Effect of Oral Carnosine Supplementation on Urinary TGF-β in Diabetic Nephropathy: a Randomized Controlled Trial

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Abstract

Background: Activation of the transforming growth factor beta (TGF-b) pathway is a significant contributor to the pathogenesis of diabetic nephropathy. Carnosine is an amino acid that can inhibit TGF-b synthesis. We tested the hypothesis that carnosine supplement added to standard therapy will result in reduced urinary TGF-b levels among patients with diabetic nephropathy.

Methods: We randomly assigned 40 patients with diabetic nephropathy and albuminuria 30-299 mg/day to treatment with carnosine (2 g/day) or placebo for 12 weeks. Urinary TGF-b level was determined using ELISA, urine albumin was ascertained by immunonephelometric assay, and renal function and metabolic profiles were determined at baseline and during 12 weeks of active treatment. Primary outcome was decrease in urinary levels of TGF-b.

Results: The 2 groups were comparable for baseline characteristics, blood pressure, urine albumin, urine TGF-b and renal function measurements. Urinary TGF-b significantly decreased with carnosine supplement (-17.8% of the baseline values), whereas it tended to increase with placebo (+16.9% of the baseline values) (between-group difference P <0.05). However, blood urea nitrogen, serum creatinine, glomerular filtration rate and other biochemical parameters remained unchanged during the study period including urinary albuminuria. Both groups were well tolerated with no serious side-effects.

Conclusions: These data indicated an additional renoprotective effect of oral supplementation with carnosine to decrease urinary TGF-b level that serves as a marker of renal injury in diabetic nephropathy.

Trial registration

Thai Clinical Trials, TCTR20200724002. Retrospectively Registered 24 July 2020.

Background

Diabetic nephropathy was the leading cause of chronic kidney disease (CKD), and the foremost cause of end stage renal disease (ESRD) [1]. The standard treatment for diabetic nephropathy includes controlling glycemia and blood pressure and reducing albumin leakage in urine using angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) [2]. These can reduce the number of patients receiving renal replacement therapy which eventually reduces cost of treatment for patients with diabetic nephropathy.

Hyperglycemia induces an abnormal activation of glucose-dependent pathways. i.e., the polyol pathway, hexosamine pathway and protein kinase C pathway in producing multiple substances including transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), interleukine-1 (IL-1), interleukine-6 (IL-6) and tissue necrosis factor (TNF) [3, 4]. Increased urinary TGF-β level among patients with diabetes stimulates the canonical pathway (ALK 5, Smad 2/3) and alternate pathway (ALK 1, Smad 1/5) [5]. The activation of the canonical pathway induces extracellular matrix accumulation at the

glomerular basement membrane (GBM) and mesangium. In addition, the activation of the alternate pathway induces podocyte injury causing foot process effacement. Therefore, TGF-β and activation of the metabolic pathway are important factors in developing diabetic nephropathy [6]. Treatment to reduce TGF-β level in the urine may be able to slow the deterioration of diabetic nephropathy [7].

Carnosine is an amino acid found in nature, synthesized from L-Histidine and beta-alanine (carnosine synthase) and degraded by the enzyme carnosinase[8]. Currently, carnosine has many biological qualities that can slow CKD progression and prevent diabetic nephropathy from developing [9, 10]. One of the proposed mechanisms is inhibition the synthesis of TGF-β [11]. It has been hypothesized that the population with CNDP1 genotype has low activity of carnosinase, causing higher level of carnosine in the blood which decreased the risk of diabetic nephropathy [11]. One study has shown that oral carnosine supplementation could reduce albuminuria and urinary alpha-1 microglobulin level in type 1 diabetes [12]. Presently, no studies have yet been conducted among adult patients with type 2 diabetes mellitus (T2DM). The study aimed to demonstrate the level of urinary TGF-β and albumin after oral carnosine supplementation among patients with diabetic nephropathy from T2DM.

