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前列地尔联合益肾化湿颗粒对糖尿病肾病患者血糖、血脂、肾功能以及尿足细胞相关蛋白的影响*

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摘要 目的:分析前列地尔联合益肾化湿颗粒对糖尿病肾病患者血糖、血脂、肾功能以及尿足细胞相关蛋白的影响。**方法:**98例糖尿病肾病患者按抽签法分为对照组与实验组,各49例,对照组予以前列地尔治疗,实验组基于对照组加用益肾化湿颗粒治疗,比较两组疗效,糖化血红蛋白(HbA1c)、血糖(FPG)、餐后2h血糖低(2h PG),甘油三酯(TG)、总胆固醇(TC)、高密度脂蛋白(HDL-C)、低密度脂蛋白(LDL-C),血尿素氮(BUN)、肌酐(Cr)、 β_2 微球蛋白(β_2 -MG)、胱抑素(Cys-C),尿足细胞标志蛋白(PCX) nephrin,安全性。**结果:**实验组总有效率高于对照组($P<0.05$)。治疗后,两组HbA1c、FPG、2hPG比较无差异($P>0.05$)。实验组TG、TC、LDL-C、BUN、Cr、 β_2 -MG、Cys-c、PCX、尿nephin/尿Cr低于对照组($P<0.05$)。实验组HDL-C高于对照组($P<0.05$)。**结论:**前列地尔联合益肾化湿颗粒治疗对糖尿病肾病的疗效确切,可利于血糖、血脂、肾功能的改善,降低尿足细胞相关蛋白的浓度。

关键词:糖尿病肾病;前列地尔;益肾化湿颗粒;血糖;血脂;肾功能;尿足细胞相关蛋白

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Effects of Alprostadil and Yishen Huashi on Blood Glucose, Blood Lipid, Renal Function and Urinary Podocyte Proteins of Patients with Diabetic Nephropathy*

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ABSTRACT Objective: To analysis the effects of alprostadil and yishen huashi particles on blood glucose, blood lipid, renal function and urinary podocyte proteins of patients with diabetic nephropathy. **Methods:** 98 patients with diabetic nephropathy were selected and randomly divided into the control group and the experimental group with 49 cases in each group. The patients in the control group were treated with alprostadil, while the patients in the experimental group were treated with yishenhuashui particles on the basis of the control group. Then the curative effect, the levels of glycosylated hemoglobin (HbA1c), blood glucose (FPG), 2 h postprandial blood glucose (2h PG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL-C), low density lipoprotein (LDL-C), blood urea nitrogen (BUN), creatinine (Cr), β_2 microglobulin (β_2 - MG), bladder inhibition (Cys-C) and urinary podocyte proteins (PCX) in the two groups were observed and compared between the two groups before and after the treatment. **Results:** The total effective rate of experimental group was higher than control group ($P<0.05$). After treatment, there was no statistically significant difference about the HbA1c, FPG and 2 HPG between the two groups ($P>0.05$). After the treatment, the levels of TG, TC, LDL-C, BUN, Cr, β_2 MG, Cys C, PCX and urinary nephrin/urine Cr of the experimental group were lower than those of the control group ($P<0.05$). The HDL-C of experimental group was higher than that of the control group ($P<0.05$). **Conclusion:** The curative is effect of alprostadil and yishen huashi particles in treatment diabetic nephropathy patients, can conducive to the improvement of blood glucose, blood lipid, renal function, reduce the concentration of urinary podocyte related proteins.

Key words: Diabetic nephropathy; Alprostadil; Yishen huashi particles; Blood glucose; Blood lipid; Renal function; Urinary podocyte related proteins

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前言

糖尿病肾病是糖尿病最为严重的慢性并发症,主要是因糖尿病的糖脂代谢出现障碍,诱导肾小球发生硬化,使尿蛋白含

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量超标,是导致糖尿病患者死亡的关键因素^[1]。糖尿病肾病初期症状不明显,仅伴微量蛋白尿出现,且尿常规等无明显改变,随着病情的不断进展,可导致肾脏产生器质性病变,造成肾功能出现异常。近年来有研究报道,尿足细胞相关蛋白于糖尿病肾病发展中起着关键作用,可确保肾脏过滤屏障的正常状态^[2]。药物治疗是糖尿病肾病的主要方式,前列地尔是本病常用药物,可起到降低血脂、改善微循环等多种作用,从而发挥一定临床效果^[3]。有文献报道,中医药对糖尿病肾病的效果肯定,可延缓疾病的进展,益肾化湿颗粒可发挥去水消肿、温阳益肾等作用^[4]。目前临床上鲜有关于二者联合用药的报道,本研究旨在分析前列地尔联合益肾化湿颗粒对糖尿病肾病患者血糖、血脂、肾功能以及尿足细胞相关蛋白的影响。

