

Original Article

Acute effect of a soy protein-rich meal-replacement application on renal parameters in patients with the metabolic syndrome

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Background: Soy protein is used for meal replacement therapy in obesity, however the influence on renal function parameters is not adequately investigated. This study evaluates glomerular filtration rate (GFR) and renal plasma flow (RPF) in patients with the metabolic syndrome and healthy controls after ingestion of different amounts of soy protein. **Methods:** 10 patients with the metabolic syndrome but no signs of kidney disease and 10 healthy controls ingested 1 g protein/kg body weight of a commercial soy-yoghurt-honey-preparation. The patient group was also given a protein challenge of 0.3 g/kg body weight. **Results:** Baseline GFR and RPF both were significantly higher in the patient group (147 ± 34.8 vs. 116 ± 21.1 ml/min, $p=0.01$ and 848 ± 217 vs. 637 ± 121 ml/min, $p=0.02$) and were strongly correlated with body weight. Use of different algorithms to estimate GFR resulted in underestimation of GFR, particularly in the patients with the metabolic syndrome. The challenge with an acute protein load of 1g protein per kilogram body weight induced a significant increase in GFR and RPF in healthy controls (GFR: $+12.6\pm 11.0$ % ($p=0.01$), RPF: $+13.6\pm 15.6$ % ($p=0.04$)) and even more in patients with the metabolic syndrome (GFR: $+31.5\pm 32.2$ % ($p=0.01$); RPF: $+19.4\pm 22.7$ % ($p=0.02$)). The ingestion of 0.3 g protein/kg body weight did not induce significant changes. **Conclusions:** Basic renal function is changed in patients with the metabolic syndrome, even without microalbuminuria. In addition, there is an elevated susceptibility for protein load. However, the protein amount recommended for use in soy-protein based meal replacement therapy induced no significant changes.

Key Words: renal function, metabolic syndrome, glomerular filtration rate, renal plasma flow, soy protein

INTRODUCTION

Several groups have examined the relationship between the metabolic syndrome and chronic kidney disease (CKD).¹⁻³ It has been demonstrated that increased blood pressure and hyperglycemia are risk factors for CKD in patients with the metabolic syndrome. In addition it was observed that increased waist circumference significantly correlated with microalbuminuria and decline of glomerular filtration rate (GFR), suggesting that obesity may be an independent risk factor for CKD.² The association between obesity and the nephrotic syndrome has been demonstrated in different countries and for different ethnicity groups.⁴⁻⁹ In accordance with the epidemic spread of obesity, a large renal pathology study demonstrated that the incidence of obesity-related glomerulopathy increased from 0.2 to 2% during the 15-year period of the study.¹⁰ On the other hand, it has been shown that weight reduction reduces the incidence of the metabolic syndrome in obese adults¹¹ and improves proteinuria and microalbuminuria.¹²⁻¹⁴

Therefore, weight reduction is a preventive strategy to preserve renal function in obese patients with the metabolic syndrome. Nevertheless, a high dietary protein content, for example in a very-low carbohydrate diet or protein based meal replacement therapy, has been suspected to affect kidney function by increasing glomerular pressure and hyperfiltration possibly leading to progressive loss of renal function.^{15,16} However, high protein diets have been shown to be effective and safe in weight reduction in overweight and obese subjects.¹⁷⁻²²

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In a recent study, we reported the effect of a meal replacement regimen with a commercially available product containing a soy-yoghurt-honey preparation.²³ Soy protein seems to be preferable to other proteins, especially animal protein, with respect to glomerular function changes.^{24,25} To our knowledge no investigation has evaluated the effect of a soy-protein based product on renal function in patients with the metabolic syndrome.

Therefore, we investigated the influence of a protein load of 1 g/kg body weight and 0.3 g/kg, in patients with the metabolic syndrome and healthy controls. By these experiments we intended to detect a different sensitivity of the kidney in patients with the metabolic syndrome to a protein challenge, and to provide support for the use of a soy-protein based meal replacement in patients with the metabolic syndrome in order to reduce weight. Furthermore, we wanted to investigate the usefulness of algorithms to estimate glomerular filtration rate in these patients.

