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Effects of Irbesartan combined Atorvastatin on serum levels of Cys C, Hcy, TNF−α, ET, TGF−b1 in patients with early diabetic nephropathyn

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ABSTRACT

Objective: To observe the effects of Irbesartan combined with Atorvastatin on early diabetic nephropathy patients' serum Cys C, Hcy, TNF-α, ET and TGF-b1 levels. **Methods:** A total of 60 early diabetic nephropathy patients were randomly divided into observation group (30 cases) and control group (30 cases). Observation group: Irbesartan combined with Atorvastatin; control group: patients were treated only by Irbesartan. Recording and comparing the levels of Cys C, Hcy, TNF-α, ET and TGF-b1 before and after treatment. **Results:** (1) Before treatment, there was no statistically significant difference in the serum FBG, TG, Scr, BUN levels between the two groups. After treatment, compared with the same group before treatment, the serum TG, Scr, BUN levels of the two groups were significantly lower, and those levels of observation group were significantly better than the control group, the difference between two groups was statistically significant; (2) Before treatment, there was no statistically significant difference in the serum Cys C, Hcy, TNF-α, ET, TGF-b1 levels between the two groups. After treatment, compared with the same group before treatment, the serum Cys C, Hcy, TNF-α, ET, TGF-b1 levels of the two groups were significantly lower, and those levels of observation group were significantly better than the control group, the difference between two groups was statistically significant. **Conclusion:** Irbesartan combined with Atorvastatin for early diabetic nephropathy patients can reduce the levels of serum Cys C, Hcy, TNF-α, ET, TGF-b1 and be beneficial to protect their nephritic function.

1. Introduction

Diabetic nephropathy (DN) is not only one of the major microvascular complications of diabetes, but also one of the important causes of chronic renal failure[1]. Pathological findings include thickening of basement membranes, hypertrophy of glomeruli, and accumulation of extracellular matrix, which develop into interstitial fibrosis and glomerulosclerosis. In recent years, with the increase of diabetic patients, the incidence of DN has increased, which has adverse effects on the health and quality of life of the patients[2]. Several studies have shown that a variety of cytokines, such as tumor necrosis factor alpha (TNF-α), transforming growth factor beta 1 (TGF-b1), and endothelial dysfunction, are involved in the pathogenesis of diabetic nephropathy[3,4]. Therefore, this study aimed to treat patients with early diabetic nephropathy with irbesartan and atorvastatin, and to explore the effect of the program on serum levels of Cys, C, Hcy, TNF-α, ET and TGF-b1 in patients with early diabetic nephropathy, so as to provide a theoretical basis for the clinical treatment of early diabetic nephropathy.

2. Information and methods

2.1. General information

A total of 60 cases of early diabetic nephropathy were treated in our hospital from September 2014 to September 2016. They were randomly divided into two groups: control group and observation group. The control group consisted of 30 patients, including 18

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males and 12 females, with an average age of (57 ± 11) years, with an average duration of (9 ± 2) years; The observation group consisted of 30 patients, 17 males and 13 females, aged (58 ± 13) years, with an average duration of (10 ± 5) years. There was no significant difference in age, sex and other data between the two groups (P>0.05). Inclusion criteria for cases included: (1) The patient was diagnosed with type 2 diabetes mellitus; (2) Consistent with the international standard for staging of early diabetic nephropathy: standard urinary albumin excretion rates continued to rise by 20-200 g/min; urinary albumin 30-300 mg/24 h; urinary albumin/urine creatinine was 30-300 Mogensen g/mg[5]. (3) Exclude those with serious diseases such as heart and lung. (4) Patients and their families were informed of the treatment and signed informed consent.

2.2 Treatment method

(1) All subjects received routine treatment for type 2 diabetes, including oral hypoglycemic agents or insulin injections, diet control, exercise enhancement, and fasting blood glucose control at 5.6-7.2 mmol/L; (2) Patients in the control group received oral irbesartan 150 mg/time, once/d; The patients in the observation group were combined with Atorvastatin Calcium Tablets on the basis of control group for 20 mg/time, 1/d. The two groups were treated continuously for 6 months.