1 资料与方法

1.1 一般资料

选择2014年8月~2016年1月于我院就诊的98例糖尿病肾病患者,入选标准:均与糖尿病肾病的相关诊断标准吻合^[5]:糖尿病史明确,排除酮症酸中毒、泌尿系统感染等因素所致的尿蛋白阳性;糖尿病肾病早期;属中医脾肾两虚、湿气雍阻证候;未合并其他肾脏疾病;近期未使用影响本研究指标药物。排除原发性肾脏疾病;心脏及肝脏等器官明显病变;血液及内分泌系统病变;恶性肿瘤;妊娠及哺乳阶段等。本研究已征得医院伦理委员会许可,且签署家属及患者知情同意书,按抽签法分组。对照组26例男,23例女;年龄33~71岁,平均(53.26±5.61)岁。实验组24例男,25例女;年龄32~73岁,平均(52.87±5.94)。比较两组性别等无差异($P>0.05$),有可比性。

1.2 方法

对照组予以前列地尔治疗,将10 μg 前列地尔(安徽生物药业有限责任公司,2 mL:10 μg,国药准字H10980024,批号140721)溶于10 mL 0.9%氯化钠中,予以患者静脉注射,每日1次。实验组基于对照组予以益肾化湿颗粒治疗,口服10 g 益肾化湿颗粒(烟台元生药业有限公司,10 g/袋,国药准字Z20090250,批号140723),早中晚各1次。两组均持续用药2个月,期间均常规口服降糖药,保持空腹血糖(FPG)低于8.0 mmol/L、餐后2h血糖低(2h PG)低于9.0 mmol/L,并配合血脂调节、健康教育、糖尿病饮食、合理运动等治疗。

1.3 观察指标

1.3.1 疗效观察 于用药结束时评估疗效^[6]:临床体征及症状

全部缓解,肾功能基本恢复正常即显效;临床体征及症状显著改善,肾功能也明显缓解即有效;临床体征及症状、肾功能未见改变或者加剧即无效,显效、有效均判定为总有效。

1.3.2 血液指标检测 于治疗前后采集2 mL 患者空腹静脉血,2hPG、FPG、糖化血红蛋白(HbA1c)按照葡萄糖氧化酶法检测。使用放射免疫法检测高密度脂蛋白(HDL-C)、总胆固醇(TC)、低密度脂蛋白(LDL-C)。血尿素氮(BUN)、β2微球蛋白(β2-MG)、肌酐(Cr)、胱抑素(Cys-C)予以化学发光法检测。

1.3.3 尿液指标检测 于治疗前后收集患者晨尿10 mL,尿足细胞标志蛋白(PCX)予以酶联免疫双抗体夹心法检测,nephrin予以免疫比浊法检测(为排除尿量对结果的影响,以尿nephrin/尿Cr表示尿nephrin值)。

1.3.4 安全性观察 对患者肝肾功能、血常规等进行定期测定,并统计期间的不良反应。

1.4 统计学分析

选择spss18.0行数据统计,计量资料用($\bar{x} \pm s$)表示,用t检验比较,计数资料用[(例)%]表示,用 χ^2 检验比较,以 $P<0.05$ 有统计学意义。

2 结果

2.1 比较两组疗效

实验组总有效率高于对照组,比较有统计学差异($P<0.05$),见表1。

表1 比较两组疗效[(例)%]

Table 1 Comparison of effect blood glucose between two groups [(n)%]

Items	Control group (n=49)	Experimental group (n=49)
Effective	23(46.94)	30(61.22)
Markedly	16(32.65)	17(34.70)
Invalid	10(20.41)	2(4.08)
Total effective rate	39(79.59)	47(95.91) ^b

Note: Compared with control group, ^b $P<0.05$.

2.2 比较两组治疗前后血糖水平

治疗前,比较两组HbA1c、2hPG、FPG无差异($P>0.05$);治疗后,两组HbA1c、2hPG、FPG均降低,但比较无差异($P<0.05$),见表2。

表2 比较两组治疗前后血糖水平($\bar{x} \pm s$)

Table 2 Comparison of the levels of blood glucose between two groups before and after treatment ($\bar{x} \pm s$)

Items	Time		
HbA _{1c} (%)	Before treatment	6.89±0.89	6.80±0.85
	After treatment	5.76±0.72 ^a	5.68±0.71 ^a
2hPG(mmo/L)	Before treatment	8.76±1.09	8.54±1.11
	After treatment	7.11±0.88 ^a	6.93±0.86 ^a
FPG(mmol/L)	Before treatment	7.60±0.95	7.51±0.94
	After treatment	5.90±0.73 ^a	5.77±0.71 ^a

Note: Compared with before treatment, ^a $P<0.05$.

