

Therapeutic Effects of Tanshinone IIA towards Early Renal Damage in Patients with Type 2 Diabetes

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ABSTRACT

Aims: The present study aims to explore the role of Tanshinone IIA administration on the protective effect of early renal damage in patients with type 2 diabetes.

Methods: 64 patients with type 2 diabetes who have not been suffered from persistent renal complaints accepted to participate. Subjects were randomly allocated in two groups of trial (oral hypoglycemic drugs plus intravenous Tanshinone IIA 1 mg/kg daily for 3 weeks period) and control (oral hypoglycemic drugs). Information on microalbuminuria, serum β 2-microglobulin, urine β 2-microglobulin and serum cystatin C was collected from subjects. Although significant improvement was not observed between two groups in glycated hemoglobin A1c (HbA1c), the primary outcome parameters were significantly reduced.

Results: At the endpoints of observation for 21 days of Tanshinone IIA infusion, all patients in the trial group obtained reduction of the levels of microalbuminuria ($P < 0.05$), serum β 2-microglobulin ($P < 0.05$), urine β 2-microglobulin ($P < 0.01$) and serum cystatin C ($P < 0.05$).

Conclusions: Our results suggest that Tanshinone IIA might have protective effects on early renal damage with Type 2 diabetes and improve renal function. We believe that Tanshinone IIA could be a new evidence-based therapies in diabetic nephropathy.

Keywords: Renal damage, Tanshinone IIA, type 2 diabetes

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INTRODUCTION

Type 2 diabetes comprise 90% of people with diabetes characterized by high blood sugar levels around the world (1). Diabetic nephropathy has become the single most frequent cause of end-stage renal disease which is one of the most serious complications associated with type 2 diabetes (2). In 10 to 20 years from the onset of diabetes, more than 30% of diabetes patients could develop into clinical diabetic nephropathy (3). Effective control blood glucose and blood pressure could be able to minimize the risk of chronic renal injury induced by diabetes. But as the number of patients with diabetes increases, how to improve renal function in the use of drugs is a topic worth studying now.

Tanshinone IIA is the main pharmacological components isolated from Danshen, a traditional Chinese herbal, is in the wide therapies of multiple diseases (4, 5). In the past, it has been shown to play a role of a variety of treatment in antibiosis, anti-inflammatory, antioxidation, antifibrosis, vasodilatation, antiatherosclerosis, organo-protection and so on (6, 7, 8). Especially to deserve to be mentioned, the study by Su Kang KIM et al. showed that Tanshinone IIA would decrease glucose and have a protective role in a rat model with diabetic nephropathy (3). On the other hand, some detection indexes have been recognized as early sensible indicators of renal damage, including microalbuminuria, serum β 2-microglobulin, urine β 2-microglobulin and serum cystatin C (10, 11). Meanwhile, glycated hemoglobin A1c (HbA1c) is recommended for continuing assessment routinely in all patients with diabetes (12). Based on the previous studies, we seek to evaluate the efficacy of Tanshinone IIA on early renal damage for the patients with type 2 diabetes. Thus, the purpose of the present trial study offers an entry point for examining the clinical applications

of Tanshinone IIA in treating patients with early renal damage induced by type 2 diabetes, which was conformed to the provisions of the Declaration of Helsinki.

METHODS

This trial was conducted from late August 2014 to early February 2015 at PLA 281 Hospital in Qinghuangdao, China. The Medical Ethics Committee of 281 Hospital approved all procedures of the study and written informed consent was obtained from each of the enrolled patients. The study has been registered at the Chinese Clinical Trials Registry (ChiCTR-TQR-14005142). The present study involved 78 inpatients with the diagnoses of type 2 diabetes according to Global Guideline for Type 2 Diabetes. 14 patients were excluded from study in the case of hyperlipidemia, hypertension, hyperuricemia, chronic inflammatory diseases, active liver and kidney diseases, cancer, cardiac and cerebrovascular diseases, tobacco and alcohol hobbies due to potential impacts on the level of the indicators. The included 64 subjects had been hospitalized with urinary albumin excretion of 30–300mg/24h, who aged from 32 to 65 (average 45 ± 11) years old. They were allocated randomizedly into a control group and a trial group. For 21 days, 32 patients in the control group were treated with a standard Western therapy of oral hypoglycemic drugs according to Standards of Medical Care in Diabete-2014 (12), and patients in the trial group were additionally receive 0.75 mg/kg/day intravenous Tanshinone IIA (Commercial name “Nuoxinkang”, manufactured by Shanghai First Biochemistry Pharmaceutical Inc.) diluted by 150 mL normal saline. A 24-hour urine sample was collected and a 10 mL serum sample in the morning was drawn from each patient. Microalbuminuria, serum β 2-croglobulin, urine