2.3 Observation indexes

(1) Biochemical parameters: fasting blood glucose (FBG), total cholesterol (TG), serum creatinine (Scr) and blood urea nitrogen (BUN) levels were detected and compared before and after treatment in all subjects; (2) 4 mL fasting venous blood was taken before and after the treatment,and the levels of serum Cys, C (cystatin C), Hcy (homocysteine), TNF-alpha (tumor necrosis factor alpha), ET (endothelin) and TGF-b1 (transforming growth factor-1) were detected by ELISA.

2.4 Statistical processing

SPSS 20.0 data package was used to analyze and process data, Statistical analysis was carried out by (means ± standard deviation), frequency and so on. t test and chi square test were used to compare and analyze the differences between the observation group and the control group. And P<0.05 is considered to have statistically significant differences.

3. Results

3.1 Comparison of biochemical indexes in two groups

Before treatment, there was no significant difference in the levels of FBG, TG, Scr and BUN between the two groups (P>0.05). At the end of treatment, the levels of TG, Scr and BUN in the two groups were significantly lower than those in the same group before treatment (P<0.05). The levels of TG, Scr and BUN in the control group were (2.10±0.71) mmol/L, (116.31±19.15) μmol/L, (6.75±1.24) mmol/L, that in observation group were (1.37±0.43) mmol/L, (109.88±17.39) μmol/L, (6.28±1.01) mmol/L, were significantly lower than those in the control group, the difference between the two groups was statistically significant (P<0.05), see Table 1.

3.2 Comparison of serum Cys C, Hcy, TNF–α level in the two groups

Before treatment, there was no significant difference in serum Cys, C, Hcy and TNF- alpha levels between the two groups (P>0.05); At the end of treatment, serum Cys, C, Hcy and TNF- alpha levels in the two groups were significantly lower than those in the same group (P<0.05); The serum levels of Cys, C, Hcy and TNF- in the control group were (1.70±0.72) mg/L, (16.34±6.95) μmol/L, (20.78±8.71) ng/L, that in observation group were (1.47±0.53) mg/L, (11.52±7.56) μmol/L, (16.67±7.78) ng/L, were significantly lower than those in the control group, the difference between the two groups was statistically significant (P<0.05), see Table 2.

Table 1.

Comparison of biochemical indexes between control group and observation group (n=30).

Group	Time	FBG (mmol/L)	TG (mmol/L)	Scr (μmol/L)	BUN (mmol/L)
Observation group	Before treatment	6.45±1.26	2.56±0.55	124.93±21.54	7.19±1.17
	After treatment	7.01±0.95	1.37±0.43*#	109.88±17.39*#	6.28±1.01*#
Control group	Before treatment	6.21±1.47	2.51±0.67	121.48±20.76	7.22±1.32
	After treatment	7.13±1.82	2.10±0.71*	116.31±19.15*	6.75±1.24*

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

Table 2.

Comparison of serum Cys C, Hcy, TNF-α levels between control group and observation group (n=30).

Group	Time	Cys C (mg/L)	Hcy (μmol/L)	TNF-α (ng/L)
Observation group	Before treatment	2.10±0.67	20.16±6.54	22.53±9.16
	After treatment	1.47±0.53*#	11.52±7.56*#	16.67±7.78*#
Control group	Before treatment	2.06±0.66	21.23±7.18	23.05±10.34
	After treatment	1.70±0.72*	16.34±6.95*	20.78±8.71*

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

3.3 Comparison of serum ET and TGF–b1 levels in the two groups

Before treatment, there was no significant difference in serum ET and TGF-b1 levels between the two groups (P>0.05). At the end of treatment, the blood ET and TGF-b1 levels of the two groups were significantly lower than those in the same group before treatment, and the level was significantly higher (P<0.05). The serum levels of ET and TGF-b1 in the control group were (83.62±12.78) pg/mL, (230.12±36.94) pg/mL, that in observation group were (64.65±10.89) pg/mL, (154.32±31.46) pg/mL, were significantly lower than those in the control group, the difference between the two groups was statistically significant (P<0.05), see Table 3.

Table 3.

Comparison of serum ET and TGF-b1 levels between control group and observation group (n=30).

