

Hepatocyte growth factor shows benefits for patients with chronic renal failure induced type 2 diabetes.

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Abstract

Chronic renal failure patients receiving haemodialysis and continuous ambulatory peritoneal dialysis often encounter inflammation troubles during long-period treatment. Patients with type 2 diabetes induce different degree chronic renal failure and represent low quality of life. Type 2 diabetes may be one of the most important arch-criminal factors that aggravate syndrome and renal insufficiency. These impairments of kidney's function may lead to chronic renal failure though disqualify of cellular activities. Hepatocyte Growth Factor (HGF) is one of the most extensive biological activity factors and presents multifunctional anti-fibrosis factor that plays a critical role in the progression of chronic renal failure. The purpose of this study was to investigate whether HGF treatment could decrease inflammation and improve chronic renal failure. Clinical investigations were performed in 138 (75 men and 63 women) chronic renal failure patients induced by type 2 diabetes with 98 healthy volunteers (51 men and 41 women) as control. Our experimental data showed that serum level of HGF and IL-6 were decreased and correlated with age and sex in patients with chronic renal failure induced by type 2 diabetes ($r=0.864$, $r=0.743$, respectively). Serum levels of IL-1, MCP-1 and TNF- α were increased compared between patients with severe renal failure and healthy volunteers (** $P<0.01$). HGF injection (MTD dose) improved the inflammatory factor expression levels for patients with chronic renal failure compared to placebo group. The most common treatment-emergence adverse events were hypertension and proteinuria. Taken together, level of HGF in serum was correlated with inflammation in chronic renal failure patients induced by type 2 diabetes, which presented beneficial outcomes through improvement of inflammatory factor expression in clinical.

Keywords: Hepatocyte growth factor, Chronic renal failure, Type 2 diabetes, Inflammation.

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Introduction

Chronic renal failure is syndrome with serious metabolic disorders and other damage of a group of syndrome caused by a variety of chronic kidney disease [1]. Chronic renal failure is disease of chronic progressive renal parenchyma damage caused by a variety of reasons which leads to kidney obvious atrophy and irreversible damage of function [2]. The majorities of pathogenesis are glomerulonephritis, interstitial nephritis, high blood pressure, diabetes and obstructed kidney disease [3]. Currently, diabetes related chronic renal failure presented a raise trend in clinical investigation with the rapid increase of diabetes sufferers throughout the world [4,5]. Chronic renal failure induced by diabetes mellitus that significantly affects patients' quality of life [6]. Therefore, it is vital to explore new horizon for diagnosis and treatment of chronic renal failure patients induced by type 2 diabetes.

Inflammatory cytokines, such as TNF- α , IL-1, IL-8, and IL-10 are the most common characteristics for patients with chronic renal failure [7-9]. Inflammation in patients with type 2 diabetes is related to dysfunction of urinary albumin excretion, endothelial function and cellular metabolism [10]. Long-term hypertension contributes to kidney damage and slowly develops chronic renal failure for patients with type 2 diabetes [11]. In addition, previous study has reported that inhibition of the renin-angiotensin system exerted potent decreasing blood pressure by reducing vascular inflammation [12]. However, long-term medication of anti-hypertension drug, Fimasartan, also leads to decline of renal function and even causes chronic renal failure in patients with type 2 diabetes [13].

Hepatocyte Growth Factor (HGF) is produced by mesenchymal cells during organ injury [14]. HGF is one of the most extensive a biological activity factor and presents multifunctional anti-fibrosis factor that plays a critical in kidney development, acute injury and regeneration, which is

activated by proteolytic cleavage at the site of injury and results in a biological HGF protein [15]. Biologically active HGF suppresses fibrosis and molecular basis for HGF-mediated regression of renal fibrosis was elaborated in previous report [16,17]. Notably, plasma concentration of HGF exhibited decreasing trend in patients with type 2 diabetes, who may be regulated other inflammatory factor expression levels [18]. Therefore, HGF may be regarded as a local acute phase protein with chronic renal failure.

