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阿托伐他汀联合厄贝沙坦对老年早期糖尿病肾病患者肾功能及微炎症状态的影响 *

吴琳虹¹ 张 萌¹ 陈兴强² 韦明辉¹ 符薇薇²

(1 海南省三亚市人民医院血液净化中心 海南 三亚 572000; 2 海南省三亚市人民医院肾内科 海南 三亚 572000)

摘要 目的:探讨阿托伐他汀联合厄贝沙坦对老年早期糖尿病肾病(DN)患者肾功能及微炎症状态的影响。方法:选取2016年4月到2017年2月在我院肾内科接受治疗的老年早期DN患者84例,根据随机数字表法将患者分为对照组和观察组,各42例。对照组给予厄贝沙坦进行治疗,观察组给予阿托伐他汀联合厄贝沙坦进行治疗。比较两组患者的尿微量白蛋白排泄率(UAER)及两组患者血肌酐(Scr)、血尿素氮(BUN)、 β_2 微球蛋白(β_2 -MG)、白细胞介素-1(IL-1)、白细胞介素-10(IL-10)、肿瘤坏死因子- α (TNF- α)水平,并比较两组患者治疗过程中出现的不良反应。结果:治疗后两组患者的UAER、Scr、BUN、 β_2 -MG水平均降低,且观察组的UAER、Scr、BUN、 β_2 -MG均低于对照组($P<0.05$)。治疗后两组患者血清中IL-1、TNF- α 水平均降低,IL-10水平升高($P<0.05$);治疗后观察组血清中IL-1、TNF- α 水平低于对照组,IL-10水平高于对照组($P<0.05$)。两组不良反应发生率比较差异无统计学意义($P>0.05$)。结论:阿托伐他汀联合厄贝沙坦对老年早期DN患者有较好的治疗效果,可显著改善患者的肾功能,减轻微炎症状态,且安全性较好,值得临床推广应用。

关键词:阿托伐他汀;厄贝沙坦;糖尿病肾病;肾功能;微炎症

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Effect of Atorvastatin Combined with Irbesartan on Renal Function and Micro Inflammatory State in Elderly Patients with Early Diabetic Nephropathy*

WU Lin-hong¹, ZHANG Meng¹, CHEN Xing-qiang², WEI Ming-hui¹, FU Wei-wei²

(1 Blood Purification Center, Sanya People's Hospital of Hainan Province, Sanya, Hainan, 572000, China;

2 Department of Nephrology, Sanya People's Hospital of Hainan Province, Sanya, Hainan, 572000, China)

ABSTRACT Objective: To investigate the effect of Atorvastatin combined with irbesartan on renal function and micro inflammatory state in elderly patients with early diabetic nephropathy (DN). **Methods:** 84 elderly patients with DN who were treated in the department of nephrology of our hospital from April 2016 to February 2017, and the patients were divided into the control group and the observation group according to the random number table method, 42 cases in each group. The control group was treated with irbesartan, and the observation group was treated with Atorvastatin combined with irbesartan. Urinary albumin excretion rate (UAER) and the levels of serum creatinine (Scr), blood urea nitrogen (BUN), β_2 microglobulin (β_2 -MG), interleukin-1 (IL-1), interleukin-10 (IL-10), tumor necrosis factor- α (TNF- α) of patients in two groups were compared, and the adverse reactions in the two groups were compared between the two groups. **Results:** After treatment, the levels of UAER, Scr, BUN, β_2 -MG of patients in the two groups were decreased, and UAER, Scr, BUN, β_2 -MG in the observation group were lower than that in the control group ($P<0.05$). After treatment, the levels of serum IL-1 and TNF- α were decreased in the two groups, and the level of IL-10 was increased ($P<0.05$), after treatment, the levels of serum IL-1 and TNF- α in the observation group were lower than that in the control group, and the level of IL-10 in the observation group was higher than that in the control group ($P<0.05$). The incidence of adverse reactions in the two groups was not statistically significant ($P>0.05$). **Conclusion:** Atorvastatin combined with irbesartan is effective in the treatment of elderly patients with early DN, it can significantly improve the patient's renal function, reduce the micro inflammatory state, and the safety is good, which is worthy of clinical application.