Methods

The study was a randomized controlled trial comparing the efficacy between oral carnosine supplementation and placebo groups, as an additional treatment from conventional therapy. The study was conducted among patients with T2DM treated at Phramongkutklao Hospital between 1 April 2018 and 31 March 2019, with all subjects selected by inclusion criteria. Patients were randomized in blocks of four and allocation concealment, then divided in two groups at a ratio of 1 : 1, as shown in Fig. 1. Group 1 constituted the group receiving oral carnosine, having a powdery appearance in gelatin capsules of 500 mg (two capsules each time) after breakfast and dinner. The patients required a daily dose for 90 consecutive days. Group 2 comprised the group receiving the placebo, which had a powdered appearance in gelatin capsules, similar to carnosine in all respects. The patients had to take 2 capsules each time, after breakfast and dinner for 90 consecutive days, the same as group 1. The study complies with the Declaration of Helsinki (1964). The study was registered at Thai Clinical Trials Registry (TCTR) (TCTR20200724002).

The inclusion criteria included T2DM, age of 18 years old or older, urine albumin-creatinine ratio (UACR) of 30 to 299 mg/g creatinine (Cr) at least two in three within three to six months, stable dose of ACEIs or ARBs for blood pressure control at least three months before enrolling, and stable hemoglobinA1C (HbA1C) within three months before the study. The exclusion criteria comprised active infections, CKD from nondiabetic cause, advanced malignancy, history of hypersensitivity to protein nutrients, problems with nutrient absorption of the gastro-intestinal tract and liver disease.

The data we collected before and after in this study, were relevant information on diabetic nephropathy, including diagnostic criteria, duration of the disease and complications of diabetes mellitus such as diabetic retinopathy and diabetic neuropathy. Also, other underlying diseases, including hypertension,

heart disease, liver disease, infectious diseases and malignancy were recorded. The history of medication including antihypertensive drugs and lipid lowering agents were recorded. Physical examination data including height, weight, blood pressure and body mass index (BMI) were collected. The laboratory tests including fasting plasma glucose (FPG), HbA1C, blood urea nitrogen, Cr, calculation of estimated glomerular infiltration rate using the 2009 Chronic Kidney Disease Epidemiology Collaboration Equation, total cholesterol, triglyceride, low density lipoprotein and high density lipoprotein were noted. Participants would receive urine testing for urinary TGF-β level by enzyme linked immunosorbent assay. UACR by immunonephelometric assay method, before and after receiving carnosine or placebo for a period of 90 days is shown in Fig. 1.

Follow-up study results

The researcher verified consistent carnosine intake by asking for the remaining tablets and followed up the side effects of carnosine intake by using the adverse effects assessment form (Naranjo's algorithm). The primary outcome was the change of urinary TGF-β level after 12 weeks in the oral carnosine supplementation group, compared with that of the placebo group. The secondary outcome was the improving level of UACR after 12 weeks in the oral carnosine supplementation group compared with that of the placebo group.

Statistical analysis

Statistical software was used for statistical analysis. Descriptive statistics were used to present general information, laboratory results and urinary substances measurement level, including percentages, averages and standard deviations in the case of normal distributed continuous data. Inferential statistics was used to compare between general information, laboratory results and the percentage changes of variables in the oral carnosine supplementation and placebo groups, based on Student's test statistics. Pearson chi-square test or Fisher's exact test was used for discrete or categorical variables. Paired-sample t tests was used for the continuous variables and presented by the relative risk of 95% confidence intervals with p-value less than 0.05, regarded as statistically significant.

Results

From the screening, of a total of 104 patients with T2DM and nephropathy, 64 were excluded. The included 40 patients were randomly divided in two groups. A total of 20 patients were selected to take 2 grams of oral carnosine daily after breakfast and dinner, 1 gram per meal. The other 20 patients received placebo, having a powdery appearance in gelatin capsules similar to carnosine capsules in all respects. No differences were found in baseline characteristics between the two groups except sex and FPG level which differed significantly. We found the percentage of males in the oral carnosine group was 55%, more than that in the placebo group (10%) (P-value = 0.022). The mean FPG in the oral carnosine group (mean ± SD = 168.6 ± 52.7 mg/dL) was higher than that of the placebo group (mean ± SD = 131 ± 30.3 mg/dL) (P-value = 0.009) as shown in Table 1.

