兰氏阴性菌表层的脂多糖(lipopolysaccharide, LPS)、肽聚糖(peptidoglycan, PGN)等,从而促进炎症通路的激活<sup>[4]</sup>。双歧杆菌四联活菌片可以在肠黏膜表面形成一定的微生物环境,对内毒素血症有一定的改善<sup>[5]</sup>;但是关于双歧杆菌四联活菌片治疗糖尿病是否会直接影响糖脂代谢及其机制尚未阐述清楚。本研究以初诊超重T2DM为研究对象,观察双歧杆菌四联活菌片对糖脂代谢相关指标及血清中TLR4的影响,旨在探究其机制,为双歧杆菌四联活菌片治疗超重糖尿病

提供一定的循证医学依据。

## 1 对象与方法

### 1.1 对象

收集2019年1月至6月就诊的超重T2DM患者。入组标准:1)年龄18~65岁者;2)符合1999年WHO的T2DM诊断标准<sup>[6]</sup>者;3)既往未系统诊治者;4)根据中国肥胖问题工作组《中国成人超重和肥胖症预防与控制指南》<sup>[7]</sup>超重( $24.0 \text{ kg/m}^2 \leq \text{BMI} < 28.0 \text{ kg/m}^2$ )的定义者;5)患者均签署知情同意书,临床数据完整。排除标准:1)1型糖尿病、妊娠期糖尿病及其他特殊类型糖尿病患者;2)合并糖尿病各种急性并发症患者(感染、糖尿病酮症酸中毒、高渗高血糖昏迷等);3)合并糖尿病各种慢性并发症患者(糖尿病肾病、糖尿病周围神经病变等);4)合并肝肾功能不全;5)合并心肺功能不全者。本研究已通过吉林大学第二医院医学伦理委员会审批,最终纳入研究患者88例,对照组43例、观察组45例。

## 1.2 方法

两组均给予糖尿病患者统一的健康教育、糖尿病饮食指导、适量有氧运动处方等, 调脂治疗均给予阿托伐他汀钙片 20 mg, 每日一次睡前口服。对照组给予盐酸二甲双胍片口服(规格: 0.5 g/片, 中美上海施贵宝制药有限公司)500 mg/次, 3次/d, 观察组在对照组的基础上予以双歧杆菌四联活菌片(思连康, 规格: 0.5 g/片, 杭州远大生物制药有限公司)3片/次, 3次/d。两组均治疗3个月。统计并比较两组基线时和治疗后3个月各观察指标的变化。

### 1.2.1 临床资料收集

收集入组患者性别、年龄、病程、身高、体重, 并计算出体重指数(body mass index, BMI)等资料。治疗前后抽取入组患者空腹静脉血测得空腹血糖(fasting plasma glucose, FPG)、餐后2 h血糖(2-hour postprandial blood glucose, 2hPG)、糖化血红蛋白(glycosylated hemoglobin, HbA1c)、总胆固醇(total cholesterol, TC)、三酰甘油(triglyceride, TG)、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)、空腹胰岛素(fasting insulin, FINS), 计算稳态胰岛素评价指数(homeostasis model assessment-insulin resistance, HOMA-IR)=FINS×FPG/22.5。

### 1.2.2 血清 TLR4 检测

患者禁食8 h, 次晨抽取外周静脉血3 mL, 在室温下静置1小时, 放入离心机3 000 r/min离心10~15 min, 分离上层血清至于-70 ℃冰箱中备用。采用酶联免疫吸附测定法(enzyme-linked immunosorbent assay, ELISA)测得空腹血清TLR4

水平(试剂盒购自武汉菲恩生物科技有限公司, 灵敏度<0.188 ng/mL, 批内变异系数<8%, 批间变异系数<10%)。

## 1.3 统计学处理

使用SPSS 21.0统计软件进行分析。对于服从正态分布的计量资料, 应用均数±标准差( $\bar{x}\pm s$ )进行描述, 采用 $t$ 检验及配对 $t$ 检验进行组间比较。计数资料以构成比(%)来表示, 应用 $\chi^2$ 检验进行组间比较。 $P<0.05$ 表示差异具有统计学意义。

