doi: 10.13241/j.cnki.pmb.2017.23.034

六味地黄丸联合二甲双胍对2型糖尿病患者血清载脂蛋白的影响及疗效研究*

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摘要 目的：探讨六味地黄丸联合二甲双胍片对2型糖尿病患者血清载脂蛋白的影响及临床疗效。**方法：**选择106例2型糖尿病患者并依照随机数表法分作对照组与观察组，各53例。对照组行二甲双胍治疗，观察组基于对照组加用六味地黄丸治疗，比较两组治疗前后载脂蛋白A、B(ApoA、ApoB)、ApoA/ApoB、空腹血糖(FPG)、餐后2 h血糖(2hPG)、空腹胰岛素(FINS)、胰岛素抵抗指数(HOMA-IR)、白细胞介素-6(IL-6)、超敏C反应蛋白(hs-CRP)、内皮素-1(ET-1)、一氧化氮(NO)水平的变化，临床疗效和不良反应的发生情况。**结果：**治疗后，两组ApoA、ApoA/ ApoB、NO均较治疗前上升，但观察组ApoA、ApoA/ApoB、NO高于对照组，差异有统计学学意义 (P<0.05)。两组FPG、2PG、FINS、HOMA-IR、IL-6、hs-CRP、ET-1均较治疗前降低，但观察组FPG、2PG、FINS、HOMA-IR、IL-6、hs-CRP、ET-1低于对照组(P<0.05)。观察组总有效率高于对照组(P<0.05)，两组不良反应的发生率比较差异无统计学学意义(P>0.05)。**结论：**六味地黄丸联合二甲双胍的疗效治疗2型糖尿病患者的疗效较好，且可有效控制血糖、改善内皮功能并调节血清载脂蛋白水平。

关键词：2型糖尿病；六味地黄丸；二甲双胍；载脂蛋白；疗效

中图分类号：R587.1 **文献标识码：**A **文章编号：**1673-6273(2017)23-4545-04

Research on Curative Effect of Liuwei Dihuang Pill Combined with Metformin on Type 2 Diabetes and Serum Apolipoprotein Level*

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ABSTRACT Objective: To research the curative effect of liuwei dihuang pill and metformin on the serum levels of apolipoprotein of patients with type 2 diabetes. **Methods:** 106 cases with type 2 diabetes were selected and randomly divided into the control group and the observation group, with 53 cases in each group. The patients in the control group were treated with metformin, and the patients in the observation group were treated with liuwei dihuang capsules on the basis of the control group. Then the serum levels of apolipoprotein A and B (ApoA, ApoB), ApoA/ApoB, fasting plasma glucose (FPG), 2 h postprandial blood glucose (2 HPG), fasting insulin (FINS), insulin resistance index (HOMA IR), interleukin 6 (IL-6), hypersensitive c-reactive protein (hs-CRP), endothelin-1 (ET-1) and nitric oxide (NO), the curative effect and safety in the two groups were observed and compared before and after the treatment. **Results:** After treatment, the serum levels of ApoA, ApoA/ApoB and NO of the both groups were higher than those before, treatment, which were higher in the observation group than those of the control group (P<0.05). After treatment, the serum levels of FPG, 2hPG, FINS, HOMA IR, IL-6, hs CRP and ET-1 of both groups were lower than before treatment, which were lower in the observation group than those of the control group(P<0.05). The total effective rate of observation group was higher than that of the control group(P<0.05). There was no statistically significant difference in the drug safety between the two groups (P>0.05). **Conclusion:** Liuwei dihuang capsules and metformin had reliable curative effect on the treatment type 2 diabetes, which could regulate the serum levels of apolipoprotein, and improve the blood glucose, inflammatory factors and endothelial function.

Key words: Type 2 diabetes; Liuwei dihuang capsules; Metformin; Apolipoprotein; Curative effect

Chinese Library Classification(CLC): R587.1 Document code: A

Article ID: 1673-6273(2017)23-4545-04

前言

2型糖尿病是一种内分泌代谢性疾病，脂代谢异常与2型糖尿病的发生发展密切相关。血糖控制是治疗2型糖尿病的关键，二甲双胍作为一种口服降糖药，给药方便，能够使机体对葡萄糖摄取延缓，加强组织胰岛素的利用率[3]。载脂蛋白可维持脂

* 基金项目：陕西省自然科学基金项目(2008K259)