The purpose of this study was to investigate whether the expression and function of HGF was decreased and associated with inflammation in patients chronic renal failure induced by type 2 diabetes. HGF treatment improves inflammatory cytokines for patients with chronic renal failure induced by type 2 diabetes. These clinical data provided significant reference for doctors and clinicians in treatment of patients with chronic renal failure induced by type 2 diabetes.

Materials and Method

Ethics statement

Research protocols were approved by the University Ethical Committee of Zhujiang Hospital, Southern Medical University and Committee of The Academic Medical Center in China (20150618521). All subjects (patients and volunteers) gave written consent in this clinical investigation.

Patients

138 (75 men and 63 women) chronic renal failure in patients with type 2 diabetes and 98 healthy volunteers (51 men and 47 women) were enrolled into investigated IL-1, IL-8, IL-10, HGF, MCP-1 and IL-6 serum concentration levels and their correlations with patients' age and gender. All patients and volunteers were divided into three groups (18-30, 30-45 and 45-64 years old) according patients' and volunteers' age after giving the informed consent. Mean age of the volunteers and patients was 41 ± 21 and 41 ± 23 years, respectively. Mean value of kt/V was equal 1.1 ± 0.2 and mean value of the Glomerular Filtration rate (GFR) was 7.2 ± 2.9 ml/min in patients with chronic renal failure and Type 2 diabetes. Mean of blood glucose was 7.2 ± 3.3 mmol/l and the mean of blood pressure was 153 ± 32 mm Hg in patients with chronic renal failure and Type 2 diabetes.

Enzyme linked immunosorbent assay (ELISA)

In the protein expression assay, TNF- α , IL-1, IL-8, IL-10, HGF, MCP-1 and IL-6 proteins ELISA kits (R&D, Bio-Techne China Co. Ltd, USA) were used to determine serum concentration levels of the TNF- α , IL-1, IL-8, IL-10, HGF, MCP-1 and IL-6, respectively. The operating steps were conducted according to the manufacturer's instructions. The final results were recorded at 450 nm on an ELISA plate reader.

Study design

The double-blind study was carried out in 3 phases: baseline stage, the double-blind treatment phase (4-week dose-titration treatment) and 4-week post-treatment for patients with chronic renal failure induced by type 2 diabetes who volunteered to continue to complete the ongoing extension study. Patients were randomized to once every three days, double-blind treatment with HGF or placebo treatment. Patients with chronic renal failure induced by type 2 diabetes continued treatment with the dose of HGF (5 mg/kg) or placebo to achieve the final investigation throughout the maintenance period (52 weeks).

Outcomes measures

Renal function tests were used for assessing the function of patients with chronic renal failure induced by type 2 diabetes. Clinical chronic renal failure scores were evaluated described in previous study [19]. The date was recorded and calculated the degree of chronic renal failure.

Efficacy and safety assessments

Efficacy assessments including the median percent reduction scores and response rate were analysed in patients with knee osteoarthritis from baseline during the 4-week and double-blind period in the presence of HGF (5 mg/kg) or placebo. In addition, the overall safety and pharmacokinetic analysis were conducted according to previous clinical studies [20,21]. Furthermore, the safety assessments of the most frequent treatment-emergent adverse events were evaluated in all randomized patients who received the study drug and had at least one post-dose safety assessment. Dose-responses analysis was conducted when the last dose drugs injection.

Glomerular filtration rate

Glomerular filtration rate in patients with chronic renal failure induced by type 2 diabetes and healthy volunteers were analysed by Gates Method (BioPAL offers FIT-GFR™. The procedures were performed according to the manufacturer's instructions. The final results were recorded at 450 nm on an ELISA plate reader.

Analysis of blood glucose and blood pressure

Blood glucose in patients with chronic renal failure induced by type 2 diabetes and healthy volunteers was detected by glucometer (Sifsof Global Trade, USA). Blood pressure was recorded by electronic sphygmomanometer.