Table 1
Baseline characteristics of patients

Variables	Placebo (N = 20)	Carnosine (N = 20)	P value
Male, n (%)	4 (20.0)	11 (55.0)	0.022
Age (years)	57.0 ± 6.9	55.6 ± 4.8	0.463
Duration (years)	13.0 ± 8.8	10.5 ± 6.5	0.323
Body weight (kg)	73.2 ± 15.3	81.6 ± 18.5	0.127
Body mass index (kg/m^2)	28.4 ± 5.2	30.3 ± 5.6	0.284
Systolic blood pressure (mmHg)	134.2 ± 16.4	1341 ± 11.8	0.965
Diastolic blood pressure (mmHg)	78.2 ± 7.0	78.6 ± 11.5	0.895
Comorbid diseases (N, %)			
Hypertension	14 (70.0)	17 (85.0)	0.451
Dyslipidemia	17 (85.0)	16 (80.0)	1.000
Coronary heart disease	1(5.0)	-	1.000
Chronic lung disease	-	1 (5.0)	1.000
Anti-hypertensive drugs (N, %)			
ACEI	1 (5.0)	3 (15.0)	0.605
ARB	11 (55.0)	12 (60.0)	0.749
CCB	9 (45.0)	13 (65.0)	0.204
Thiazide	3 (15.0)	1 (5.0)	0.605
Hydralazine	1 (5.0)	-	1.000
Doxazocin	2 (10.0)	3 (15.0)	1.000
Anti-glycemic drugs (N, %)			
Metformin	15 (75.0)	20 (100.0)	0.047
Sulfonylurea	7 (35.0)	5 (25.0)	0.490

Data in the table are shown with average ± standard deviation and percentages.

ACEI; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blockade, BUN; blood urea nitrogen, CCB; Calcium channel blocker, DPP4-inhibitor; dipeptidyl peptidase-4 inhibitor, SGLT-2 inhibitor; sodium glucose co-transporter inhibitor, GLP-1 agonist; glucagon-like peptide-1 receptor agonist, GFR; estimated glomerular filtration rate, LDL; low density lipoprotein cholesterol, HDL; high density lipoprotein cholesterol

Variables	Placebo (N = 20)	Carnosine (N = 20)	P value
Thiazolidinedione	5 (25.0)	9 (45.0)	0.185
DPP4-inhibitor	7 (35.0)	5 (25.0)	0.490
SGLT-2 inhibitor	7 (35.0)	2 (10.0)	0.127
GLP-1 agonist	1 (5.0)	2 (10.0)	1.000
Laboratory parameters			
FPG (mg/dL)	131.0 ± 30.3	168.6 ± 52.7	0.009
HemoglobinA1C (%)	7.8 ± 1.8	7.8 ± 1.5	0.971
Triglycerides (mg/dL)	159.4 ± 88.8	157.5 ± 112.9	0.953
Cholesterol (mg/dL)	156.6 ± 37.6	157.8 ± 29.9	0.913
LDL-cholesterol (mg/dL)	92.3 ± 35.8	114.9 ± 81.1	0.080
HDL-cholesterol (mg/dL)	50.9 ± 2.6	49.4 ± 2.3	0.262
BUN (mg/dL)	17.1 ± 7.2	15.6 ± 5.7	0.456
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.2	0.677
GFR (mL/min/1.73 m^2)	78.6 ± 22.1	81.6 ± 19.7	0.655
Urine TGF-β (pg/mgCr)	82.9 ± 57.1	89.1 ± 75.9	0.775
UACR (mg/gCr)	114.7 ± 64.8	114.8 ± 56.4	0.997

Data in the table are shown with average ± standard deviation and percentages.