MATERIALS AND METHODS

The database of the Department of Rehabilitative and Preventive Sports Medicine of the University hospital in Freiburg, Germany was searched for patients with dyslipoproteinemia and arterial hypertension. Records were checked for other features of the metabolic syndrome according to the ATP III criteria. After recruitment of 10 male patients with the diagnosis of the metabolic syndrome, the same database was searched for 10 healthy male controls matching for age. All participants had normal serum creatinine and urea levels, and a urine test for protein (Microalbumin, Bayer, Leverkusen, Germany;

sensitivity 10-150 mg/L) had to be negative (defined by urine protein lower than 20 mg/L). Body composition was determined using the bod pod device[®], and waist circumference was measured. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease Study equation (GFR-MDRD) and Chronic Kidney Disease Epidemiology Collaboration (GFR-CKD-EPI).^{26,27}

Subjects were instructed to eat a low-protein diet (protein amount 0.6 g/kg body weight) for 2 days before the examination. Breakfast, lunch and dinner examples, in order to keep to this individual diet, were explained and handed out to the participants. The testing was conducted after a 12-hour fast. Every hour the test subjects were given 4 ml of water/kg body weight, and remained recumbent throughout the testing. The test meal (first exploration: 1.0 g protein/kg body weight diluted in 500 ml water, ratio soy protein: milk protein = 4.8:1) was given at the end of the first clearance determination. For a 70 kg subject, the meal consisted of 131 g of the commercial soy-yoghurt-honey diet (Almased[®], Almased Wellness Corp., Bienenbüttel, Germany). The second clearance determination was made 90 min after the end of the first determination. For determination of GFR and effective renal plasma flow (RPF), 2500 mg sinistrin (Inutest[®], Fresenius Pharma Austria, Linz, Austria), an inulin-like polyfructosan, and PAH (Aminohippurate[®], Merck & Co, West Point, PA, USA) in a dosage of 10 mg/kg body weight (minimal PAH dose 500 mg, maximal PAH dose 1000 mg) were given intravenously over 3 min. To exclude dietary, diurnal and environmental influences in our study, the baseline renal function determination and protein challenge took place on the same day using an evalu-

Table 1. Baseline characteristics of healthy subjects and patients with the metabolic syndrome

	Group				<i>p</i>
	Healthy subjects		Metabolic syndrome		
	mean	SD	mean	SD	
Age (yrs)	48	15	46	13	n.s.
Height (cm)	177	7	180	9	n.s.
Weight (kg)	77.0	13.7	105	15.3	0.000
BMI	24.5	3.18	32.2	3.48	0.001
Waist circumference (cm)	90.4	9.2	114	8.8	0.000
fat mass (%)	21.5	8.8	32.9	5.8	0.004
BP systolic (mmHg)	118	9	156	10	0.000
BP diastolic (mmHg)	75	11	97	7	0.000
Hb (g/dL)	15.0	1.0	15.1	0.7	n.s.
Leucocytes (10 ³ /μL)	6.9	1.5	6.7	1.5	n.s.
Erythrocytes (10 ⁶ /μL)	4.82	0.40	4.84	0.28	n.s.
hsCRP (mg/dL)	0.07	0.03	0.78	1.60	n.s.
HbA1c	5.6	0.5	6.1	0.6	n.s.
Glucose (mg/dL)	93	17	112	28	n.s.
Creatinine (mg/dL)	0.87	0.16	0.85	0.08	n.s.
Urea (mg/dL)	36	6	36	7	n.s.
AST (U/L)	28	6	40	22	n.s.
ALT (U/L)	23	13	57	42	0.003
gammaGT (U/L)	34	43	62	67	0.013
Cholesterol (mg/dL)	221	47	221	47	n.s.
Triglycerides (mg/dL)	161	101	178	90	n.s.
HDL-cholesterol (mg/dL)	66.6	27.0	57.4	15.7	n.s.
LDL-cholesterol (mg/dL)	95	49	124	27	n.s.
Lp(a) (mg/dL)	1.7	1.8	1.2	1.6	n.s.

Baseline characteristics with respect to anthropometric and laboratory data. SD=standard deviation. BP = blood pressure. hsCRP = high sensitive C-reactive protein. AST = aspartate aminotransferase. ALT = alanine aminotransferase. gammaGT = gamma-glutamyl transferase. Lp = lipoprotein.

ated model for calculating the clearances.²⁸⁻³¹

At least one week later, patients with the metabolic syndrome were given a second test meal, consisting of 0.3 g protein/kg body weight. This matches the amount of the commercial soy yoghurt honey preparation used in meal replacement therapy. The study protocol and patient information was approved by the local ethics committee.