β 2-microglobulin, serum cystatin C and HbA1c levels are being measured serve as the primary outcome parameters. Data was collected before initiating treatment, immediately after the 21-day treatment period.

Statistical analysis

In this study, the variables were expressed as mean \pm standard deviation (SD). Values of $P < 0.05$ were considered as statistically significant. Continuous variables were compared with the T-test. All data were analyzed using the statistical package for the social sciences (SPSS) version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A comparison between baseline characteristics of patients in the two groups was no significant differences (Table 1). All 64 patients completed the study and showed well tolerance towards the treatment throughout the study. As summarized in Fig1-4, after 21 days, there was no difference in the levels of microalbuminuria, serum β 2-croglobulin, urine β 2-microglobulin and serum cystatin C of the control group to baseline, respectively. At the endpoints of observation for 21 days of Tanshinone IIA infusion, all patients in the trial group obtained reduction of the levels of four indicators. These differences were statistically significant. Our study demonstrated that Tanshinone IIA improved renal function. Meanwhile, significant improvement was not observed between the trial and control groups in glycated hemoglobin A1c (HbA1c). There were not differences between two groups in terms of microalbuminuria, serum β 2-croglobulin, urine β 2-microglobulin and serum cystatin C at the

beginning of study. There were no adverse events during treatment in both the groups.

DISCUSSION

As observed in our current research, there was a significant improvement on microalbuminuria, serum β 2-croglobulin, urine β 2-microglobulin and serum cystatin C by Tanshinone IIA in the management of early renal damage in patients with type 2 diabetes. Furthermore, we found no statistical difference in HbA1c between the Tanshinone IIA treatment and control group. These results indicate that early renal function in these patients may benefit from short-term treatment with Tanshinone IIA accompanied with no decrease of HbA1c.

In China, Tanshinone IIA has been widespread clinical application in treating various circulatory disturbance-related diseases for its pharmacological actions, including vasodilation, improving microcirculation, anticoagulation, anti-inflammation, and free radical scavenging (13, 14, 15). Liu J *et al.* reported that Tanshinone IIA selectively increased mesenteric perfusion in newborn piglet, possibly via an endothelium-derived hyperpolarizing factor vasodilating pathway (16). Previous studies also showed Tanshinone IIA could ameliorate cardiac dysfunction by limiting apoptosis of cardiomyocytes and oxidative damage (17, 18). Tanshinone IIA could inhibit atherogenesis by reducing intracellular superoxide radical generation, NF- κ B activation and heme oxygenase-1-dependent mechanism (19, 20). Tanshinone IIA have definite neuroprotective effects by multiple mechanisms (21, 22, 23). On the other hand, Tanshinone IIA is currently used to treat patients

suffering from myocardial infarction (MI), angina pectoris, stroke, diabetes due to their potential protective effects (24). However, it remains unclear whether Tanshinone IIA has therapeutic effects on treating early renal damage in patients with type 2 diabetes.

Wu X et al. found that Tanshinone IIA had exerted anti-inflammatory and renal protective effect on uric acid-induced kidney damage (25). Tanshinone IIA also protects against doxorubicin-induced nephropathy in a mice model (26). In addition, a study by Ahn YM et al. showed that oral administration of Tanshinone IIA for 8 weeks could improve renal dysfunction in rats suffering from chronic kidney disease induced by 5/6 nephrectomy (27). Remarkably, the animal experiment *in vitro* by Su Kang KIM et al. showed that Tanshinone IIA had a protective role against the early stage of experimental diabetic nephropathy (3), but there is no randomised controlled trials performed to evaluate the use of Tanshinone IIA in patients with type 2 diabetes. As expected, our present study indicated that Tanshinone IIA significantly could improve early renal function in patients with type 2 diabetes, which had been detected by assessing the changes of the levels of microalbuminuria, serum β 2-microglobulin, urine β 2-microglobulin and serum cystatin C before and after treatment. On account of the time of intervention and follow-up was not long, Tanshinone IIA did not produce apparent effects on HbA1c.