Key words: Atorvastatin; Irbesartan; Diabetic nephropathy; Renal function; Micro inflammation

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前言

糖尿病肾病(Diabetic Nephropathy, DN)是糖尿病常见并发症, DN患者约占糖尿病患者的30%-50%^[1]。DN多发于中老

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作者简介:吴琳虹(1984-),女,本科,主治医师,从事肾脏病、血液净化方面的研究, E-mail: phtfgh@163.com

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年人,并与高血压、高血脂等疾病密切相关,随着近年来我国人口老龄化进程加剧以及人们饮食习惯的改变,DN的发病率逐年递增,已成为威胁人类健康的重要疾病^[2,3]。同时,DN也是终末期肾脏病的首要病因,此时的患者极易进入临床蛋白尿期,而处于此阶段的患者其肾功能的损害是不可逆的。老年DN患者多伴有高血压、高血脂等各类基础疾病,且体质下降明显,因此治疗难度更大^[4,5]。早期DN是患者病情发展的重要阶段,在此阶段对患者进行及时有效的治疗可延缓甚至阻止其进入临床蛋白尿期,可降低终末期肾病的发生,因而对老年早期DN患者进行及时有效的治疗具有重要的临床意义^[6-8]。厄贝沙坦属于血管紧张素Ⅱ受体拮抗剂类药物,临床上常用于治疗原发性高血压以及早期DN,但其单独治疗早期DN的疗效并不理想^[9,10]。阿托伐他汀是一种常见的他汀类药物,属于羟甲基戊二酰辅酶A还原酶抑制剂,具有调脂、降低尿微量白蛋白的作用。有研究表明^[11],阿托伐他汀联合厄贝沙坦对早期DN有较好的治疗效果,但关于两种药物联合治疗对DN患者微炎症状态的影响的报道较少。本研究探讨阿托伐他汀联合厄贝沙坦对老年早期DN患者肾功能及微炎症状态的影响,以期为临床用药提供参考依据,现将研究结果整理如下。

1 资料与方法

1.1 一般资料

选取2016年4月到2017年2月在我院肾内科接受治疗的老年早期DN患者84例,纳入标准:①所有患者均符合DN的相关诊断标准^[12];②均处于DN早期,即尿微量白蛋白排泄率(urinary albumin excretion rate, UAER)在20-200 $\mu\text{g}/\text{min}$ 的范围内;③年龄均不低于60岁;④患者及其家属对本研究知情同意。排除标准:①对本研究涉及的药物过敏者;②合并有严重器质性疾病者;③合并有恶性肿瘤者;④合并有其他肾脏疾病者;⑤近期服用过他汀类药物或血管紧张素Ⅱ受体拮抗剂类药物者;⑥依从性较差,未能按要求用药者。根据随机数字表法将患者分为对照组和观察组,各42例。对照组男24例,女18例,年龄60-76岁,平均 (66.42 ± 4.65) 岁,糖尿病病程6-24年,平均 (11.32 ± 3.41) 年,合并疾病:高血压28例,高血脂17例。观察组男23例,女19例,年龄60-78岁,平均 (67.23 ± 4.74) 岁,糖尿病病程6-22年,平均 (11.17 ± 3.65) 年,合并疾病:高血压26例,高血脂18例。两组患者的一般资料比较无统计学差异($P>0.05$)。本研究符合我院伦理委员制定的相关规定,并已审

批通过。

1.2 治疗方法

两组均给予常规的降压、降糖治疗,并指导患者合理饮食。对照组给予厄贝沙坦分散片(华润双鹤利民药业(济南)有限公司,国药准字H20100170,规格:0.15g)进行治疗,1片/次,1次/d,连续治疗6个月。观察组在对照组的基础上联用阿托伐他汀钙片(北京嘉林药业股份有限公司,国药准字H20093819,规格:20mg)进行治疗,1片/次,1次/d,连续治疗6个月。

1.3 观察指标

1.3.1 肾功能指标检测 在治疗前、治疗6个月后检测两组患者的肾功能指标,主要包括UAER、血肌酐(serum creatinine, Scr)及血尿素氮(Blood urea nitrogen, BUN)、 β_2 微球蛋白(β_2 -microglobulin, β_2 -MG)。收集患者的24h尿液,采用免疫散射比浊法检测UAER;抽取所有患者的清晨空腹静脉血5mL,采用高速离心机(长沙湘智离心机仪器有限公司)以3000 r/min的离心速度离心10 min,取上层血清,置于-20℃的低温冰箱中保存。采用化学发光匀相分析法检测Scr、BUN水平,采用电化学发光法检测 β_2 -MG水平,严格遵循试剂盒(购于上海基恩科技有限公司)操作指南进行相关操作。