Statistical analysis

All data were reported as means and SEM. Statistical significance of differences between mean values was assessed by Student's t test for unpaired data. Comparisons of data between multiple groups were performed with Analysis of Variance (ANOVA). Continuous variables were reported as mean and 95% Confidence Interval (CI). Treatment effect is

presented as median reduction in knee osteoarthritis over the treatment period. Robust nonparametric Hodges-Lehmann estimates of median drugs treatment effects and 95% confidence interval are provided. Responder rates and treatment-emergent adverse events were analysed by χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Characterizations of patients

A total of 138 chronic renal failure patients induced by type 2 diabetes (75 men and 63 women) and 98 healthy volunteers (51 men and 47 women) were enrolled for analysis in this study. The characteristics of the patient and healthy volunteer are summarized in Table 1. There were no sex significant difference in numbers both in patients and healthy volunteers. The mean blood pressure in chronic renal failure patients induced by type 2 diabetes was higher than healthy volunteers. Antihypertensive medications were not taken during the treatment period until the high pressure was more than 170 mm mercury column. In addition, the body weight in chronic renal failure patients induced by type 2 diabetes was significant lower than healthy volunteers. Furthermore, most of chronic renal failure patients induced by type 2 diabetes were needed to haemodialysis.

Table 1. Characterizations of chronic renal failure patients with Type II diabetes.

	Number of patients or parameters	%
Patients	138	100
Male	73	52.9
Female	65	47.1
Age	18-64	100
18-30	48	34.8
30-45	32	23.2
45-64	58	42
Blood pressure	153 ± 32	100
Blood glucose	7.2 ± 3.3 mmol/L	100
kt/V	1.1 ± 0.2	100
GFT	7.2 ± 2.9 ml/min	100
Health volunteers	98	100
Male	51	52
Female	47	48
Age	20-62	100
20-30	21	21.4
30-45	33	33.7
45-62	44	44.9
Blood pressure	93 ± 13	100

Blood glucose	4.4 ± 2.6 mmol/L	100
kt/V	2.6 ± 0.6	100
GFT	13.6 ± 3.3 ml/min	100

Analysis of HGF, TNF- α , MCP-1, IL-1 and IL-6 expression in serum

The serum levels from renal failure patients induced by type 2 diabetes and volunteers were used to analysis HGF, TNF- α , MCP-1, IL-1 and IL-6 expression. The analysis revealed mean serum level of HGF (-24%) and IL-6 (-11%) were decreased and correlated with age and sex in patients with chronic renal failure induced by type 2 diabetes ($r=0.864$, $r=0.743$, respectively). The patients and healthy volunteers were divided into three groups according to the age of research objects. The mean serum levels of IL-1, MCP-1 and TNF- α were increased compared between patients with severe renal failure and healthy volunteers (** $P < 0.01$). TNF- α , MCP-1, HGF, IL-8, IL-10, IL-1 and IL-6 concentration changes were summarized in Table 2. This detection showed that serum concentration levels of IL-1, MCP-1 and TNF- α were increased in chronic renal failure patients induced by type 2 diabetes compared to healthy volunteers. There was no correlation between IL-1, MCP-1 and TNF- α expression and chronic renal failure patients induced by type 2 diabetes. Also, no significant change of serum IL-10 and IL-8 concentration was observed between patients and healthy volunteers in our cohort study.

Table 2. Analysis of serum concentration levels of inflammatory factors in chronic renal failure patients with type II diabetes.

Inflammatory factors	Patients	Volunteers
IL-1	1.22 pg/ml	0.36 pg/ml**
MCP-1	1.08 pg/ml	0.40 pg/ml**
TNF- α	0.94 pg/ml	0.29 pg/ml**
IL-10	0.89 pg/ml	0.31 pg/ml**
IL-8	1.14 pg/ml	0.42 pg/ml**
IL-6	0.68 pg/ml	1.42 pg/ml**
HGF	0.35 pg/ml	1.47 pg/ml**