Statistical analysis was done using SPSS 15 software (SPSS Inc., Chicago, IL). All values are expressed as mean \pm standard deviation (SD), unless otherwise specified. As the data of glomerular filtration rate and renal plasma flow at baseline and after protein ingestions were not normally distributed (tested by Kolmogorov-Smirnov test), differences within each group were compared by Wilcoxon rank sum test. Differences between the groups were analyzed by Mann-Whitney U test or chi-square test. Correlations between various characteristics and GFR or RPF were determined using Spearman's correlation. A *p*-value <0.05 was considered significant.

RESULTS

Baseline characteristics of clinical and biochemical variables of healthy subjects and patients with the metabolic

syndrome are shown in Table 1. In the patients with the metabolic syndrome, body weight, body mass index (BMI), waist circumference and fat mass were significantly elevated (Table 1).

Patients with the metabolic syndrome also had significant higher systolic and diastolic blood pressure, as well as higher alanine aminotransferase and gamma glutamyl transferase activity. There were no significant differences between groups in terms of blood lipid levels.

Compared to the healthy subjects, patients with the metabolic syndrome had a significantly elevated baseline GFR (147 ± 34.8 vs. 116 ± 21.1 ; $p=0.02$) and RPF (848 ± 217 vs. 637 ± 121 ; $p=0.02$) (Table 2 and Figure 1). This was strongly correlated with body weight; a moderate correlation was found with BMI, body height, fat mass, blood pressure and ALT (Table 3).

Comparing the MDRD and CKD-EPI estimation, the patients with the metabolic syndrome only had slightly higher eGFR. However, both estimations significantly underrated the glomerular filtration rates, particularly in patients with the metabolic syndrome. As both estimations use creatinine, age, sex and ethnicity, they are inappropriate to detect an acute change in glomerular filtration rate.

Table 2. Comparison of estimated glomerular filtration rate (according to MDRD and CKD-EPI algorithm) with measured glomerular filtration rate measured by inulin clearance and renal plasma flow measured by para-aminohippurate clearance

	Group				<i>p</i> -value
	Healthy subjects		Metabolic syndrome		
	mean	SD	mean	SD	
GFR-MDRD (ml/min)	102	20.2	105	10.8	n.s.
GFR-CKD-EPI (ml/min)	104	13.4	105	8.9	n.s.
Glomerular filtration rate (baseline; ml/min)	116	21.1	147	34.8	0.02
Glomerular filtration rate (after 1 g/kg protein challenge; ml/min)	130	26.4	188	46.7	0.002
Renal plasma flow (baseline; ml/min)	637	121	848	217	0.02
Renal plasma flow (after 1 g/kg protein challenge; ml/min)	719	144	1006	303	0.02

p for differences between groups. SD=standard deviation. GFR-MDRD = estimated GFR according to MDRD algorithm,²⁶ GFR-CKD-EPI = estimated GFR according to CKD-EPI algorithm.²⁷