1.3.2 微炎症指标检测 在治疗前、治疗6个月后检测两组患者的微炎症指标,主要包括白细胞介素-1(Interleukin-1, IL-1)、白细胞介素-10(Interleukin-10, IL-10)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)。采用酶联免疫吸附法检测血清中IL-1、IL-10、TNF- α 水平,严格遵循试剂盒(购于上海基恩科技有限公司)操作指南进行相关操作。

1.3.3 不良反应 记录患者治疗过程中出现的不良反应。

1.4 统计学方法

采用SPSS22.0进行统计分析,男女比例、总不良反应发生率等计数资料以率(%)的形式表示,采用卡方检验,UAER、Scr水平等计量资料以($\bar{x} \pm s$)的形式表示,采用t检验。检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组患者肾功能指标的比较

治疗前两组患者的UAER、Scr、BUN、 β_2 -MG水平比较无统计学差异($P>0.05$);治疗后两组患者的UAER、Scr、BUN、 β_2 -MG水平均降低,且观察组的UAER、Scr、BUN、 β_2 -MG均低于对照组($P<0.05$)。具体见表1。

表1 两组患者肾功能指标的比较($\bar{x} \pm s$)

Table 1 Comparison of renal function indexes between the two groups($\bar{x} \pm s$)

Groups	n	Time	UAER($\mu\text{g}/\text{min}$)	Scr($\mu\text{mol}/\text{L}$)	BUN(mmol/L)	β_2 -MG(mg/L)
Control group	42	Before treatment	120.78 $\pm$ 30.21	96.24 $\pm$ 12.42	7.31 $\pm$ 1.79	1.43 $\pm$ 0.31
		After treatment	85.07 $\pm$ 22.13 [#]	88.61 $\pm$ 10.32 [#]	6.82 $\pm$ 1.09 [#]	1.13 $\pm$ 0.42 [#]
Observation group	42	Before treatment	121.72 $\pm$ 31.98	94.23 $\pm$ 13.86	7.28 $\pm$ 1.73	1.46 $\pm$ 0.32
		After treatment	61.40 $\pm$ 18.96 ^{#*}	79.62 $\pm$ 10.11 ^{#*}	6.33 $\pm$ 0.86 ^{#*}	0.84 $\pm$ 0.26 ^{#*}

Note: compared with before treatment, [#] $P<0.05$; compared with the control group, ^{*} $P<0.05$.

2.2 两组患者的微炎症指标比较

治疗前两组患者血清IL-1、IL-10、TNF- α 水平比较差异无统计学意义($P>0.05$);治疗后两组患者血清IL-1、TNF- α 水平

均较治疗前降低,IL-10水平较治疗前升高($P<0.05$);治疗后观察组血清IL-1、TNF- α 水平均低于对照组,IL-10水平高于对照组($P<0.05$)。具体见表2。

表 2 两组患者的微炎症指标比较($\bar{x} \pm s$)Table 2 Comparison of micro inflammation indexes between the two groups($\bar{x} \pm s$)

Groups	n	Time	IL-1(pg/mL)	IL-10(ng/L)	TNF- α (ng/mL)
Control group	42	Before treatment	17.42 $\pm$ 6.32	82.61 $\pm$ 31.27	37.34 $\pm$ 5.41
		After treatment	14.37 $\pm$ 6.76 [#]	107.33 $\pm$ 29.74 [#]	31.66 $\pm$ 4.38 [#]
Observation group	42	Before treatment	17.37 $\pm$ 6.24	83.09 $\pm$ 30.34	36.98 $\pm$ 5.36
		After treatment	11.56 $\pm$ 6.43 ^{**}	136.45 $\pm$ 34.16 ^{**}	26.43 $\pm$ 4.05 ^{**}

Note: compared with before treatment, [#]P<0.05; compared with the control group, ^{*}P<0.05.