2.3 比较两组治疗前后血脂水平 疗后,两组 TC、LDL 均降低,实验组下降更明显,两组 HDL-C 治疗前,比较两组 TC、HDL-C、LDL-C 无差异($P>0.05$);治 均上升,实验组高于对照组($P<0.05$),见表 3。

表 3 比较两组治疗前后血脂水平($\bar{x}\pm s$)

Table 3 Comparison of the levels of blood fat between two groups before and after treatment ($\bar{x}\pm s$)

Items	Time	Control group(n=49)	Experimental group(n=49)
TC(mmol/L)	Before treatment	6.33± 0.79	6.40± 0.80
	After treatment	5.78± 0.72 ^a	5.12± 0.64 ^{ab}
HDL-C(mmol/L)	Before treatment	0.83± 0.10	0.84± 0.11
	After treatment	1.21± 0.15 ^a	1.32± 0.16 ^{ab}
LDL-C(mmol/L)	Before treatment	5.47± 0.68	5.52± 0.69
	After treatment	4.95± 0.61 ^a	4.30± 0.53 ^{ab}

Note: Compared with before treatment, ^a $P<0.05$; Compared with control group, ^b $P<0.05$.

2.4 比较两组治疗前后肾功能 05);治疗后,两组 BUN、Cr、 β 2-MG、Cys-c 均降低,实验组下降 治疗前,比较两组 BUN、Cr、 β 2-MG、Cys-c 无差异($P>0$. 更明显,比较有统计学差异($P<0.05$),见表 4。

表 4 比较两组治疗前后肾功能($\bar{x}\pm s$)

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

Items	Time	Control group(n=49)	Experimental group(n=49)
BUN(nmol/L)	Before treatment	6.64± 0.83	6.59± 0.82
	After treatment	6.11± 0.76 ^a	5.30± 0.66 ^{ab}
Cr(μ mol/L)	Before treatment	69.80± 8.72	68.74± 8.59
	After treatment	64.56± 8.07 ^a	61.42± 7.67 ^{ab}
β 2-MG(mg/L)	Before treatment	4.05± 0.51	4.08± 0.51
	After treatment	2.82± 0.3 ^{sa}	1.94± 0.24 ^{ab}
Cys-c(mg/L)	Before treatment	2.70± 0.33	2.69± 0.33
	After treatment	1.75± 0.21 ^a	1.13± 0.14 ^{ab}

Note: Compared with before treatment, ^a $P<0.05$; Compared with control group, ^b $P<0.05$.

2.5 比较治疗前后两组尿足细胞相关蛋白水平 05);治疗后,两组 PCX、尿 nephrin/尿 Cr 均降低,实验组低于 治疗前,比较两组 PCX、尿 nephrin/尿 Cr 无差异($P>0$. 对照组,比较有统计学差异($P<0.05$),见表 5。

表 5 比较治疗前后两组尿足细胞相关蛋白水平($\bar{x}\pm s$)

Table 5 Comparison of the levels of urinary podocyte related protein between two groups before and after treatment ($\bar{x}\pm s$)

Items	Time	Control group(n=49)	Experimental group(n=49)
PCX(μ g/L)	Before treatment	2.89± 0.36	2.87± 0.35
	After treatment	1.56± 0.19 ^a	2.50± 0.31 ^{ab}
Cr(μ g/mg)	Before treatment	35.42± 4.38	35.89± 4.48
	After treatment	23.67± 2.95 ^a	18.40± 2.30 ^{ab}

Note: Compared with before treatment, ^a $P<0.05$; Compared with control group, ^b $P<0.05$.

2.6 比较两组安全性 中糖尿病肾病是其常见微血管合并症,可出现蛋白尿、浮肿等 对照组有 2 例头晕、3 例头痛、1 例口干,实验组各有 2 例 症状^[7]。糖尿病肾病目前的发病机制尚未明确,研究报道与遗传 头晕、头痛,1 例口干,比较无差异($P>0.05$)。 易感性、代谢紊乱、血流动力学异常等多种因素有关,因此其治 疗难度较其他肾脏疾病更高^[8,9]。

3 讨论

糖尿病是一种内分泌代谢性疾病,可出现多种并发症,其 前列地尔是一种最新研发的载体制剂,可于脂微球中包裹 前列腺素 E1,能够使脂微球于组织内特异性分布,可减轻肾小

球的高滤过、高压状态,使尿液中蛋白浓度降低,促进肾脏血管扩张,缓解肾脏缺氧。同时研究报道前列地尔可使机体免疫反应受到抑制,阻止细胞因子的合成与释放,缓解肾脏炎症反应,从而对肾脏起到保护作用^[10]。国外研究发现,者前列地尔单独治疗糖尿病肾病患者的效果欠佳,总有效率相对较低,本研究也进一步证实此观点^[11]。

