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Original Article

C-reactive Protein Positively Correlates With Metabolic Syndrome in Kidney Transplantation Patients

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Abstract

Objective: C-reactive protein (CRP) is an independent risk factor for renal allograft loss and predicts all-cause mortality in kidney transplantation patients. Metabolic syndrome has also been associated with increased mortality in kidney transplantation patients. The aim of this study was to investigate the relationship between CRP and metabolic syndrome in kidney transplantation patients.
Materials and Methods: Fasting blood samples were obtained from 55 kidney transplantation patients. Metabolic syndrome and its components were defined using diagnostic criteria from the International Diabetes Federation.
Results: In total, 13 kidney transplantation patients (23.6%) had metabolic syndrome. Fasting CRP levels positively correlated with metabolic syndrome ($p=0.001$). Univariate linear regression analysis indicated that fasting serum CRP values were positively correlated with body weight ($p=0.001$), waist circumference ($p=0.008$), body mass index ($p<0.001$), and body fat mass ($p=0.042$). Multivariate forward stepwise linear regression analysis of the significant variables showed that body mass index ($\beta=0.455$, $R^2=0.207$, $p<0.001$) was an independent predictor of serum CRP levels in kidney transplantation patients.
Conclusion: CRP level positively correlated with metabolic syndrome in kidney transplantation patients. Body mass index was an independent predictor of ser*um CRP levels in kidney transplantation patients. (Tzu Chi Med J* 2010;22(3):131–136)

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1. Introduction

C-reactive protein (CRP) is a hepatic-derived pentraxin that plays a key role in the innate immune response (1) and is an independent risk factor for renal allograft loss (2,3). An elevated pre-transplant serum CRP level is a risk predictor for major cardiac events in renal transplant patients (4) and the CRP level predicts all-cause mortality in these patients (5). Metabolic syndrome is a condition of insulin resistance (6) and

is considered a significant risk factor for cardiovascular disease and mortality in the general population [7,8]. Tacrolimus and glucocorticoids are risk factors resulting in insulin resistance when used as treatment in kidney transplant patients [9,10]. Metabolic syndrome is a risk factor for post-transplant diabetes mellitus, chronic graft dysfunction, graft loss, atherosclerotic events and patient death in renal transplant recipients [11–13]. The aim of the present study, therefore, is to explore the relationship between serum CRP concentrations and the presence of metabolic syndrome in kidney transplant patients.

2. Materials and methods

2.1. Patients

Fifty-five kidney transplantation patients were studied in September 2008 in a medical center in Hualien, Taiwan. This group comprised 27 men and 28 women, who ranged in age from 40 to 61 years. The study was approved by the Protection of Human Subjects Institutional Review Board of Tzu Chi University and Hospital. Patients were excluded if they had an acute infection or if they refused to provide informed consent. No kidney transplantation patients in this study took aspirin or other nonsteroidal anti-inflammatory drugs.

2.2. Anthropometric analysis

Body weight to the nearest half kilogram was measured with patients wearing only light clothing without shoes. Height was measured to the nearest half centimeter. Waist circumference was measured to the nearest half centimeter at the shortest point below the lower rib margin and the iliac crest. The body mass index (BMI) was calculated as the weight (in kilograms) divided by the height squared (in meters). Bioimpedance measurements of fat mass were performed at bedside according to the standard tetrapolar whole body (hand-foot) technique, using a single-frequency (50 kHz) analyzer (Biodynamic-450; Biodynamics Corp., Seattle, WA, USA). Measurements were carried out by the same operator; fat mass was collected and analyzed by specific formulae offered by the manufacturer [14,15].

2.3. Biochemical investigations

Fasting blood samples were taken from each subject. Approximately 0.5 mL was used to determine the white blood cell count (Sysmex K-1000; Sysmex Corp., Bohemia, NY, USA) and the remaining blood was immediately centrifuged at 3000*g* for 10 minutes for biochemical study. The serum was stored at 4°C for biochemical examination within 1 hour after collection. Serum levels of creatinine, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, albumin, globulin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and CRP were measured using an autoanalyzer (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland).

2.4. Metabolic syndrome and its components

The prevalence of metabolic syndrome was defined using the International Diabetes Federation definition [6]. People were classified as having metabolic syndrome if they had central (abdominal) obesity with a waist circumference ≥90 cm for men or ≥80 cm for women (Chinese criteria), and had two or more of the following criteria: fasting serum glucose ≥110 mg/dL, triglycerides ≥150 mg/dL, HDL cholesterol level <40 mg/dL in men or <50 mg/dL in women, and blood pressure ≥130/85 mmHg. In this analysis, a patient who was on antihypertensive medication was considered to have high blood pressure. Type 2 diabetes was determined according to World Health Organization criteria [16]. A person was regarded as diabetic if fasting plasma glucose was ≥126 mg/dL, if 2-hour glucose from an oral glucose tolerance test was ≥200 mg/dL, or if they were on diabetes medication (oral or insulin).