## 2 结果

### 2.1 两组患者一般资料比较

未发现两组研究对象的性别、年龄、病程和BMI差异存在统计学意义(表1)。

### 2.2 基线时对照组和观察组患者血液生化指标的比较

未发现两组患者治疗前FPG, 2hPG, HbA1c, TC, TG, LDL-C, HDL-C, FINS, HOMA-IR的水平具有显著差异(表2)。

### 2.3 对照组和观察组患者治疗前后血液生化指标的比较

治疗3个月后, 两组患者FPG, 2hPG, HbA1c, TG, FINS, HOMA-IR, TLR4较前下降, HDL-C较前升高, 且观察组下降/升高更明显( $P<0.05$ ); 两组患者TC, LDL-C均较前下降, 但两组治疗后差异无统计学意义( $P>0.05$ , 表2)。

表1 两组患者一般资料的比较

Table 1 Comparison of general information between two groups of patients

组别	<i>n</i>	男/[例(%)]	女/[例(%)]	年龄/岁	病程/周	体重指数/(kg·m <sup>-2</sup> )
对照组	43	22 (51.2)	21 (48.8)	47.26 ± 6.55	16.84 ± 4.35	26.17 ± 0.95
观察组	45	22 (48.9)	23 (51.1)	45.44 ± 5.30	18.27 ± 3.60	26.10 ± 0.69
$\chi^2/t$		0.045		1.429	-1.684	0.401
<i>P</i>		0.831		0.157	0.096	0.689

表2 对照组和观察组患者治疗前后血液生化指标的比较

Table 2 Comparison of blood biochemical parameters between the control group and the observation group before and after treatment

组别	n	FPG/(mmol·L <sup>-1</sup> )		2hPG/(mmol·L <sup>-1</sup> )		HbA1c/%		TC/(mmol·L <sup>-1</sup> )		TG/(mmol·L <sup>-1</sup> )	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照组	43	8.92 ± 1.00	7.32 ± 0.69*	11.90 ± 0.59	9.46 ± 0.74*	8.56 ± 1.01	7.38 ± 0.66*	4.62 ± 1.37	3.02 ± 0.68*	2.70 ± 1.74	1.54 ± 0.73*
观察组	45	8.57 ± 0.78	6.44 ± 0.63*	11.50 ± 1.13	8.42 ± 1.19*	8.38 ± 0.52	6.79 ± 0.86*	4.17 ± 0.84	2.90 ± 0.17*	3.09 ± 1.44	1.38 ± 0.54*
t		1.800	2.845	1.373	2.304	1.114	2.091	1.862	1.042	-1.152	2.077
P		0.075	0.006	0.173	0.024	0.268	0.039	0.066	0.214	0.253	0.041

  

组别	LDL-C/(mmol·L <sup>-1</sup> )		HDL-C/(mmol·L <sup>-1</sup> )		FINS/(mmol·L <sup>-1</sup> )		HOMA-IR		TLR4/(ng·mL <sup>-1</sup> )	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照组	3.43 ± 0.64	2.36 ± 0.35*	0.89 ± 0.23	1.46 ± 0.25*	22.92 ± 2.87	18.07 ± 4.12*	6.36 ± 2.41	4.43 ± 1.41*	36.82 ± 2.69	33.58 ± 2.57*
观察组	3.27 ± 0.75	2.63 ± 0.24*	0.80 ± 0.21	1.65 ± 0.25*	23.89 ± 2.76	16.26 ± 2.70*	7.24 ± 1.75	4.54 ± 1.00*	35.72 ± 4.11	28.07 ± 5.33*
t	1.07	1.23	1.929	-5.065	-1.602	2.941	-1.962	3.368	1.473	9.202
P	0.288	0.065	0.057	<0.001	0.113	0.004	0.053	0.001	0.145	<0.001

\*P&lt;0.001.