ACEI; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blockade, BUN; blood urea nitrogen, CCB; Calcium channel blocker, DPP4-inhibitor; dipeptidyl peptidase-4 inhibitor, SGLT-2 inhibitor; sodium glucose co-transporter inhibitor, GLP-1 agonist; glucagon-like peptide-1 receptor agonist, GFR; estimated glomerular filtration rate, LDL; low density lipoprotein cholesterol, HDL; high density lipoprotein cholesterol

The percentage of patients using antihypertensive agents affecting albuminuria level was reported as described below. The ACEIs was 15% in the carnosine and 5% in the placebo group, ARBs in the carnosine group was 60% and 55% in the placebo group, without significant differences (P = 0.605 and P = 0.749, respectively). Furthermore, the percentage of patients using antihyperglycemic agents affecting albuminuria level was reported as described below. The sodium glucose cotransporter-2 inhibitor (SGLT-2inhibitor) was found at 10% in the carnosine group and 35% in the placebo group. The glucagon-like peptide-1 receptor agonist (GLP-1 agonist) was found at 10% in the carnosine group and 5% in the placebo group, without significant differences in both groups (P = 0.127 and P = 1.000, respectively). No

significant differences on baseline laboratory tests and metabolic profiles were found between the two groups as shown in Table 1.

After 12 weeks, no significant differences were found on mean change of urine TGF-β between the two groups as shown in Fig. 2A. After additional analysis, the oral carnosine supplement group had a decreased percentage of mean change of urine TGF-β Cr ratio from baseline by 17.14%. Whereas, the percentage of placebo increased by 16.87%. Both groups had a percent mean difference of 34.01 and differed significantly (P = 0.03, 95% CI 3.48 to 64.54), as shown in Fig. 2B.

The percentage of mean change of UACR increased from baseline by 10.83% (mean ± SD = 10.83 ± 77.99 mg/gCr) in the carnosine group. However, in the placebo group, the percentage of mean change of UACR increased by 41.46% (mean ± SD = 41.46 ± 112.9 mg/gCr). Both groups exhibited a percent mean difference of 30.64%, without significance (P = 0.324, 95% CI -31.48 to 92.76) and did not differ significantly concerning mean change of urine albuminuria as shown in Figs. 3A and 3B.

After 12 weeks, BMI, blood pressure, renal function, HbA1C and lipid profiles of all patients remained unchanged from baseline, as shown in Table 2. Our studies did not experience any side effects of carnosine during the study, such as allergic reactions, rash or insomnia. These side effects of carnosine have been reported in related studies.

Table 2
Change of variables after 12 weeks of treatment

Variables	Placebo (N = 20)	Carnosine (N = 20)	P value
Body weight (kg)	-0.65 ± 1.64	-0.22 ± 2.23	0.164
Body mass index (kg/m^2)	-0.25 ± 0.65	-0.18 ± 0.97	0.097
Systolic blood pressure (mmHg)	-0.90 ± 7.38	-3.15 ± 12.40	0.214
Diastolic blood pressure (mmHg)	-1.95 ± 6.20	0.35 ± 6.32	0.426
BUN (mg/dL)	1.76 ± 5.23	0.48 ± 5.59	0.197
Creatinine (mg/dL)	0.01 ± 0.11	-0.03 ± 0.13	0.522
GFR (mL/min/1.73 m^2)	-0.29 ± 8.04	4.18 ± 11.82	0.237
HemoglobinA1C (%)	-0.07 ± 1.46	-0.33 ± 0.78	0.286
LDL (mg/dL)	10.30 ± 47.40	-23.40 ± 86.60	0.140
HDL (mg/dL)	1.60 ± 12.10	-1.90 ± 11.0	0.331
Cholesterol (mg/dL)	9.84 ± 51.90	-10.10 ± 41.60	0.187
Triglyceride (mg/dL)	-9.20 ± 70.70	-0.50 ± 63.70	0.684
Data in the table are shown with average ± standard deviation.			
BUN; blood urea nitrogen, GF; glomerular filtration rate, LDL; low density lipoprotein cholesterol, HDL; high density lipoprotein cholesterol			