Previously there are a series of researchs demonstrated that Tanshinone IIA enhances insulin sensitivity, improves glucose metabolic disorders, reduces high glucose-induced intracellular oxidative stress and delays the process of cellular senescence induced by high glucose (28, 29, 30). In particular, in the diabetic rat experiments, Tanshinone IIA decreased the expression of advanced glycation end-products(AGEs), angiotensin II (Ang II),

transforming growth factor β 1(TGF- β 1), collagen IV, and monocyte/macrophage (ED-1) in the early stage of diabetic nephropathy, and significantly ameliorated renal hypertrophy, blood urea nitrogen (BUN) and 24-h urine protein excretion (3). Therefore, we speculated that a variety of mechanisms above, either alone or together, could be involved in the renal protective effects of Tanshinone IIA. Moreover, Tanshinone IIA might inhibit oxidative stress, inflammation, and hemodynamic changes to hold back the deterioration of diabetic nephropathy.

CONCLUSIONS

In conclusion, we firstly suggested that Tanshinone IIA could have therapeutic effects on early renal damage in patients with type 2 diabetes. As should be pointed out, the long-term protective effects on Tanshinone IIA for these patients and its side-effect is required for further research.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest in this study.

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Table 1: Distribution of basic information in two groups

Variable	Control	Trial	<i>P</i> value
Age (years)±SD	50.24±8.23	47.36±7.58	0.22
Male	13	16	0.80
Female	19	16	0.64
Disease duration (years)±SD	3.30±0.78	2.96±0.95	0.28
Glomerular filtration rate (GFR) (mL/min/1.73 m ²) ±SD	93±18	87±16	0.39

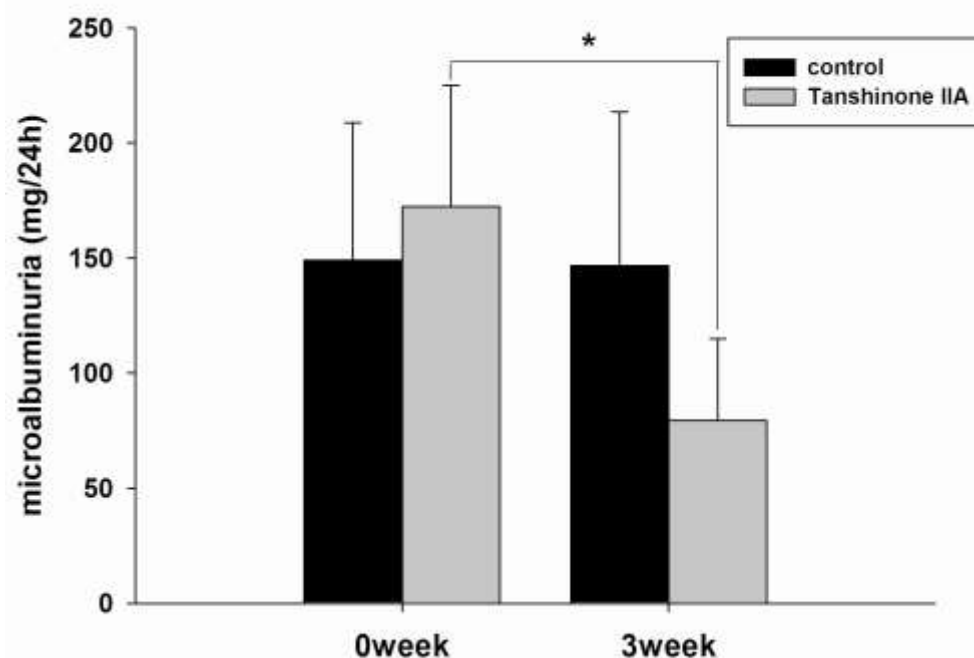


Fig. 1. Tanshinone IIA significantly reduced serum level of microalbuminuria compared to control group ($P < 0.05$).