糖尿病肾病属中医学“水肿、消渴、虚劳”等范畴,其病程迁延,久治不愈,可致肾阴亏虚,胃失和降,脾失健运,引水湿滞留,正虚邪实是其主要病机^[12]。临床应以升阳补肾、祛瘀化湿治疗,益肾化湿颗粒中黄芪入肺、脾经,性温味甘,可脾肾双补,利尿消肿;苍术性温,味苦,可消除风湿、健脾益气;山药入肾、脾经,味甘,可健脾益肾;党参可补中益气^[13]。茯苓入肾、脾经,味甘、性平,可宁心健脾、利水化湿;山茱萸味酸、性温,可滋阴敛精、补养肝肾。另配伍大黄可活血行气、山楂可行滞散瘀。现代药理研究表明,益肾化湿颗粒存在抗氧化、抑制炎症及血栓形成,健脾、增强肾功能等多种作用^[14]。本结果显示,联合益肾化湿颗粒治疗后总有效率显著高于单用前列地尔组,说明二者联合治疗可促进患者症状的缓解,控制疾病的进展,提高疗效。

临床研究发现,糖尿病肾病患者血糖多存在不同程度的异常,FBG及2hPG是检测糖尿病的常用指标,能够反应机体基础性胰岛素的分泌功能,但是多种因素可造成其水平波动,准确率较小^[15]。HbA1C是机体血液中血糖与血红蛋白的代谢产物,其稳定性好,难以分解,与血糖浓度呈正相关,可客观反应患者近3个月内的血糖控制状况^[16]。同时HbA1C能够造成组织与细胞出现供氧不足,增加血粘度与血脂,且可诱导肾小球的滤过压增加,导致肾小球出现损伤^[17]。本结果显示,两组治疗后血糖均明显降低,但比较无差异($P>0.05$),表明二者均可促进机体血糖的控制,缓解高血糖状态。

由于胰岛素与脂蛋白脂肪酶的发生过程有着密切联系,因此糖尿病肾病患者的脂蛋白脂肪酶活性会有一定程度的下降,引起血脂升高^[18]。血脂上升可增加患者尿蛋白的排出量,诱导肾小球的过滤细胞表达TC及LDL-C受体,从而形成细胞毒作用,引起肾小球功能受到影响,造成血管内皮细胞出现受损;且可促使肾脏的血流出现变化,减少肾小球的过滤率,诱导肾脏出现伤害^[19]。本结果显示,联合益肾化湿颗粒治疗后血脂改善较为明显,表明二者联合治疗可利于机体血脂的调节,改善血脂的异常代谢,降低其危险性。

糖尿病肾病早期的肾功能无明显改变,随着病情的进展,肾功能可呈进行性减弱,肾功能多采用BUN、Cr等指标表示,但Cr的个体差异比较大,容易受到年龄、体质量等因素的影响^[20]。BUN浓度受肾功能影响的同时容易被蛋白质分解代谢所干扰,进而影响其测定水平。Cys-c主要由肾脏所排泄,其稳定性好,肾前性等因素对Cys-c无影响,肾小球出现微小病变时其滤过与重吸收可产生异常,导致其浓度上升,可反映早期糖尿病肾病患者的肾功能损伤^[21]。 β_2 -MG是小分子球蛋白,主要经肾小球滤过,几乎可于近曲小管处发生重吸收,机体正常生理情况下其血清含量极低,当肾脏受损时能够导致其代谢障碍,从而使血液中的含量上升^[22]。本结果显示,联合益肾化湿颗粒治疗后BUN、Cr、 β_2 -MG、Cys-c明显下降,表明二者联合治疗

可促进肾功能的改善,减轻肾脏损伤,抑制其进展。

最新研究发现,足细胞损伤可促进糖尿病肾病中蛋白尿的形成,PCX作为唾液酸黏蛋白,于肾小球基底膜分布,可参与肾小球的分子屏障,其损伤后可破坏肾小球屏障,导致尿液中蛋白增加^[23]。Nephrin作为一种跨膜蛋白,正常状态下尿液中的含量极低,临床报道,早起糖尿病肾病患者nephrin蛋白可产生代偿性增多,引起足细胞表层的蛋白排列紊乱,引起肾小球屏障受损^[24]。本结果显示,联合益肾化湿颗粒治疗后尿足细胞相关蛋白水平平均明显降低,表明二者联合治疗可利于蛋白尿的改善,恢复肾小球屏障,进一步促进肾功能的改善。此外,两组不良反应均比较轻微,安全性比较可靠。

综上所述,前列地尔联合益肾化湿颗粒治疗对糖尿病肾病的疗效确切,可利于血糖、血脂、肾功能的改善,降低尿足细胞相关蛋白的浓度。

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