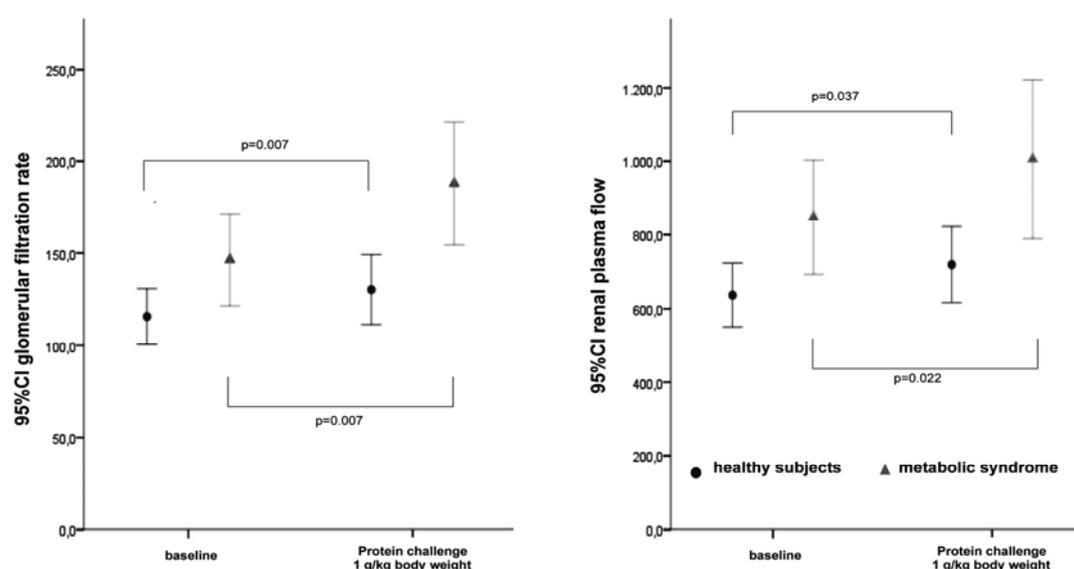


Figure 1. Glomerular filtration rate and renal plasma flow (in ml/min) before and after protein challenge (1 g protein per kg body weight) in healthy subjects and patients with the metabolic syndrome, shown as mean \pm 95% CI. *p* is provided for change after protein ingestion compared to baseline in each group. Differences between the groups were also significant (Table 2). The increase of GFR in patients with the metabolic syndrome was significantly higher than in healthy controls ($p=0.04$).

Table 3. Correlations of baseline renal function parameters with anthropometric and clinical parameters

	BMI	Body weight (kg)	Body height (cm)	Waist circumference (cm)	Fat mass (kg)	Relative fat mass (%)	BP diastolic (mmHg)	BP systolic (mmHg)	ALT (U/L)	LDL-Cholesterol (mg/dL)
Glomerular filtration rate (baseline)										
Spearman Rho	0.499*	0.707**	0.648**	0.476*	0.385	0.192	0.532*	0.566**	0.447*	-0.230
<i>p</i> -value (2-sided)	0.025	0.000	0.002	0.034	0.094	0.416	0.016	0.009	0.048	0.344
Renal plasma flow (baseline)										
Spearman Rho	0.573**	0.702**	0.506*	0.494*	0.465*	0.257	0.445*	0.443	0.330	-0.282
<i>p</i> -value (2-sided)	0.008	0.001	0.023	0.027	0.039	0.274	0.049	0.050	0.155	0.241

* The correlation is significant for a two-sided test with $p=0.05$.

** The correlation is significant for a two-sided test with $p=0.01$.

GFR: glomerular filtration rate; RPF: renal plasma flow; BP: blood pressure; ALT: alanine aminotransferase

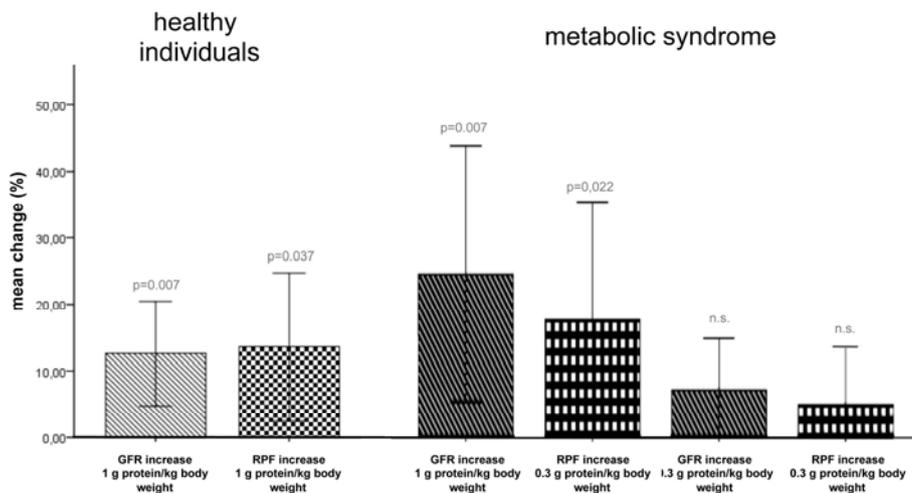


Figure 2. Relative changes in glomerular filtration rate and renal plasma flow before and after ingestion of different protein amounts, shown as mean \pm 95% CI. *p* is provided for comparison of relative changes between the groups (n.s. = non significant).

After ingestion of 1g protein per kg body weight, glomerular filtration rate and renal plasma flow was enhanced. The difference between the groups was still statistically significant (patients vs. controls: GFR: 188 ± 46.7 vs. 130 ± 26.4 ; $p=0.002$; RPF: 1006 ± 303 vs. 719 ± 144 ; $p=0.02$) (Table 2 and Figure 1).