Correlation analysis of HGF

To study levels of HGF in serum correlate with chronic renal failure in patients, we analysed HGF serum concentration levels and correlation analysis with gender and age of chronic renal failure patients induced by type 2 diabetes. Statistical analysis in Table 2 showed that mean concentration of HGF in chronic renal failure in male patients induced by type 2 diabetes was 0.35 pg/ml (Inter Quartile Range, IQR: 0.18-0.52 pg/ml), and healthy male volunteers was 1.46 pg/ml (IQR: 0.59-2.32 pg/ml). However, concentration of HGF in chronic renal failure in female patients with Type 2 diabetes was 0.54 pg/ml (IQR: 0.28-1.04 pg/ml), and healthy female volunteers was 0.49 pg/ml (IQR: 0.32-0.76 pg/ml), which suggested that

HGF concentration presented a positive correlation with gender. In addition, no difference between male and female patients in 45-64 years old groups was observed in this study (Table 3). Furthermore, 18-30 and 30-45 years old groups presented a higher serum concentration in male patients compared to female patients. The correlative analysis showed a positively relative between HGF concentration and patients' age (Figure 1). Our date indicated that all chronic renal failure patients induced by type 2 diabetes were in condition of high blood pressure (Table 1).

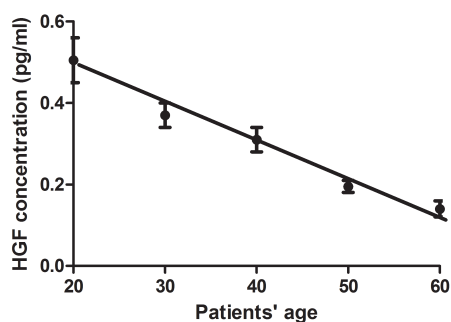


Figure 1. Correlative analysis between HGF concentration and renal chronic failure patients' age.

Table 3. Correlation analysis of HGF serum concentration levels in chronic renal failure patients with type II diabetes.

	Male	Female
Patients	0.45 pg/ml	0.23 pg/ml*
18-30	0.64 pg/ml	0.30 pg/ml*
30-45	0.51 pg/ml	0.24 pg/ml**
45-64	0.15 pg/ml	0.17 pg/ml
Volunteers	1.26 pg/ml	1.28 pg/ml
20-30	1.28 pg/ml	1.32 pg/ml
30-45	1.18 pg/ml	1.34 pg/ml
45-62	1.32 pg/ml	1.27 pg/ml

Correlation analysis of IL-6

We also analysed serum concentration levels of IL-6 and correlation analysis with gender and age of chronic renal failure patients induced by type 2 diabetes. Statistical analysis in Table 4 showed that mean serum concentration level of IL-6 in chronic renal failure patients was 0.66 pg/ml (IQR: 0.39-1.22 pg/ml), and healthy male volunteers was 1.35 pg/ml (IQR: 0.78-1.72 pg/ml). And mean serum concentration level of IL-6 in chronic renal failure in female patients induced by type 2 diabetes was 0.89 pg/ml (IQR: 0.58-1.35 pg/ml), and healthy female volunteers was 1.47 pg/ml (IQR: 0.82-1.81 pg/ml). With contrary to HGF, mean concentration of IL-6 were higher (IQR: 0.61-1.82 pg/ml) in 18-30 years old groups and its serum concentration levels were relative lower in 30-45

(IQR: 0.42-0.82 pg/ml) and 45-64 (IQR: 0.33-0.68 pg/ml) years old groups in patients (Figure 2). Date indicated that a positively relative between IL-6 serum concentration levels in chronic renal failure patients induced by type 2 diabetes. However, the correlation between IL-6 serum concentration levels with gender was not observed in this study. These date suggested that serum concentration level of IL-6 was decreased with aged older in chronic renal failure in male patients.

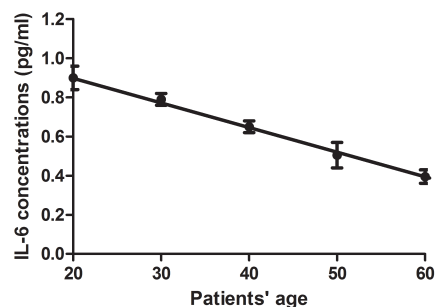


Figure 2. Correlative analysis between IL-6 concentration and renal chronic failure patients' age.

Table 4. Correlation analysis of IL-6 serum concentration levels in chronic renal failure patients with type II diabetes.