Group	Time	ET (pg/mL)	TGF-b1(pg/mL)
Observation group	Before treatment	90.23±14.25	280.53±64.15
	After treatment	64.65±10.89*#	154.32±31.46*#
Control group	Before treatment	91.74±13.43	288.64±33.78
	After treatment	83.62±12.78*	230.12±36.94*

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

4. Discussion

The condition of early diabetic nephropathy patients was mild, Symptoms are not obvious, once entered the stage of clinical proteinuria, and the condition will often deteriorate rapidly, greatly increasing the risk of end-stage renal failure. Therefore, the early diagnosis and treatment of diabetic nephropathy plays an important role in controlling the condition of DN patients, reducing the damage of renal function, improving the quality of life and prolonging the life span[6,7]. The incidence of diabetic nephropathy involves such aspects as metabolic disorder, cytokines, endothelial dysfunction, etc. the risk factors of hypertension include hypertension, hyperlipidemia, hyperglycemia and so on[8]. Cys C belongs to the endogenous cystine protease inhibitor, is a small molecule of protein that is produced by the metabolism of the glomerulus. When the renal function is impaired, the excretion of Cys and C is blocked, and the level of serum Cys and C can better reflect the glomerular filtration rate[9,10]. Hcy is a sulfur-containing non-essential amino acid derived from food. The kidney is the major organ of its metabolism. Therefore, the reduction of glomerular filtration rate will lead to an increase in serum Hcy levels[11,12]. TNF-α is a polypeptide cytokine secreted by cells such as mesangial cells. Studies have shown that it can increase the level of inflammatory factors through a variety of signal transduction pathways, and play an important role in the development of diabetic nephropathy from inducing renal damage[13,14]. Endothelin (ET) is an endogenous long-acting vasoconstrictor factor produced by endothelial cells. It is one of the markers of vascular endothelial injury[6]. In addition, the role of the renin angiotensin system (RAS) in the development of diabetic nephropathy has been demonstrated. Early diabetic nephropathy is often accompanied by increased glomerular blood flow, local RAS hyperfunction, angiotensin II and the interaction of high glucose can stimulate the activation of TGF-b1 gene, induced mainly increased expression in renal tubular epithelial cells TGF-b1[15].

Irbesartan is an angiotensin II (Ang II) receptor inhibitor, through inhibiting the angiotensin-converting enzyme 1 receptor (AT1) and selectively blocking the binding of Ang II to the AT1 receptor, it can inhibit the contraction of blood vessels, release of aldosterone, and the expression of TGF-b1 in mesangial cells, reduce the glomerular pressure, protect the vascular endothelial cells and inhibit the proliferation of mesangial cells, and delay the progression of diabetic nephropathy[16–18]. Atorvastatin belongs to statins, which has a good effect on regulating blood lipids, and actively control high blood lipids can also improve proteinuria symptoms[19]. But many studies show that statins also has protective effect on kidney non lipid dependent, can inhibit the inflammatory reactions, improve endothelial function, reduce the expression of cytokines, inhibit the proliferation of mesangial cells and so on, thus delaying the progression of diabetic nephropathy[20–22]. In this study, the effect of irbesartan combined with atorvastatin on early diabetic nephropathy was demonstrated as follows: The improvement of serum TG, Scr and BUN levels was better than that of the control group, the serum Cys, Hcy, C TNF-α, ET and TGF-b1 levels after treatment in the observation group were lower than the control group, it showed that irbesartan combined with atorvastatin had better renal protective function.

In summary, the combination of Maher Bbe Chatain and atorvastatin can significantly improve the serum levels of various biochemical indicators and cytokines, and protect the renal function of patients with early diabetic nephropathy.

Reference

[1] Ziyadeh FN, Sharma K. Overview: combating diabetic nephropathy. *J Am Soc Nephrol* 2003; **14**(05): 1355-1357.

[2] Liu Shan, Liu Lunzhi, Zhang Mingxia. Effect of Atorvastatin combined with irbesartan on serum VEGF in patients with early diabetic nephropathy. *Chin J Integr Tradit Western Med* 2014; **15**(06): 543-544.