The increase in GFR and RPF after a challenge with an acute protein load of 1g protein per kilogram was significant in patients with the metabolic syndrome as well as in healthy controls (relative intra-individual changes are shown in Figure 2). GFR increased about $+41.5 \pm 39.8$ ml/min ($p=0.01$) in patients and $+14.5 \pm 12.0$ ml/min ($p=0.01$) in healthy controls. RPF increased about 158 ± 190 ml/min ($p=0.02$) in patients and 82.2 ± 105 ml/min ($p=0.04$) in controls. The absolute increase in GFR in the patient group was significantly greater than in the healthy controls ($p=0.04$). However, the more enhanced relative increases of GFR and RPF in the patient group were not statistically significant higher than that found in the controls, due to the small numbers of participants and the large 95% confidence interval (Figures 1 and 2).

The absolute and relative increase in GFR and RPF showed no relation to fat mass, relative body fat, waist circumference, or ALT. The only variable that correlated with both the absolute and relative increase in GFR and RPF after ingestion of 1 g/kg protein was baseline systolic blood pressure ($p=0.014$ and $p=0.036$, respectively).

Systolic and diastolic blood pressure and ALT correlated significantly to relative fat mass and waist circumference (each $p < 0.02$).

In patients with the metabolic syndrome the effect of a protein challenge with 0.3g protein per kilogram body weight induced only a slight non-significant increase in GFR and RPF. The GFR was elevated by about $+12.5 \pm 6.2$ ml/min, the RPF increased by about $+33.3 \pm 27.8$ ml/min.

DISCUSSION

This study shows that patients with the metabolic syndrome have a significantly higher glomerular filtration rate and renal plasma flow than healthy, age-matched controls.

Our findings confirm the data of Chagnac *et al.*³² In their study GFR was 51% and RPF was 31% higher in obese subjects than for non-obese controls. In severely obese people this elevation was even more pronounced.³³ In our study, the underlying metabolic syndrome was associated with a 27% increase of GFR and a 33% increase of RPF. The lower increment of GFR in patients compared to Chagnac *et al* may be due to the inclusion criteria of our study, excluding patients with overt nephropathy and microalbuminuria. Our results not only confirm a hyperfiltration in obese patients and patients with the metabolic syndrome, but also show that these patients seem to be more susceptible to a protein load. This may

have impact on the dietary advice for obese patients with renal impairment willing to reduce weight.

We therefore investigated the effect of a commercially used soy protein based meal replacement supplement on kidney function. Administration of a protein amount of 1 g protein (containing 83% soy protein) per kilogram body weight induced a significant increase in healthy participants and even more pronounced in patients with the metabolic syndrome. This effect is attributable to the amino acids ingested, as the applied amount of sodium is too low to have a marked impact on renal function (for a 70 kg person, 775 mg sodium is contained in the supplied product at this dosage). Furthermore, blood pressure and heart rate did not change significantly during the experiment (data not shown), ruling out cardiovascular changes as a cause for renal hemodynamic changes. Application of the reduced protein amount (ie, 0.3 g protein per kg body weight) tended to slightly increase glomerular filtration rate and renal plasma flow. Therefore, we relate the changes in glomerular function solely to the protein supply. However, the meal replacement with a protein dose of the soy based product of 0.3 g protein per kg body weight has no clinically relevant effect on kidney function and may be regarded as safe in patients with the metabolic syndrome. This corresponds to the protein amount used in meal replacement therapy.

The effect of an oral protein load on renal function has been studied in several settings. Some studies have suggested that vegetable protein, especially soy protein, may have less effect on renal function compared to animal protein,^{25,34-37} however results have been mixed.^{38,39} Studies performed in normoalbuminuric individuals with diabetes have suggested that changing the composition of the diet by altering the source of protein from animal to plant, might produce beneficial renal effects.^{25,40} Weight loss in overweight and obese subjects with mild to moderate chronic kidney disease has been associated with a significant decrease in proteinuria and albuminuria, regardless of study design and method of weight loss.^{14,21,41} In obese patients with diabetic nephropathy, a formula diet consisting of liquid protein (low-calorie: 11-19 kcal/kg/day; normal protein: 0.9-1.2 g/kg/day) significantly improved renal function and proteinuria.⁴² Use of a soy protein based meal replacement resulted in a significant reduction of body weight in overweight or obese patients with normal renal function without a change in lean body mass.²³ In this prospective study of over 48 weeks, we could not observe changes in serum creatinine values. In a cohort study with a long term follow up it was shown that absolute fat mass is a risk factor for change in eGFR⁴³. The attributable risk was larger for BMI and waist circumference than for fat mass. This is in accordance with our data, as the correlation of enhanced filtration rate was most prominent for body weight, and correlation was stronger with BMI and waist circumference than with fat mass. However, our data emphasize that only a sophisticated measurement of renal function is able to actually describe changes in glomerular function, as eGRF data are dependent from serum creatinine levels being correlated to lean body mass and underestimate actual GFR in patients with the metabolic syndrome.