2.3 两组患者不良反应比较

两组患者均未出现严重的不良反应,对照组出现 1 例头晕,不良反应发生率为 2.38%(1/42),观察组出现 1 例肠胃道不适,1 例头晕,不良反应发生率为 4.76%(2/42),两组不良反应发生率比较差异无统计学意义(P>0.05)。

3 讨论

早期 DN 的主要病理改变为肾小管上皮细胞受损、肾小管间质纤维化、肾小球硬化。DN 患者血糖过高可导致糖基化终末产物(Advanced glycation end products, AGEs)的水平增高,而过多的 AGEs 易形成沉积,可改变细胞外基质的结构,导致其出现功能异常,另外 AGEs 还可促进巨噬细胞迁移至细胞外基质,当其过度沉淀时会增加活性基团的含量,使机体清除低密度脂蛋白的能力降低,进而导致肾小球硬化,损害患者的肾功能^[13-15]。早期 DN 除了伴随着不同程度的肾功能损伤之外,患者体内还存在着慢性低度炎症反应,主要表现为炎症细胞浸润,炎症趋化因子、致炎因子、黏附分子水平上升,然而其与风湿性关节炎等传统的炎性疾病相比,症状非常轻微,因此这种慢性低度炎症又被称为微炎症^[16,17]。有关研究结果显示^[18],微炎症与 DN 的发生、发展密切相关,并推测微炎症反应中所涉及到的炎症因子可能成为 DN 治疗的新靶点。早期 DN 患者的肾功能和微炎症状况可间接反映其病情进展情况,因此对患者的肾功能和微炎症指标进行检测具有重要的临床意义。

UAER 是早期 DN 的诊断指标,在生理条件正常的情况下尿液中仅出现极少的白蛋白,但在肾功能受损时,白蛋白水平将明显上升,UAER 越大提示肾功能损害越严重^[19,20]。Scr、BUN 是衡量肾小球滤过率的重要指标,两者均主要由肾小球滤过,几乎全部通过尿液排出体外,若肾功能受损,血清 Scr、BUN 水平将会上升^[21]。 β 2-MG 可以从肾小球自由滤过,大部分在近端肾小管被吸收,并在肾小管上皮细胞中被分解破坏,因此正常情况下血液中 β 2-MG 很低,但肾脏受损后肾小管和肾小管上皮细胞吸收和分解 β 2-MG 的能力下降,导致血液中的 β 2-MG 水平上升^[22,23]。在本次研究中,治疗后两组患者的 UAER、Scr、BUN、 β 2-MG 水平均降低,且观察组的 UAER、Scr、BUN、 β 2-MG 均低于对照组(P<0.05),这提示两种治疗方案均能有效改善老年早期 DN 患者的肾功能,但阿托伐他汀联合厄贝沙坦的改善程度更大,说明联合用药有更好的疗效。血管紧张素 II 可介导肾小球小动脉的收缩,并可促进肾小球压力上升,对肾脏造成损伤,而厄贝沙坦一种血管紧张素 II 受体拮抗剂,其可阻断血管紧张素 II 引发的全身微动脉收缩效应,进而扩张肾小球小动脉,能够有效降低肾小球囊血压,并保护血管内皮细胞,

防止肾间质出现纤维化^[24-26]。阿托伐他汀属于他汀类药物,其可通过减少胆固醇的合成,起到较强的调脂作用,进而减少血脂异常引起的肾内大血管和(或)微血管硬化,减少对肾功能的损害^[27]。同时阿托伐他汀还能够改善血管内皮细胞功能,抑制肾小球系膜细胞增殖,进而改善肾小球硬化情况,对肾脏起到保护作用。本研究结果还显示,治疗后两组患者血清中 IL-1、TNF- α 水平均降低,IL-10 水平均升高(P<0.05);治疗后观察组血清中 IL-1、TNF- α 水平均低于对照组,IL-10 水平均高于对照组(P<0.05)。这说明两种治疗方案均有有效的改善老年早期 DN 患者体内的微炎症状态,但阿托伐他汀联合厄贝沙坦的改善情况更明显。IL-1 是由活化的巨噬细胞所产生,主要有 IL-1 α 和 IL-1 β 两种形式,是炎症反应的重要调节因子^[28]。IL-10 是机体内重要的免疫调节因子,能对多种炎症因子的合成及其活性产生抑制作用,是一种常见的抗炎因子。TNF- α 是一种由活化的单核巨噬细胞产生的促炎细胞因子,参与了机体的炎症反应和免疫调节。阿托伐他汀可抑制 Toll 样受体 2(TLR2)和 Toll 样受体 4(TLR4)启动的炎症反应,同时阿托伐他汀还能抑制单核细胞的聚集,减少巨噬细胞分泌 IL-1、TNF- α 等炎症因子,进而改善微炎症状态^[29]。另有研究显示^[30],阿托伐他汀还可以通过调控微小 RNA 和过氧化体增殖物激活型受体的表达来降低体内的炎症反应。两组患者在治疗过程中不良反应均较轻,且两组间比较差异不明显(P>0.05),这说明阿托伐他汀联合厄贝沙坦治疗并不会增加患者的不良反应,具有较好的安全性。