[3] Yeo ES, Hwang JY, Park JE. Tumor necrosis factor (TNF-alpha) and

C-reactive protein (CRP) are positively associated with the risk of chronic kidney disease in patients with type 2 diabetes. *Yonsei Med J* 2010; **51**(04): 519-525.

[4] Ilic V, Ilic M, Soldatovic I. Association of renin-angiotensin system genes polymorphism with progression of diabetic nephropathy in patients with type 1 diabetic mellitus. *Vojnosanit Pregl* 2014; **17**(07): 254-257.

[5] Navarro JF, Mora C, Macia M. Inflammatory parameters are independently associated with urinary albumin in type 2 diabetes mellitus. *Am J Kidney Dis* 2003; **41**(01): 56-61.

[6] Li Jian, Yan Shuangtong, Gong Yanping. Effects of irbesartan and atorvastatin on endothelin and serum cystatin C in elderly patients with early diabetic nephropathy. *Pract Med Clin* 2016; **19**(04): 458-460.

[7] Li L, Song HY, Liu K. Correlation of secreted protein acidic and rich in cysteine with diabetic nephropathy. *Int J Clin Exp Med* 2015; **8**(08): 12746-12755.

[8] Chen Liyun, Wang Aimin, Chen Fushun. Study on chronic complications of diabetes mellitus and its influencing factors. *Jiangsu Prevent Med* 2007; **18**(4): 1-2.

[9] Jiang Peng, Liang Ming. Observation and study of combined detection of Csy, C and B_2-MG on diabetic nephropathy in the arid stage. *Chin Gen Med Sci* 2010; **24**(01): 27-29.

[10]Tong Junrong,He Feng, Luo Zhengmao. The significance of serum NGAL and Cystatin C in the early diagnosis of diabetic nephropathy. *Chin Gen Med Sci* 2010; **13**(08): 810-812.

[11]Xue Ailing. The value of combined detection of serum cystatin C and homocysteine in the diagnosis of type 2 diabetic nephropathy. *J Med Sci Forum* 2012; **33**(10): 87-89.

[12]Li Hui. Value of combined detection of homocysteine and serum cystatin C in the early diagnosis of diabetic nephropathy. *Anhui Med Univ* 2013; **34**(09): 1370-1371.

[13]Lin Luping, Li Xing. The role of TNF-α and IGF-1 in diabetic nephropathy. *Med Rev* 2005; (12): 1095-1097.

[14]Cui Haiying, Ren Hongtao, Jiang Tao, Liu Bo. Determination of serum TNF-α , IL-18 and ADPN levels in patients with type 2 diabetic nephropathy. *Chin Exp Diagn* 2012; **16**(09): 1658-1660.

[15]Wang Yunfeng, Zhang Jianping, Lin Wei. Effect of irbesartan combined with atorvastatin on early diabetic nephropathy and its influence on renal function and serum inflammatory factors. *Chin Pharm Ind* 2017; **26**(10): 69-71.

[16]Du Xiaoli, Shen Jing, Li Ting. Curative effect observation on patients with diabetic nephropathy with normal blood by Lipitor and irbesartan combined treatment. *Sichuan Med J* 2015; **36**(03): 404-406.

[17]Du Xiaoli, Yang Daxing. Clinical observation of different doses of irbesartan in the treatment of diabetic nephropathy. *Hainan Med Univ* 2010; **21**(02): 20-22.

[18]Siddiqi L, Joles JA, Oey PL. Atorvastatin reduces sympathetic activity in patients with chronic kidney disease. *J Hypertens* 2011; **29**(11): 2176-2178.

[19]Fassett RG, Robertson IK, Ball MJ. Effects of atorvastatin on oxidative stress in chronic kidney disease. *Nephrology* 2015; **20**(10): 697-700.

[20]Takazakura A, Sakurai M, Bando Y. Renoprotective effects of atorvastatin compared with pravastatin on progression of early diabetic nephropathy. *J Diabetes Investig* 2015; **6**(03): 346-349.

[21]Wu Yuntao, Xing Aijun, Guan Fenghuan, Huang Yuling, Zheng Xiaoming. Clinical study of different routine doses of statins in prevention of contrast nephropathy. *Chin J Pract Med* 2013; **29**(09): 1471-1472.