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## $\alpha$ -硫辛酸对糖尿病肾病患者氧化应激, Hcy, CysC 的影响

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**摘要 目的:**探讨  $\alpha$ -硫辛酸对糖尿病肾病患者的疗效及对氧化应激、同型半胱氨酸(homocysteine, Hcy)、血清胱抑素 C(cystatin C, CysC)的影响。**方法:**将 82 例于我院进行治疗的 2 型糖尿病肾病患者随机分为观察组和对照组, 对照组患者接受常规治疗, 观察组患者在对照组的基础上加用  $\alpha$ -硫辛酸。治疗时间均为 2 周。观察两组治疗效果并比较两组患者治疗前、后氧化应激指标超氧化物歧化酶(superoxide dismutase, SOD)、丙二醛(malondialdehyde, MDA)及 Hcy、CysC 水平变化。**结果:**治疗后, 观察组氧化应激指标 SOD 水平均较治疗前显著升高( $P<0.05$ ), MDA 水平均较治疗前显著降低( $P<0.05$ ), 对照组氧化应激指标 SOD 及 MDA 水平与治疗前无明显差异( $P>0.05$ ), 两组治疗后 SOD 及 MDA 水平差异显著( $P<0.05$ ); 治疗后, 观察组 Hcy、CysC 水平较治疗前显著降低( $P<0.05$ ), 对照组 Hcy、CysC 水平与治疗前无明显差异( $P>0.05$ ), 两组治疗后 Hcy、CysC 水平差异显著( $P<0.05$ )。**结论:** $\alpha$ -硫辛酸可缓解糖尿病肾病患者氧化应激状态, 降低 Hcy、CysC 水平, 改善患者肾功能。

**关键词:**糖尿病肾病;  $\alpha$ -硫辛酸; 氧化应激; Hcy; CysC

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## Effect of $\alpha$ -lipoic Acid on Oxidative Stress, Hcy and CysC in Patients with Diabetic Nephropathy

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**ABSTRACT Objective:** To investigate the effect of  $\alpha$ -lipoic acid on oxidative stress, Hcy and CysC in the patients with diabetic nephropathy. **Methods:** 82 patients with type 2 diabetic nephropathy were divided into control group (41 cases) and observation group (41 cases). The patients in two groups were given the conventional therapy, and the patients in observation group were received extra  $\alpha$ -lipoic acid, they were all treated for 2 weeks. The treatment effects were observed and the levels of oxidative stress indexes (SOD and MDA), Hcy and CysC were tested and compared. **Results:** After treatment, the level of SOD was increased significantly, the level of MDA was decreased significantly in observation group ( $P<0.05$ ), the levels of SOD and MDA had no significant difference before and after treatment in control group ( $P>0.05$ ), but the levels of SOD and MDA had significant difference after treatment in two groups ( $P<0.05$ ); After treatment, the levels of Hcy and CysC were decreased significantly in observation group ( $P<0.05$ ), the levels of Hcy and CysC had no significant difference before and after treatment in control group ( $P>0.05$ ), but the levels of Hcy and CysC had significant difference after treatment in two groups ( $P<0.05$ ). **Conclusions:**  $\alpha$ -lipoic acid can alleviate oxidative stress, reduce Hcy, CysC levels and improve renal function in patients with diabetic nephropathy.

**Key words:** Diabetic nephropathy;  $\alpha$ -lipoic acid; Oxidative stress; Hcy; CysC

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### 前言

糖尿病肾病(diabetic nephropathy, DN)是因糖尿病微血管病变引起的一种较常见的糖尿病慢性并发症,我国进行肾替代治疗的终末期肾病患者中 DN 患者的比例逐年增高, DN 是导致糖尿病患者死亡的重要原因<sup>[1-3]</sup>。目前其发病机制还不十分明确,一般认为其发生、发展与氧化应激状态等有关,因此抗氧化