Discussion

This study was the first randomized controlled trial showing the statistically significant differences in the data regarding oral carnosine supplementation among patients with T2DM and nephropathy, to reduced urinary TGF-β compared with placebo. This was consistent with related research investigating patients with type 1 diabetes and nephropathy. Elbarbary NS et al. reported that carnosine could reduce urine alpha-1 microglobulin, which is a urine biomarker of glomerular and tubular injury among diabetic patients, as well as urinary TGF-β [12]. Several studies in animal models also demonstrated anti-inflammatory, anti-oxidant, antiglycation, antiproteinuric and vasculoprotective effects of carnosine [13, 14].

Reduced urinary TGF-β is a biomarker for CKD progression.[7] It has been shown that carnosine may have a reno-protective effect on ischemia/reperfusion-induced acute kidney injury in animal models [15] and attenuates the development of patients with T2DM and nephropathy [16]. Whereas, we found that oral carnosine supplementation did not reduce urine albumin, which differed from one related study [12]. The

finding might be explained in that baseline patients' conditions in this study were more severe regarding the degree of diabetic nephropathy. Higher age, urine albumin and comorbid illness including hypertension, dyslipidemia, and obesity were observed in our study. On the contrary, the subjects in related studies had shorter duration of diabetes without history of underlying diseases reported. Our study found that early biomarkers of kidney injury including urine TGF-β level was lower in the carnosine group. Thus, a follow-up of longer duration might show significantly decreased levels of urine albumin.

Additional renal benefits of carnosine treatment were improved glycemic and metabolic control. An in vivo study in diabetes-induced mice receiving carnosine supplements showed reduced FPG levels, decreased insulin resistance and increased β-cell mass [17–19]. In addition, a study among children with type 1 diabetes mellitus found that oral carnosine supplementation for 12 weeks could significantly reduce HbA1C, compared with placebo [12], which differed from our study. This was due to the difference in baseline HbA1C where average baseline HbA1C level was 7.8 and 8.2% in our study and a related study. Patients with T2DM in our study were already able to effectively control their HbA1C levels, as we could not see any additional benefit of carnosine on reducing HbA1C level. Another in vitro study of Lee YT, et al. showed that carnosine could improve lipid metabolism [20]. Moreover, carnosine could reduce lipid peroxidation, atherogenic ApoB lipoproteins and triglycerides in plaques of mice [21]. The study among children with type 1 diabetes found that receiving carnosine for 12 weeks could improve cholesterol level [12]. The lipid outcome was undetected in our study, because approximately 80% of our adult subjects received strong lipid lowering agents.

The limitation of our study was that we did not evaluate major renal outcomes including ESRD, double serum Cr and dialysis. The main outcome was only biomarkers of kidney progression including urine TGF-β and albumin. Due to the short duration, our study could not conclude any long term effects of carnosine on urine TGF-β reduction and renal outcomes. Therefore, the long term side effects of carnosine are needed to be further investigated.

Conclusion

In summary, the study showed that oral carnosine supplementation could reduce urinary TGF-β level in T2DM with diabetic nephropathy, but without significant effects on urine albumin, indicating an additional renoprotective effect from conventional therapy. Further study is needed to determine the long term effects of oral carnosine supplementation on delayed renal progression in T2DM as a result of the decreased level of urinary TGF-β.

Abbreviations

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; Cr, creatinine; ESRD, end stage renal disease; FPG, fasting plasma glucose; HbA1C, hemoglobinA1C; GBM, glomerular basement membrane; GLP-1 agonist, glucagon-like peptide-1 receptor agonist; IL-1, interleukine-1; IL-6, interleukine-6; SGLT-2inhibitor, sodium glucose

cotransporter-2 inhibitor; TGF-β, transforming growth factor beta; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor; TNF, tissue necrosis factor; UACR, urine albumin creatinine ratio

Declarations

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Availability of data and materials

The excel of individual clinical data used to support the findings of this study are available from the corresponding author upon request.