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(收稿日期：2017-01-04 接受日期：2017-01-29)

蛋白结构的稳定,结合并诱导脂质转运,调控脂蛋白代谢[1,2]。研究表明西医结合治疗可明显提高 2 型糖尿病的临床效果,六味地黄丸是其常用中成药,具有降血脂、血糖、提高免疫等多种功效[4]。因此,本研究主要探讨了六味地黄丸联合二甲双胍治疗 2 型糖尿病患者的疗效及其对血清载脂蛋白水平的影响。

1 资料与方法

1.1 一般资料

选择 2014 年 5 月 ~2016 年 5 月于我院就诊的 106 例 2 型糖尿病患者。入选标准:(1)与 2 型糖尿病诊断标准相符[5]:伴体重降低、多尿、多食、多饮、视力模糊、皮肤瘙痒等典型症状,餐后 2 h 血糖(2 h PG)在 11.1 mmo/L 以上或者空腹血糖(FPG)在 7.0 mmol/L 以上;(2)与中医肾阴虚证相符[6]:主症(五心烦热、颧红咽干、腰膝酸软、口渴多饮),次症:(心悸、盗汗潮热、多梦失眠、多食),舌脉:舌红、少苔、少津、脉数、细;(3)无糖尿病肾病等严重合并症;排除标准:(1)重要脏器功能明显不全;(2)合并血液、免疫系统疾病;(3)急性感染、创伤。依照随机数表法将患者分为两组,每组 53 例。对照组包括男性 30 例,女性 23 例;年龄 33~68 岁,平均(51.36± 4.51)岁。观察组包括男性 28 例,女性 25 例;年龄 31~70 岁,平均(52.48± 4.63)岁。两组患者的基线资料比较差异无统计学意义(P>0.05),具有可比性。本研究已得到医院伦理委员会许可,且签署家属及患者知情同意书,

1.2 治疗方法

对照组行二甲双胍治疗,口服 0.5 g 二甲双胍(山东益康药业股份有限公司,0.5 g/ 片,140420),早晚各 1 次。观察组基于对照组加用六味地黄丸治疗,口服 24 g 六味地黄丸(广东新南方青蒿药业有限公司,3 g/ 粒,140416),早中晚各 1 次。两组均持续治疗 3 个月,期间均适量运动,严格控制饮食,嘱患者少食多餐,并食用富含微生素、纤维素及微量元素的食物。于治疗结束时评估疗效,并观察药物安全性。

1.3 观察指标

1.3.1 指标检测 于治疗前后各抽取患者 2 mL 空腹静脉血及餐后 2 h 静脉血,于室温下分离血清保存待检。参照酶联免疫吸附法检测载脂蛋白 A、B(ApoA、ApoB)。参照葡萄糖氧化酶法检测 FPG 及 2 hPG, 参照放射免疫法检测空腹胰岛素(FINS),并计算胰岛素抵抗指数(HOMA-IR)。参照电化学发光法检测白细胞介素 -6(IL-6)及超敏 C 反应蛋白(hs-CRP)。参照酶联免疫双抗体法检测内皮素 -1(ET-1)及一氧化氮(NO)。

1.3.2 疗效观察 参照相关文献进行[7],症状基本缓解,FPG 在 7.2 mmol/L 以下,2 hPG 在 8.3 mmol/L 以下即显效; 症状显著减轻,FPG 在 8.3 mmol/L 以下,2 hPG 在 10 mmol/L 以下即好转;症状未见缓解,血糖水平无改善即无效。显效 + 好转即总有效。

1.4 统计学分析

选择 SPSS18.0 行数据统计,计量资料用($\bar{x}$± s)表示,组间比较用 t 检验,计数资料用[(例)%]表示,用 x^2 检验比较,等级资料用秩和检验,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组患者治疗前后血清载脂蛋白水平的比较

治疗后,两组 ApoA1、ApoA1/ApoB 水平均较治疗前上升,观察组上升更明显;两组 ApoB 均较治疗前降低,观察组下降更明显,差异均有统计学意义(P<0.05),见表 1。

表 1 两组患者治疗前后血清载脂蛋白水平的比较($\bar{x}$± s,n=53)

Table 1 Comparison of the serum apolipoprotein levels between two groups before and after treatment ($\bar{x}$± s, n=53)

Items	Time	Control group	Observation group
ApoA1(g/L)	Before treatment	1.16± 0.14	1.15± 0.15
	After treatment	1.37± 0.17[b]	1.56± 0.19[ab]
ApoB(g/L)	Before treatment	1.59± 0.19	1.60± 0.21
	After treatment	1.22± 0.15[b]	1.07± 0.13[ab]
ApoA1/ ApoB(g/L)	Before treatment	0.89± 0.11	0.88± 0.10
	After treatment	1.17± 0.14[b]	1.32± 0.26[ab]

Note: Compared with control group [a]P<0.05; Compared with before treatment [b]P<0.05.