治疗十分重要<sup>[4]</sup>。有研究显示,  $\alpha$ -硫辛酸能减轻体内过氧化反应,抑制肾小球足细胞、肾小管细胞凋亡,保护肾功能<sup>[5]</sup>。本研究旨在探讨  $\alpha$ -硫辛酸对 DN 患者氧化应激指标超氧化物歧化酶(superoxide dismutase, SOD)、丙二醛(malondialdehyde, MDA)及同型半胱氨酸(homocysteine, Hcy)、血清胱抑素 C(cystatin C, CysC)的影响,现报告如下。

### 1 资料与方法

#### 1.1 一般资料

将 2015 年 2 月 -2016 年 4 月于我院就诊的 82 例 2 型 DN 患者随机对照表法分为观察组和对照组,各 41 例。观察组:男 23 例,女 18 例,年龄 37-70 岁,平均年龄( $55.32 \pm 13.56$ )岁,糖

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尿病病程为 5-15 年,平均病程( $9.46 \pm 3.25$ )年;对照组:男 24 例,女 17 例,年龄 56-77 岁,平均年龄( $56.12 \pm 14.61$ )岁,糖尿病病程为 5-15 年,平均病程( $9.29 \pm 3.46$ )年。纳入标准:所有患者符合 2 型 DN 的诊断标准;本研究所有受试者均自愿加入本试验,且签订知情同意书。排除标准:原发性及其他原因导致的肾脏疾病患者;心、肺、肝功能衰竭患者;急性并发症患者;近期抗氧化剂使用患者。两组患者性别、年龄、病程等一般资料经统计学分析显示无明显差异( $P > 0.05$ )。

## 1.2 方法

对两组患者均给予糖尿病患者标准饮食,并使用胰岛素或降糖药进行控制血糖治疗。患者血糖稳定后,观察组加用  $\alpha$ -硫辛酸(亚宝药业太原制药有限公司),将 300 mg  $\alpha$ -硫辛酸加入 250 mL 生理盐水中,静脉滴注,每日 1 次,治疗时间均为 2 周。

## 1.3 观察指标

所有入选者均于清晨抽取空腹静脉血 5 mL,离心 10 min ( $3000 \text{ r/min}$ ),分离血清,于  $-20^\circ\text{C}$  冰箱保存待测。于治疗前、后

分别测定空腹血糖(FPG)、总胆固醇(TC)、三酰甘油(TG)、糖化血红蛋白(Hb A1c)、超氧化物歧化酶(SOD)及丙二醛(MDA)活性采用分光光度计法检测。试剂盒均来源于北京中生物科技股份有限公司;采用全自动生化分析仪进行血清 CysC、Hcy 检测,仪器采用日立 7180 全自动生化分析仪,试剂均来源于日立 7180 原装生化试剂。按照说明书严格执行所有试验操作。观察两组治疗期间出现的不良反应。

## 1.4 统计学处理

计量资料以  $\bar{x} \pm s$  表示,采用 t 检验进行组间对比,采用  $\chi^2$  检验进行率的比较,在 SPSS 16.0 软件上进行统计学处理,以  $P < 0.05$  为差异存在统计学意义。

# 2 结果

## 2.1 两组患者治疗前、后血糖、血脂比较

两组患者治疗前、后血糖、血脂水平无明显差异( $P > 0.05$ ) (见表 1)。

表 1 两组患者治疗前、后血糖、血脂比较

Table 1 Comparison of blood glucose and blood lipid level before and after treatment in two groups

| Groups            | Time             | Cases | FPG(mmol/L)     | HbA1C(%)        | TG(mmol/L)      | TC(mmol/L)      |
|-------------------|------------------|-------|-----------------|-----------------|-----------------|-----------------|
| Observation group | Before treatment | 41    | $7.35 \pm 1.41$ | $7.23 \pm 1.32$ | $2.56 \pm 0.32$ | $6.63 \pm 0.78$ |
|                   | After treatment  |       | $7.13 \pm 1.21$ | $7.01 \pm 1.35$ | $2.51 \pm 0.23$ | $6.27 \pm 0.71$ |
| control group     | Before treatment | 41    | $7.32 \pm 1.43$ | $7.16 \pm 1.25$ | $2.53 \pm 0.35$ | $6.36 \pm 0.62$ |
|                   | After treatment  |       | $7.23 \pm 1.35$ | $7.20 \pm 1.41$ | $2.50 \pm 0.28$ | $6.24 \pm 0.56$ |