	Male	Female
Patients	0.66 pg/ml	0.89 pg/ml†
18-30	0.75 pg/ml	1.14 pg/ml†
30-45	0.52 pg/ml	0.85 pg/ml†
45-64	0.35 pg/ml	0.57 pg/ml†
Volunteers	1.35 pg/ml	1.47 pg/ml
20-30	1.57 pg/ml	1.63 pg/ml
30-45	1.48 pg/ml	1.47 pg/ml
45-62	1.24 pg/ml	1.25 pg/ml

Duration of treatment, dose-limiting toxicities, and maximum tolerated dose

Median overall duration of HGF treatment was eight weeks. Across all dosing cohorts were 1.0, 2.5, 5.0, 8.5, and 13.0 mg/kg. Our date in Table 5 showed that 13 mg/kg ml of HGF once every three days was identified as the Maximum Tolerated Dose (MTD) and 8.5 mg/kg of HGF once a week was identified as dose-limiting toxicity (DLT). The lowest-dose cohorts of HGF presented the fewest number of HGF dose reductions. We observed that the common treatment-emergent adverse events of HGF injection were hypertension, diarrhoea, rash, proteinuria, fatigue, and oedema peripheral. Most of patients with knee osteoarthritis required to reduce drug dose for cumulative toxicity after treatment with DLT dose. Therefore, most of patients were enrolled at a dose of 5.0 mg/kg of HGF to meet further clinical experiment of the

tolerability and therapeutic effects for patients with chronic renal failure.

Table 5. Treatment-emergence adverse events of HGF with an overall incidence.

	Total (n=36)	1.0-2.5 mg/kg (n=12)	5.0-8.5 mg/kg (n=16)	13.0 mg/kg (n=8)
Adverse event				
Hypertension	8	2	3	3
Diarrhoea	4	1	1	2
Proteinuria	7	1	3	3
Rash	4	0	2	2
Fatigue	4	0	1	3
Oedema peripheral	4	1	1	2

Treatment-emergent adverse events were analysed by χ^2 test.

Treatment-emergent adverse events of HGF treatment

Patients with chronic renal failure received at least one dose of study therapy with post-baseline safety evaluation were included in the safety population. After the last dose of PRP, we observed that the most common treatment-emergent adverse events of HGF treatment (0.5 mg/kg) were

hypertension and proteinuria ($\geq 10\%$ each) (Table 6). The data for the 0.85 mg/kg (n=10) and 13.0 mg/kg (n=8) doses are not advisable for more side effects and few patients were treated at these dose levels. Of the total patients, 72 patients with chronic renal failure completed the overall maintenance period of this study.

Table 6. Treatment hypertension and proteinuria by common toxicity criteria grade.

	Total (n=36)	1.0-2.5 mg/kg (n=12)	5.0-8.5 mg/kg (n=16)	13.0 mg/kg (n=8)
Adverse event				
Hypertension	8	2	3	3
Grade 1	2	0	1	1
Grade 2	4	1	1	2
Grade 3	2	1	1	0
Proteinuria	7	1	3	3
Grade 1	4	1	1	2
Grade 2	2	0	1	1
Grade 3	1	0	1	0

Treatment-emergent adverse events were analysed by χ^2 test.

Table 7. Renal function index changes during the study period.

Study groups	Urinary concentration (mean and SEM)								
	UPO	BUN	Scr	BUA	Cr	SPI	PSP	Ccr	β 2mc
Placebo group									
Baseline	98	8.6	158.8	86.6	3.2	0.48	0.32	3.8	89
week 52	84	8.2	144.2	80.2	3.5	0.38	0.36	3.7	82
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

	HGF group								
Baseline	96	8.5	163.8	94.8	3.1	0.46	0.34	4.3	86
week 52	58	4.2	87.4	52.2	6.8	0.068	0.61	1.3	41
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

Efficacy of HGF treatment

The clinical outcomes of HGF treatment were analysed in this analysis. Preliminary clinical analyses exhibited that renal functions were markedly improved in drug-treatment groups after 8 weeks therapy regiment compared to placebo. Treatment of HGF improved meaningfully in physical function and renal function for patients with chronic renal failure (Table 7). These clinical outcomes showed that HGF therapy of PRP (5.0 mg/kg) improved the clinical features of patients with chronic renal failure induced by type 2 diabetes.