Soy protein has been shown to exhibit several benefi-

cial effects on renal function in non-diabetic patients with nephropathy, and to improve serum lipids in male patients,⁴⁴ providing a possible explanation for the advantage of soy protein in renal disease. We have previously shown that a meal replacement therapy with the commercial soy-yoghurt-honey preparation has distinct effects on blood lipids and other metabolic and inflammatory risk factors.⁴⁵ Furthermore, the results of this study support the hypothesis that in overweight patients with the metabolic syndrome the protein amount given in a formula based meal (about 0.3 g protein/kg body weight), does not alter renal hemodynamics in a relevant way.

Our study also reveals the unreliability of algorithms to estimate glomerular function in patients with the metabolic syndrome. There is difficulty in utilizing the estimated glomerular filtration rate (eGFR) in overweight and obese people. The correction of eGFR to actual body surface area in obese patients results in significant underestimation compared to the absolute GFR measured by⁵¹ Cr-EDTA.⁴⁶ The goal of this study was to determine GFR and RPF in male patients with the metabolic syndrome but normal retention parameters and without microalbuminuria. Estimation of eGFR according to the MDRD or CKD-EPI algorithm resulted in lower eGFR values. This underrating of actual GFR was even more pronounced in patients with the metabolic syndrome. Our study revealed a marked hyperfiltration in male patients with the metabolic syndrome in comparison to age matched controls. Using algorithms to estimate GFR may fail to describe effects of a weight reduction on renal function.

The findings of our study document that the amount of protein used in meal replacement therapy of a commercially available soy-yoghurt honey preparation is not harmful to renal function in male patients with the metabolic syndrome. However, additional research is warranted to evaluate the long term benefits of a soy-based meal replacement therapy leading to weight reduction on renal function indices in patients with the metabolic syndrome. Whether similar effects would be evident in obese individuals of both sexes with pre-existing impaired renal function, including patients with diabetes, has to be examined in further studies.

AUTHOR DISCLOSURES

Almased Wellness Corp., Bienenbüttel, Germany provided the soy protein supplement (Almased®) and funding for this trial. Aloys Berg has received grants from Almased Wellness Corp. All other authors declare there is no conflict of interest.

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Original Article

Acute effect of a soy protein-rich meal-replacement application on renal parameters in patients with the metabolic syndrome

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大豆蛋白代餐對代謝症候群病人腎臟參數之急性效應

背景：大豆蛋白常被使用在肥胖的代餐治療，然而對於腎臟功能參數的影響尚未被充分研究。本研究評估代謝症候群病人及健康對照，在攝取不同量的大豆蛋白後的腎絲球過濾率(GFR)和腎血漿流量(RPF)。方法：10名患有代謝症候群但沒有腎臟疾病症狀的病人及10名健康對照，攝取每公斤體重1公克蛋白質的大豆-優格-蜂蜜烹調商品。病人組還給予一個蛋白質挑戰，每公斤體重0.3公克。結果：病人組的基礎GFR和RPF均顯著性較高(147±34.8 vs. 116±21.1 ml/min, $p=0.01$ 和 848±217 vs. 637±121 ml/min, $p=0.02$)，且與體重有強相關。使用不同的演算法去評估GFR導致低估GFR，特別是有代謝症候群的病人。每公斤體重1公克蛋白質的急性蛋白質負荷挑戰，導致健康對照的GFR和RPF增加(GFR: +12.6±11.0% ($p=0.01$), RPF: +13.6±15.6% ($p=0.04$))，有代謝症候群病人則增加更多(GFR: +31.5±32.2% ($p=0.01$); RPF: +19.4±22.7% ($p=0.02$))。每公斤體重攝取0.3公克蛋白質不會誘發顯著改變。結論：代謝症候群病人，即使在沒有微白蛋白尿的情況下，其基礎腎功能已經改變了。此外，蛋白質負荷量的感受性也升高了。然而，使用在大豆蛋白基礎代餐治療的蛋白質建議量，不會產生顯著改變。

關鍵字：腎臟功能、代謝症候群、腎絲球過濾率、腎血漿流量、大豆蛋白