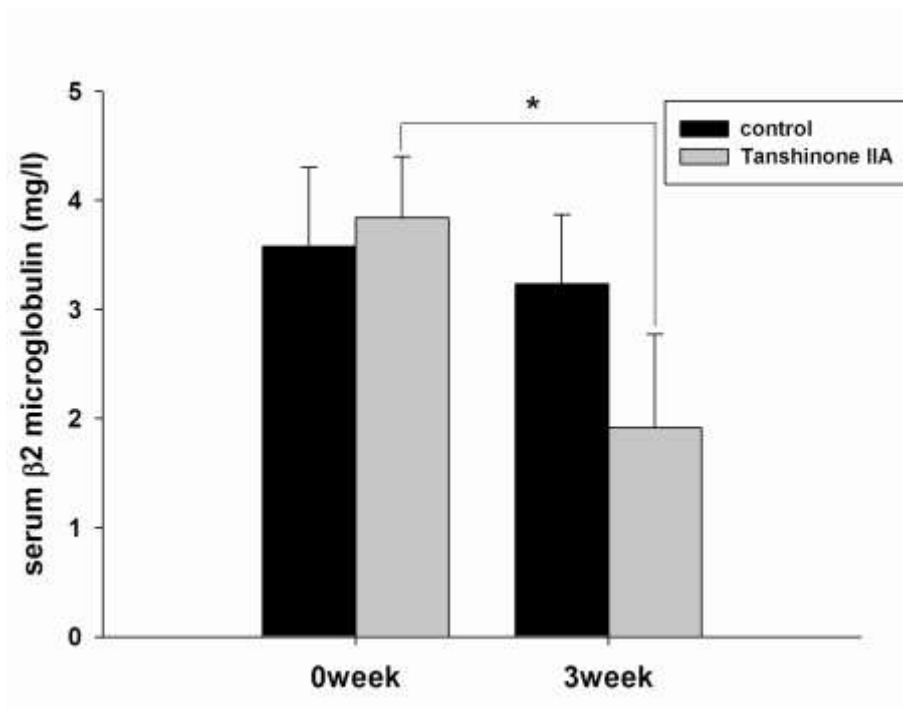


Fig. 2. There was a significant difference in serum β 2-microglobulin between trial and control groups in 3 weeks ($P < 0.05$).

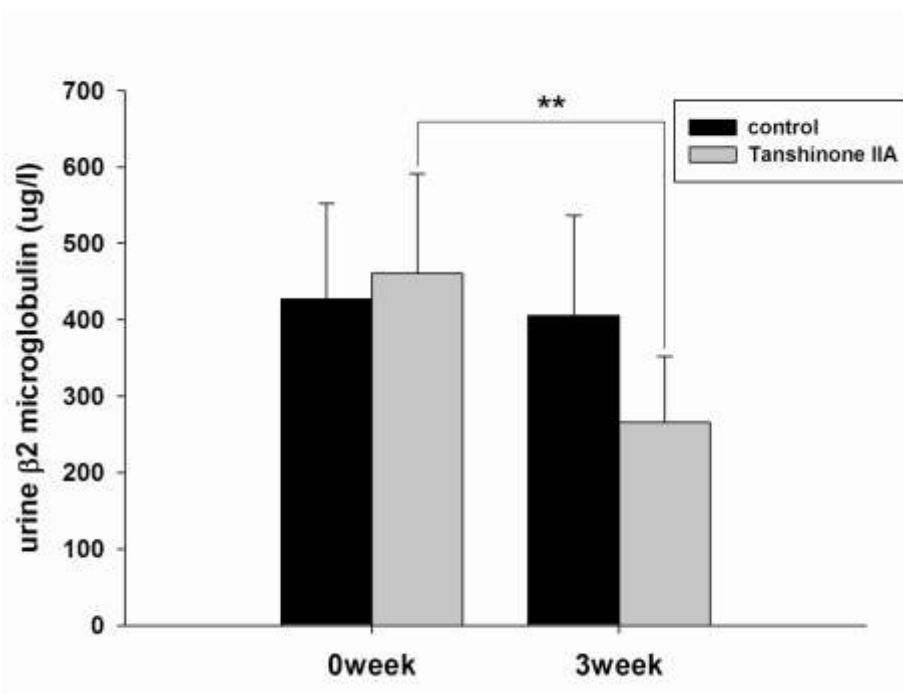


Fig. 3. It is found that a significant decrease in urine β 2-microglobulin within trial group after study ($P < 0.01$).