综上所述,阿托伐他汀联合厄贝沙坦对老年早期 DN 患者有较好的治疗效果,可显著改善患者的肾功能,减轻微炎症状态,且安全性较好,值得临床推广应用。

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育^[9,10]。因此,探讨 O 型血产妇发生 HDN 的影响因素或方法对于改善新生儿结局具有十分重要的临床意义。本研究从丈夫 ABO 血型、孕妇产前 IgG 抗 -A(B)效价及新生儿性别三个方面探讨了其与 O 型血产妇发生 HDN 的相关性,结果显示丈夫 ABO 血型及新生儿性别均与其无关,而随着产妇 IgG 抗 -A(B)抗体效价的增加,HDN 的发生率逐渐升高,提示 IgG 抗 -A(B)抗体效价的增加与 HDN 的发生密切相关,孕妇 IgG 抗 -A(B)抗体检测可能有助于预测 HDN。

IgG 抗体是体内唯一能通过胎盘的抗体,研究表明其效价的增加与 ABO 血型不合所致的 HDN 有关^[5,11,12]。但目前关于母体 IgG 抗 -A(B)效价筛查是否可用于评估 ABO 血型不合所致 HDN 的发生风险观点仍存在矛盾。有研究表明母体 IgG 抗 -A(B)效价可用于指导 ABO 血型不合所致的 HDN 的治疗。如 Owa JA 等发现母体 IgG 抗 -A(B)抗体效价为 1:64 为治疗的截断值,高于 1:64 时需要进行换血治疗^[13]。也有研究显示母体 IgG 抗 -A(B)抗体效价截断值为 1:512,即 $\geq 1:512$ 时需要进行光疗、免疫球蛋白治疗或输血治疗^[14]。还有研究结果并不支持用 IgG 抗 -A(B)效价筛查评估 ABO 血型不合所致 HDN 的发生风险^[15]。Li P 等通过 meta 分析也发现母亲体内 IgG 抗 -A(B)抗体与 O 型血产妇发生 HDN 的风险显著相关,可用于预测 O 型血产妇发生 HDN 的风险,当抗体效价 $\geq 1:512$ 时则提示需要介入治疗^[5]。本研究中,IgG 抗 -A(B)抗体效价 $\geq 1:512$ 时,HDN 的发生率高达 90.5%,风险极高,与 Li P 等研究结果一致。

值得注意的是,有些 O 血型孕妇血清 IgG 抗 -A(B)抗体效价 ≥ 64 ,却没有发生 HDN。分析原因可能与胎儿 A、B 抗原的强弱、血型物质的含量、胎盘的屏障作用以及 IgG 中亚类不同有关。换言之,即使 O 血型孕妇血清 IgG-A(B)抗体效价 ≥ 64 也不能说明新生儿一定会发生 HDN。对于这部分 O 血型孕妇,我们需要定期监测其 IgG-A(B)抗体效价,从其抗体水平的变化进行综合评估,必要时采取适当的措施进行控制,进而降低 HDN 发生的风险。

总之,本研究结果表明 O 型血孕妇产后 HDN 的发生率较高,与丈夫 ABO 血型和新生儿性别均无关,与孕妇产前血清 IgG 抗 -A(B)抗体效价有关,HDN 的发生风险随抗体效价增高而升高。此外,对于 O 型血孕妇血清 IgG 抗 -A(B)抗体效价偏低者,需定期复查和监测以综合评估其 HDN 发生风险,最大程度改善新生儿预后。

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