Authors' contributions

NS, BS, and OS collected the data, drafted the article, reviewed the literature and revised it critically. NS provided valuable inputs in study design, data collection and literature review. BS provided revision of the draft. All authors read and approved the manuscript and met the criteria for authorship.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Institutional Review Board. Royal Thai Army Medical Department (IRB Number S004h/57), Bangkok, Thailand. All patients gave written informed consent.

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Figures

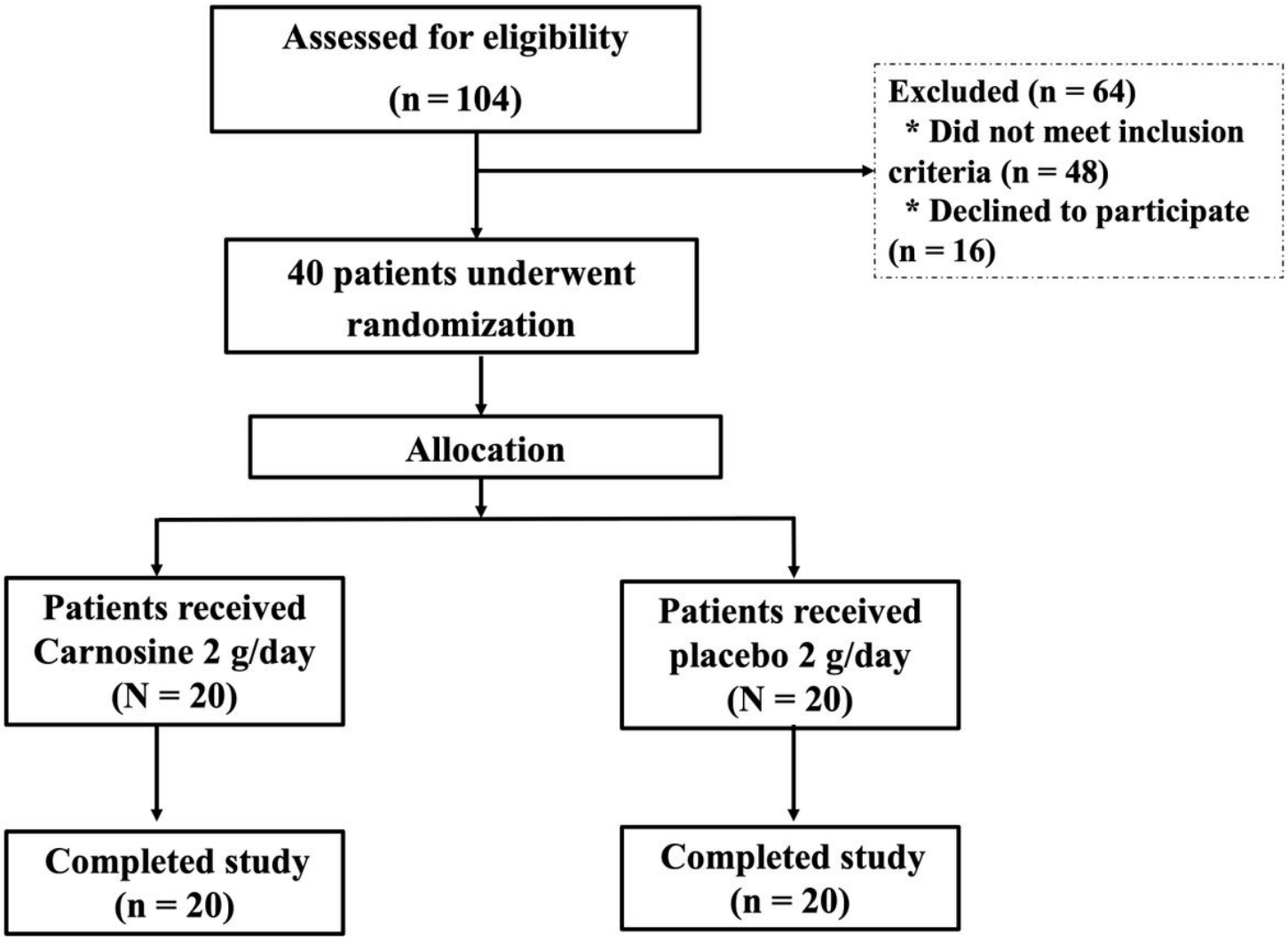

Figure 1

Flow chart of study

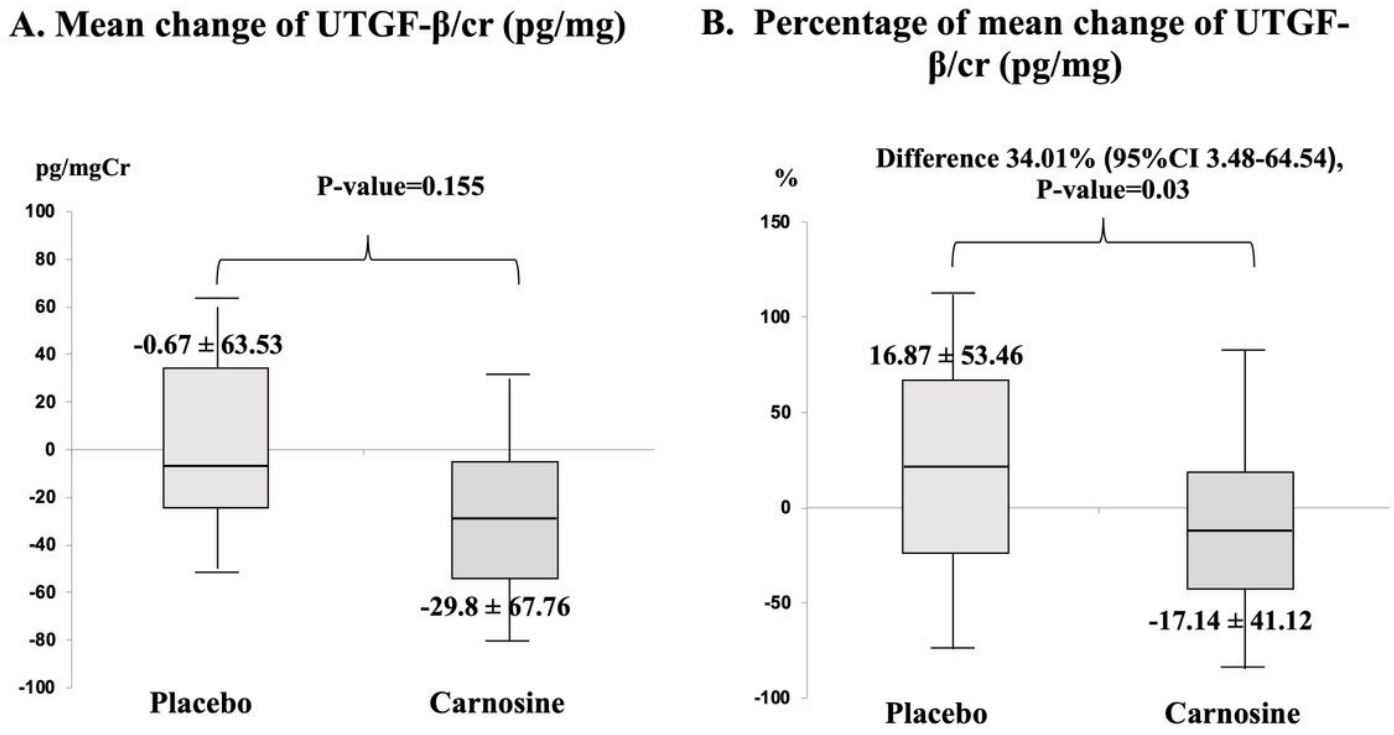

Figure 2

Change of urine TGF-β after treatment. Box-and-whisker-plot diagrams show the (A) mean change of urine TGF-β (pg/mgCr) and (B) percentage of mean change of urine TGF-β (pg/mgCr) after 12 weeks of taking carnosine. The figure shows the percentage of mean change that decreased from baseline at 17.14% in the carnosine group, and in the placebo group increased percentage of mean change from baseline 16.87%. The percent mean significantly differed at 34.01% (P=0.03).