### 3 讨论

肥胖是T2DM发展的危险因素之一。肠道菌群的变化易导致肥胖、T2DM等代谢紊乱性疾病<sup>[8-9]</sup>。T2DM与非T2DM成人肠道菌群有很大的差异,双歧杆菌含量下降,肠球菌和大肠埃希菌增加,肠道菌群可能会影响宿主的炎症途径和能量代谢<sup>[10]</sup>。毋庸置疑,超重T2DM患者肠道菌群失调严重。

双歧杆菌四联活菌片是一种口服的复方制剂,主要由婴儿双歧杆菌、嗜酸乳杆菌、粪肠球菌、蜡样芽孢杆菌构成,前三者属于健康人体肠道正常菌群,补充该菌群后可抑制肠道中某些致病菌,维持肠道正常蠕动,后者在肠道中定植,消耗氧气,为双歧杆菌等厌氧菌营造厌氧环境,促进其生长和繁殖<sup>[11]</sup>。国外文献<sup>[12]</sup>指出,益生菌补充剂对于T2DM的FPG, HbA1c, HOMA-IR有一定的改善,有效改善葡萄糖代谢。亦有研究<sup>[13]</sup>表明一种新型益生菌治疗新发超重T2DM有助于降低血糖,改善胰岛素敏感性。国内多中心临床研究<sup>[14]</sup>结果显示:对于肥胖的糖尿病患者观察组予以双歧杆菌四联活菌片治疗3个月后, HbA1c较基线的下降趋势比对照组更明显。本研究结果显示:治疗3个月后,两组患者指标均较之前有所改善,以盐酸二甲双胍为对照组,观察组的PG, 2hPG, HbA1c, HOMA-IR, FINS下降更明显。说明观

察组在二甲双胍的基础上给予双歧杆菌四联活菌片,对葡萄糖代谢有一定的改善,并且缓解了胰岛素抵抗,增加了胰岛素的敏感性,与上述研究结果一致。在一项动物试验<sup>[5]</sup>中,给予高脂饮食的小鼠双歧杆菌后显示具有一定的降血脂作用。国外一项Meta分析<sup>[15]</sup>表示:益生菌对于T2DM而言,具有升高HDL-C的作用,就TC, TG, LDL-C指标而言无显著作用。本研究结果显示:治疗3个月后,观察组的TG较对照组下降更明显, HDL-C较对照组升高更明显,两组治疗后的TC, LDL-C差异无统计学意义。此次入选患者均为T2DM合并超重,往往伴有高三酰甘油血症,肠道菌群紊乱更严重,给予一定的干预措施,三酰甘油降低更显著。本研究结果显示两组治疗后的TC, LDL-C差异无统计学意义,考虑与入选患者数量及治疗时间较短有关,有待进一步研究。

T2DM是一种慢性低度炎症, T2DM伴有超重或肥胖的发病机制较复杂,近年来研究<sup>[16]</sup>表明肠道菌群成为其研究靶点。TLR4信号是外源性病原体相关分子或内源性危险相关因子激活的主要促炎途径<sup>[17-19]</sup>。LPS是革兰氏阴性菌细胞壁的组成成分,同时是一种强的TLR4刺激因子,在这一机制中可能引起炎症反应和细胞因子的分泌<sup>[20]</sup>。笔者前期研究结果显示TLR4与超重及肥胖T2DM的发生、发展密切相关,超重T2DM的TLR4水平

较高, TLR4与糖脂代谢及炎症状态呈正相关。益生菌可改善肠道菌群, 肠上皮的完整性及通透性会有一定的改善, 调节免疫系统和减少TLR4信号通路可能说明其降血糖作用<sup>[21]</sup>。本研究结果显示治疗3个月后, 治疗组的TLR4水平下降较观察组显著, 从侧面反映双歧杆菌四联活菌片治疗超重T2DM具有一定的疗效, 可能的机制为: 双歧杆菌四联活菌片使肠道益生菌数量增多, 并定植在肠上皮, 其可改善肠上皮的通透性, 从而降低TLR4水平, 进而减弱TLR4介导的炎症通路, 减轻内毒素血症, 使全身炎症状态得到改善, 糖脂代谢得到一定的调节。

综上, 口服双歧杆菌四联活菌片对于超重T2DM患者的血糖、血脂及胰岛素抵抗有一定的改善, 其机制可能是通过降低TLR4水平从而改善炎症状态, 因此其可作为辅助降糖治疗的一种新的方法。

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