2.2 两组患者治疗前后血糖水平的比较

治疗后, 两组 FPG、2hPG、HOMA-IR、FINS 均较治疗前降低,观察组下降更明显,差异有统计学意义(P<0.05),见表 2。

表 2 两组患者治疗前后血糖水平的比较($\bar{x}$± s,n=53)

Table 2 Comparison of the blood glucose between two groups before and after treatment ($\bar{x}$± s, n=53)

Items	Time	Control group	Observation group
FPG(mmol/L)	Before treatment	8.29± 1.03	8.11± 1.01
	After treatment	7.36± 0.92[b]	6.34± 0.79[ab]
2hPG(mmol/L)	Before treatment	11.28± 1.41	11.35± 1.35
	After treatment	8.35± 1.05[b]	6.57± 0.81[ab]
HOMA-IR	Before treatment	7.33± 0.91	7.46± 0.94
	After treatment	5.14± 0.64[b]	3.80± 0.48[ab]
FINS(mU/L)	Before treatment	21.06± 2.63	20.85± 2.60
	After treatment	10.38± 1.29[b]	7.26± 0.91[ab]

Note: Compared with control group [a]P<0.05; Compared with before treatment [b]P<0.05.

2.3 两组患者治疗前后血清 IL-6、hs-CRP 水平的比较

治疗后，两组血清 IL-6、hs-CRP 水平均较治疗前降低，且观察组以上指标下降更明显，差异有统计学意义(P<0.05)，见表3。

表 3 两组患者治疗前后血清 IL-6、hs-CRP 水平的比较($\bar{x}\pm s$，n=53)

Table 3 Comparison of the serum IL-6, hs-CRP levels between two groups before and after treatment ($\bar{x}\pm s$, n=53)

Items	Time	Control group	Observation group
IL-6(pg/L)	Before treatment	4.23± 0.52	4.20± 0.52
	After treatment	3.75± 0.46[b]	3.14± 0.39[ab]
hs-CRP(mg/L)	Before treatment	6.85± 0.85	6.94± 0.87
	After treatment	5.13± 0.64[b]	4.02± 0.50[ab]

Note: Compared with control group [a]P<0.05; Compared with before treatment [b]P<0.05.

2.4 两组患者治疗前后血清 ET-1、NO 水平的比较

治疗后，两组血清 ET-1 水平均较治疗前降低，且观察组低于对照组；两组血清 NO 水平均较治疗前上升，且观察组高于对照组，差异均有统计学意义(P<0.05)，见表 4。

表 4 两组患者治疗前后血清 ET-1、NO 水平的比较($\bar{x}\pm s$，n=53)

Table 4 Comparison of the serum ET-1, NO levels between two groups before and after treatment ($\bar{x}\pm s$, n=53)

Items	Time	Control group	Observation group
ET-1(ng/L)	Before treatment	84.65± 10.52	83.27± 10.41
	After treatment	63.11± 7.89[b]	56.20± 7.02[ab]
NO(μmol/L)	Before treatment	29.48± 3.65	28.63± 3.56
	After treatment	42.16± 5.26[b]	49.35± 6.16[ab]

Note: Compared with control group [a]P<0.05; Compared with before treatment [b]P<0.05.

2.5 两组临床疗效的比较

观察组总有效率为 96.23%，显著高于对照组，差异有统计学意义(P<0.05)，见表 5。

表 5 两组临床疗效比较[例(%)]

Table 5 Comparison of the curative effect between two groups [n(%)]

Items	Control group	Observation group
Markedly	18(33.96)	33(62.27)
Better	25(41.17)	18(33.96)
Invalid	10(18.87)	2(3.77)
Total effective rate	43(81.13)	51(96.23)a

Note: Compared with control group [a]P<0.05.