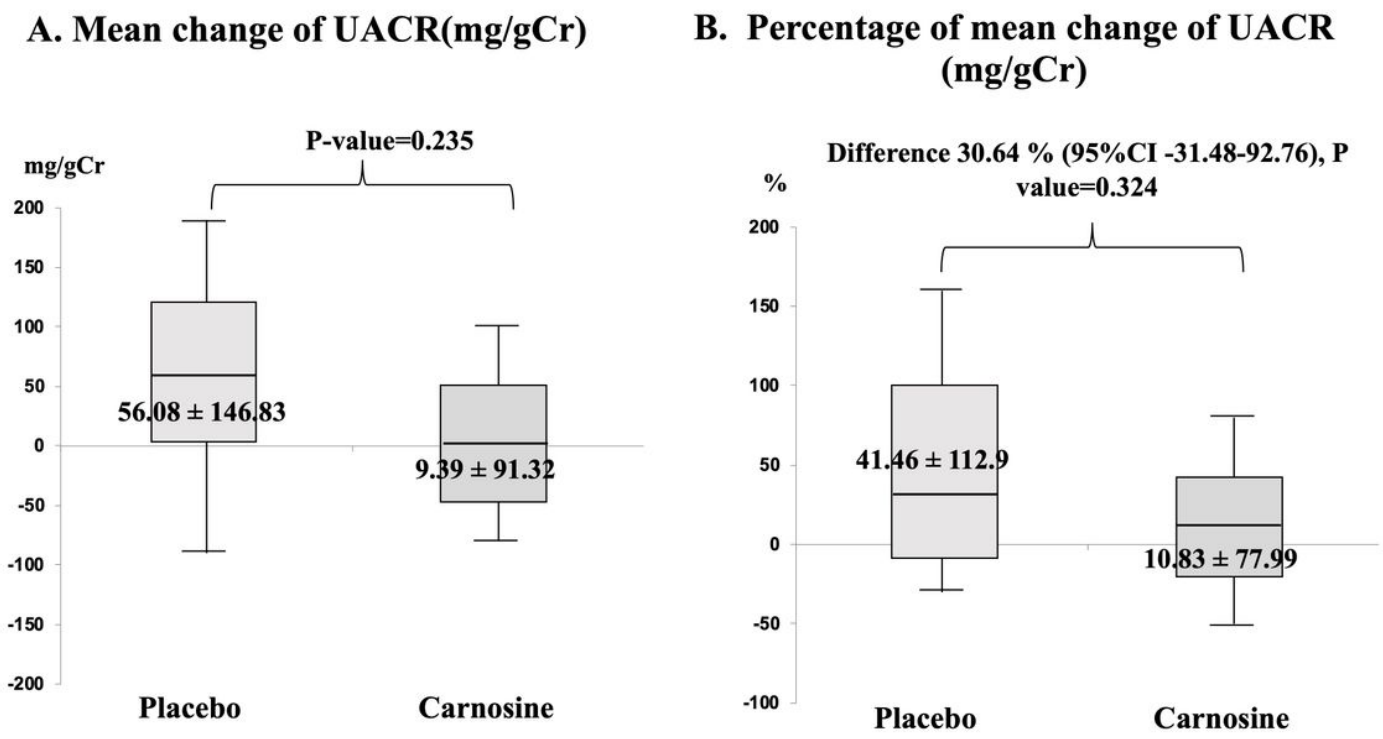

Figure 3

Change of urine albumin after treatment. Box-and-whisker-plot diagram shows the (A) mean change of UACR and (B) percentage of mean change of UACR (mg/gCr) after 12 weeks of taking carnosine. The percentage of mean change increased from the baseline 10.83% in the carnosine group and the percentage of mean change increased by 41.46% in the placebo group. The percent mean was 30.64% without significant difference (P = 0.324).

Supplementary Files

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