## 2.2 两组患者治疗前后 SOD、MDA 变化比较

治疗后,观察组氧化应激指标 SOD 水平均较治疗前显著升高( $P < 0.05$ ),MDA 水平均较治疗前显著降低( $P < 0.05$ ),对照组

氧化应激指标 SOD 及 MDA 水平与治疗前无明显差异( $P > 0.05$ ),两组治疗后 SOD 及 MDA 水平差异显著( $P < 0.05$ ) (见表 2)。

表 2 两组患者治疗前后 SOD、MDA 变化比较

Table 2 Comparison of SOD and MDA level before and after treatment in two groups

| Groups            | Time             | Cases | SOD( kU/L )        | MDA( nmol/mL )       |
|-------------------|------------------|-------|--------------------|----------------------|
| Observation group | Before treatment | 41    | $72.71 \pm 1.54$   | $7.63 \pm 0.91$      |
|                   | After treatment  |       | $88.74 \pm 2.86^a$ | $4.32 \pm 0.73^{ab}$ |
| Control group     | before treatment | 41    | $73.12 \pm 1.61$   | $7.56 \pm 0.86$      |
|                   | After treatment  |       | $74.97 \pm 1.86$   | $7.31 \pm 0.81$      |

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

## 2.3 两组患者治疗前后 Hcy、CysC 变化比较

治疗后,观察组 CysC、Hcy 水平较治疗前显著降低( $P < 0.05$ ),对照组 CysC、Hcy 水平与治疗前无明显差异( $P > 0.05$ ),两组治疗后 CysC、Hcy 水平差异显著( $P < 0.05$ ) (见表 3)。

## 2.4 不良反应

观察组患者治疗期间共有 2 例出现轻度恶心但无呕吐,随着治疗进行自行缓解,对照组未出现不良反应。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

DN 主要是由糖尿病人糖代谢紊乱引起的肾小球硬化并伴

随尿蛋白含量超出常态的一种较常见的糖尿病慢性并发症,其发生与糖尿病预后关系密切,且发病隐匿,病情进展快,疾病预后差。DN 发病率在糖尿病人占 20%-40%,我国进行肾替代治疗的终末期肾病患者中 DN 患者的比例逐年增高,终末期肾病的患者 5 年生存率小于 20%<sup>[6-8]</sup>。受多因素影响,DN 发病机制较复杂,一般认为其发生、发展与氧化应激、炎症反应及大量细胞因子激活等有关<sup>[9]</sup>。 $\alpha$ -硫辛酸已广泛应用于临床治疗,它是一种强氧化剂,既能在水溶性又能在脂溶性环境中发挥抗氧化作用,被认为是治疗糖尿病神经病变症状的安全有效药物<sup>[10]</sup>。Liu 等研究证明<sup>[11]</sup>DN 患者经  $\alpha$ -硫辛酸多疗程治疗,具有明显的抗氧化作用,改善患者肾功能,减缓肾脏病变速度。

表 3 两组患者治疗前后 Hcy、CysC 变化比较

Table 3 Comparison of Hcy and CysC before and after treatment in two groups

| Groups            | Time             | Cases | Hcy(μmol/L)              | CysC(mg/L)               |
|-------------------|------------------|-------|--------------------------|--------------------------|
| Observation group | before treatment | 41    | 14.23± 2.53              | 2.52± 1.41               |
|                   | After treatment  |       | 8.59± 2.28 <sup>ab</sup> | 2.12± 0.71 <sup>ab</sup> |
| Control group     | before treatment | 41    | 14.51± 3.62              | 2.43± 1.52               |
|                   | After treatment  |       | 13.10± 3.11              | 2.31± 1.23               |

Note: Compared with before treatment, <sup>a</sup>P<0.05; Compared with control group, <sup>b</sup>P<0.05.