Discussion

Many clinical trials and studies have demonstrated that chronic renal failure could induce symptom complex and markedly decreased the quality of life in patients [22,23]. In addition, clinical survey has showed that incidence rate of chronic renal failure was increasing with the rapid increase of diabetes in the world [24]. Patients with chronic renal failure frequently developed into uremia for dysfunctions of glomerular cells and led to loss of the biological activity of kidney cells [25]. Dialysis is the most effective treatments for kidney failure and deterioration of the quality of the life and that pathogenesis is genetic and multifactorial [26,27]. Previous study has indicated that age of the patients with chronic renal failure played a fatal factor for survival period, limitation of physical activity and quality of life in patients with chronic renal failure [28]. In this study, we investigated whether the expression and function of HGF was decreased and associated with inflammation. Data confirmed previous observations and presented that inflammatory factors may be correlate with the age and gender of patients with chronic renal failure.

Inflammation is one of the most common characteristics of in patients with type 2 diabetes [29]. Temelkova et al. reported that subclinical inflammation was up-regulated in patients with type 2 diabetes that indicated that inflammatory responses may be associated with the occurrence, degree and prognosis of diabetes [30]. Varughese et al. reported that inflammation was related with hypertension and urinary albumin excretion in patients with type 2 diabetes [10]. In addition, previous study demonstrated vascular inflammation played important role in drug induced rapid and persistent reduction of in patients with hypertension and type 2 diabetes [29]. Furthermore, Bitar et al. showed that inflammation was associated with degree pathogenesis condition in aortic tissues of aged type 2 diabetes by phosphatidylinositol 3-kinase/Akt- dependent signal pathway [31].

In this study, our investigation found that HGF and IL-6 serum concentration levels were decreased and correlated with age of

patients with chronic renal failure induced by type 2 diabetes. In addition, we also found that serum concentration levels of HGF were positive correlated with gender of patients with chronic renal failure induced by type 2 diabetes based on our mathematical statistics. These investigations were focused on HGF treatment for patients with chronic renal failure induced by diabetes mellitus and provided new horizon for reducing inflammation and improving patient's quality of life.

Though previous study has reported that inflammation indeed associated with hypertension in patients with type 2 diabetes, correlations between these inflammatory factors with type 2 diabetes were not analysed in clinical [32]. For data on HGF and IL-6 serum concentration levels related the hypertension, clinical survey has been performed with the recorded by blood pressure values in patients with chronic renal failure induced by type 2 diabetes in our study. In addition, our mathematical statistics indicated that serum concentration level of HGF was positive correlation with blood pressure values in patients with chronic renal failure induced by type 2 diabetes. However, serum concentration level of HGF was significantly increased when patients received antihypertensive drugs (date not shown). Furthermore, the therapeutic effects of HGF for patients with chronic renal failure induced by type 2 diabetes were investigated in this clinical trial. Our data suggested that HGF presented benefits for patients with chronic renal failure induced by type 2 diabetes through improvement of renal function. However, symptoms of type 2 diabetes were not systematically investigated in this work.

Conclusion

In summary, based on our clinical date, serum concentration levels of IL-1, TNF- α and MCP-1 were increased renal failure patients with type 2 diabetes. However, no correlation was found between their concentration with age or gender of chronic renal failure patients induced by type 2 diabetes. In contrary, serum concentration levels of IL-6 and HGF were not only down-regulated in renal failure patients with type 2 diabetes, which suggested that IL-6 and HGF should factored in forming clinical diagnosis and prognosis guidelines for patients with renal failure induced by type 2 diabetes. Importantly, HGF treatment improved symptoms of patients with chronic renal failure. This clinical study was researched in a small sample size, which will be further study in large number of patients with renal failure induced by type 2 diabetes.

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Disclosure of Conflict of Interest

There was no conflict of interest in this study.

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