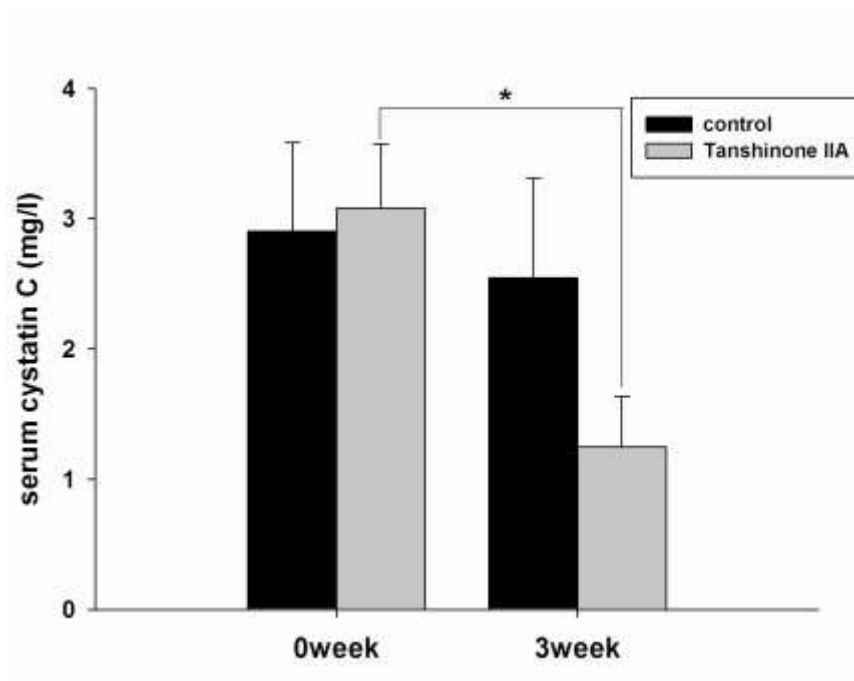


Fig. 4. A significant difference in serum cystatin C between both groups of control and trial was observed at 3rd week ($P < 0.05$).

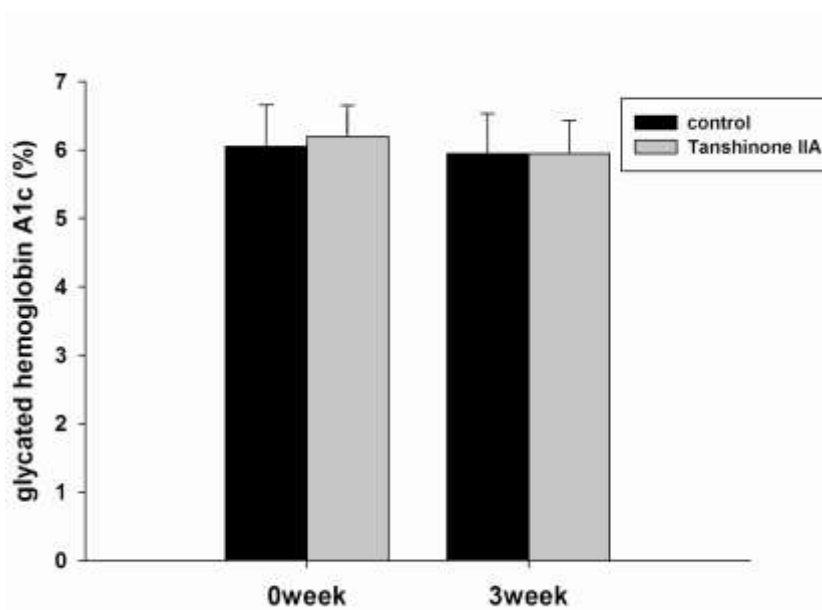


Fig. 5. Aglycated hemoglobin A1c (HbA1c) in control and trial groups at baseline and 3rd weeks ($P > 0.05$).