氧化应激与 DN 的发生、发展密不可分<sup>[12,13]</sup>。肾脏是对氧化损伤比较敏感的器官之一,过量的活性氧(ROS)对肾小球及系膜细胞的直接损伤和趋化作用,增加了肾脏负担,引起机体过氧化反应。MDA<sup>[14]</sup>的产生是由于其细胞膜上的多不饱和脂肪酸被氧自由基激发而产生脂质过氧化反应,使膜损伤加重,MDA 水平越高,氧自由基水平也越高,故机体组织损伤也就越严重。SOD<sup>[15]</sup>能有效清除体内氧自由基,防止氧自由基致机体损伤,患者体内的过氧化导致 SOD 活性降低,SOD 属于清除超氧阴离子自由基的酶类抗氧化物质,活性降低,过氧化反应越强烈,恶性循环,使机体氧化-抗氧化状态严重失衡<sup>[16]</sup>。本研究治疗后,观察组患者 MDA、SOD 水平明显改善,这是因为 α- 硫辛酸在体内转变的二氢硫辛酸发挥抗氧化特性有效清除大部分氧自由基,同时 α- 硫辛酸可螯合金属离子,与其他抗氧化剂协同作用,从而使肾脏组织细胞得到保护。

Hcy<sup>[17]</sup>是由蛋氨酸代谢的中间产物,属于含硫非必需氨基酸的一种,主要通过肾脏进行排泄,正常情况下,Hcy 水平在血循环中维持平衡状态。DN 是一种肾脏病变,主要以肾小球损伤为主,肾小球滤过功能受损引起 Hcy 体内蓄积导致肾脏结构的完整性受损,早期 DN 患者中就会表现出 Hcy 升高,Hcy 升高会引起机体过氧化,使血管内皮功能受损,从而导致患者肾脏微血管损伤,Hcy 升高被认为是 DN 的致病因素<sup>[18]</sup>。Hcy 在体内很不稳定,极易氧化形成超氧化物和过氧化物,影响肾脏血管内皮细胞及肾小球基底膜的功能,造成肾小球滤过功能损伤,引起蛋白尿。CysC 是半胱氨酸蛋白酶抑制剂家族成员,是反应肾小球滤过作用的重要指标<sup>[19]</sup>。CysC 是低分子量蛋白质,化学性质相对稳定,基本可在有核细胞持续转录与表达,不表现组织学特异性,受其他因素影响小,可进入原尿,因其可被肾小球滤过却不被肾小管重吸收的特点,因此血清中 CysC 的水平可体现机体肾小球滤过率情况,肾功能早期损伤其水平就会出现明显异常<sup>[20]</sup>。本研究治疗后,观察组患者 Hcy、CysC 水平明显改善,这表明 α- 硫辛酸可以降低 Hcy、CysC 水平,改善 DN 患者肾功能,α- 硫辛酸的进一步作用机制仍需加大样本量做进一步研究。靳新东等<sup>[21]</sup>发现 α- 硫辛酸能改善 DN 患者的氧化应激状态和肾功能,但其选择的指标与本文不同,本文采用 MDA 和 SOD 评价氧化应激状态,更具有代表性。此外,本研究结果未发现 α- 硫辛酸对血糖和血脂产生明显影响,与姚伟峰等<sup>[22]</sup>研究结果一致,这可能与 α- 硫辛酸的药理作用有关,目前尚未见 α- 硫辛酸具有改善血糖和调节血脂方面的作用。

综上所述,α- 硫辛酸可缓解糖尿病肾病患者氧化应激状态,降低 Hcy、CysC 水平,改善患者肾功能,延缓 DN 病情发

展。

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