2.6 两组不良反应发生情况的比较

两组治疗期间均未见发生严重不良反应。

3 讨论

口服降糖药物是 2 型糖尿病的常用西医治疗方式，二甲双胍可使肝过度产生的糖原异生受到抑制，从而使血糖降低，同时作为一种胰岛素的增敏剂，其可使胰岛素受体活性增强，诱导外周组织对胰岛素敏化，提高其对葡萄糖的利用，使胰岛素抵抗状态得到缓解[10,11]。

中医学认为糖尿病属＂消渴＂范畴，情志不畅、功能衰退等使其主要诱因，肝肾阴虚所致内热是其关键病机[11,12]。虚热引肺热，致津液分布不利，口渴需多饮；脾胃阴虚致炽盛胃热，易饥多食；肝肾阴虚，致肝过度疏泄，肾藏泻宣失，津液趋至膀胱，引尿频、尿多；肾藏精所失，引精微下漏，致尿液生甘味或浑浊；水谷所失则难以达到肌肤濡养，致干燥、瘙痒[13]。治疗需以补益肝肾、祛除内热。六味地黄丸作为经典的补益肝肾方剂，山药可滋阴补脾，山萸肉可涩精，滋养肝肾；熟地可生精益髓，补养肝肾，三者可共同起到肝肾脾并补[14]。白茯苓可驱毒消痈利湿祛风，泽泻祛肾浊，丹皮可清除虚热，三者共同起到泻下作用。方中辅以太子、黄芪可固表收汗、养阴益气；当归可生血活血；麦冬、天花粉、生地可清热、滋银；鸡内金、山楂可降脂化浊，消食健脾；生姜可止呕降逆；桃仁可活血祛瘀；白芍可柔肝养血；甘草可对诸药起到调和作用，全方共奏消浊祛瘀、降火滋阴之功[15]。

本结果显示联合六味地黄丸治疗后 FBG、2hPG、HOMA-IR、FINS 均显著降低，表明两者联合治疗可纠正机体糖代谢异常，改善血糖水平，可能与六味地黄丸可对胰岛 B 细胞起到保护作用，从而增强纠正胰岛素抵抗，引起血糖降低。脂代谢异常与 2 型糖尿病发病有着紧密的联系，其中机体脂代谢期间载脂蛋白可起到至关重要的作用[16]。低水平的 ApoA 可诱导代谢性疾病，ApoB 可直观反映机体胰岛素抵抗及脂代谢状态，同时也是糖尿病微血管与大血管并发症的重要标志物[17,18]。本结果显示二甲双胍联合六味地黄丸治疗后患者 ApoA、ApoB 浓度明显增加，且 ApoA/ApoB 比值显著降低，表明两者联合治疗可利于改善机体的脂代谢。

2 型糖尿病患者存在程度不一的炎症反应，多种细胞合成的炎性因子可导致胰岛素功能损伤，加重胰岛素抵抗[20]。IL-6 主要是由成纤维细胞、巨噬细胞等诱发，可参与机体系列病理生理过程，还可诱导其他促炎性因子的表达，加剧病情。hs-CRP 是血管炎性的典型标志物，其水平可预测心脑血管的不良事件。本结果显示联合六味地黄丸治疗后 IL-6、hs-CRP 浓度明显降低，表明两者联合治疗可利于机体炎性反应的改善，促进胰岛素抵抗的缓解，利于疾病的治疗。同时，长时间高血糖、炎症刺激可诱导内皮功能出现障碍，ET-1 与 NO 是血管内皮细胞的典型活性物质，ET-1 属活性生物多肽，可诱导血管收缩，NO 能够诱导血管扩张，使血压降低，导致血小板的聚集、黏附受到

抑制，可确保机体正常的血流灌注[22]。本结果显示联合六味地黄丸联合治疗后内皮功能显著改善，表明两者联合治疗可使内皮功能紊乱得到纠正，维持血管的正常功能。此外，联合六味地黄丸治疗后总有效率明显高于二甲双胍单用治疗者，且两组均未见不良反应，表明六味地黄丸联合治疗可从多方面改善疾病，提高2型糖尿病的疗效，且并未增加药物的副反应。

综上所述，应用六味地黄丸联合二甲双胍治疗2型糖尿病的疗效可靠，可调节血清载脂蛋白水平，且可利于血糖、炎性因子、内皮功能的改善。但本研究由于观察时间比较短，且纳入样本量相对较少，故结果存在一定的偏差，仍需进一步的临床考察。

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