2.5. Statistical analysis

Data are expressed as mean±standard deviation and tested for normal distribution by Kolmogorov-Smirnov statistics. Categorical variables were analyzed by the χ^2 test. Comparisons between patients were performed using Student's independent *t* test (two-tailed) for normally distributed data or the Mann-Whitney U test for parameters with non-normal distribution (fasting glucose, CRP and creatinine). Clinical variables that correlated with CRP in kidney transplantation patients were evaluated by univariate linear regression analyses. Variables that were significantly associated with CRP in kidney transplantation patients were tested for independence in multivariate forward stepwise regression analysis. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows. A p value <0.05 was considered statistically significant.

3. Results

The clinical and laboratory characteristics of the kidney transplantation patients are presented in Tables 1 and 2. Their medical histories included diabetes

Table 1 — Clinical and analytical characteristics of the 55 kidney transplantation patients*

Anthropometric data	
Age (yr)	50.16±10.34
Body weight (kg)	60.52±13.79
Height (cm)	161.25±9.13
BMI (kg/m^2)	23.34±4.18
Waist circumference (cm)	82.11±10.82
Body fat mass (%)	20.37±8.39
KT duration (mo)	43.64±40.69
Biochemical data	
Albumin (g/dL)	4.43±0.34
Triglyceride (mg/dL)	130.07±60.30
HDL cholesterol (mg/dL)	56.42±16.34
Total cholesterol (mg/dL)	198.18±52.02
GOT (IU/L)	19.44±5.58
GPT (IU/L)	17.80±8.90
WBC (×1000/μL)	6.33±1.88
Globulin (g/dL)	2.84±0.49
Fasting glucose (mg/dL)	113.00±50.86
Creatinine (mg/dL)	1.80±6.91
CRP (mg/dL)	0.27±0.40

*Data are presented as mean±standard deviation. BMI=body mass index; KT=kidney transplantation; HDL=high-density lipoprotein; GOT=glutamic oxaloacetic transaminase; GPT=glutamic pyruvic transaminase; WBC=white blood cell count; CRP=C-reactive protein.

(n=17; 30.9%), hypertension (n=34; 61.8%), and hyperlipidemia (n=17; 30.9%). The use of drugs included angiotensin receptor blockers (n=22; 40.0%), calcium channel blockers (n=22; 40.0%), β-blockers (n=6; 10.9%), sulfaurea (n=10; 18.2%), metformin (n=6; 10.9%), insulin (n=7; 12.7%), tacrolimus (n=36; 65.5%), mycophenolate mofetil (n=19; 34.5%), mycophenolic acid (n=21; 38.2%), steroids (n=38; 69.1%), rapamycin (n=7; 12.7%), and cyclosporine (n=13; 23.6%). None of these patients used angiotensin-converting enzyme inhibitors, peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists or fibrates.

The clinical characteristics and fasting serum CRP levels of the 55 kidney transplantation patients are presented in Table 2. Thirteen patients (23.6%) had metabolic syndrome. Kidney transplantation patients with metabolic syndrome had higher CRP levels than those without this syndrome (p=0.001). CRP levels did not differ statistically by sex distribution, diabetes, hypertension, hyperlipidemia, or use of any of the abovementioned drugs. Univariate linear analysis of fasting serum CRP levels in kidney transplantation patients is presented in Table 3. Body weight (p=0.001), waist circumference (p=0.008), BMI (p<0.001), and body fat mass (p=0.042) were positively correlated with serum CRP levels in these patients.

Multivariate forward stepwise linear regression analysis of the significant variables showed that BMI (β=0.455, R^2=0.207, p<0.001) was an independent predictor of serum CRP levels in kidney transplantation patients (Table 4).

4. Discussion

The results of our study showed that CRP level was positively associated with metabolic syndrome in kidney transplantation patients. BMI was an independent predictor of serum CRP levels in these patients.

Metabolic syndrome is a constellation of physical and laboratory abnormalities including hypertension, hyperglycemia, hyperlipidemia, and abdominal obesity [6]. It constitutes a major health problem in the West and is estimated to affect at least 20% of the adult population [17]. Post-transplant metabolic syndrome is comprised of hypertension, dyslipidemia, increased fat mass/obesity, and glucose intolerance, combined with other metabolic side effects derived from glucocorticoid and calcineurin inhibitor immunosuppression [10]. Tacrolimus use is also a risk factor for insulin resistance in kidney transplant recipients [9]. The prevalence of metabolic syndrome in the present study was 23.6%. These findings are in agreement with other studies in Asia [18,19], which reported prevalences ranging from 23.8% to 26.0% for subjects in Japan and Hong Kong.

CRP is an acute phase marker whose blood levels depend on interleukin-6 and other inflammatory proteins that stimulate its production in hepatocytes, lymphocytes, alveolar macrophages and monocyte-derived macrophages [20]. CRP impairs insulin signaling, contributes to atherothrombosis, and is associated with insulin resistance, adiposity and metabolic syndrome [21]. High CRP levels have been related to risk factors for dyslipidemia, hypertension, diabetes mellitus, and obesity [22].

CRP concentration is directly related to the volume of visceral fat as determined by magnetic resonance imaging [23]. Abdominal adiposity was associated with significantly elevated CRP values in non-obese people [24]. A higher BMI as well as central obesity were independently associated with higher levels of CRP in Taiwan [25]. BMI, body weight and fat mass also correlated positively with serum CRP in kidney transplantation patients [26]. Another study noted that waist circumference was an independent determinant of CRP in renal transplant recipients [27]. Our study noted that body weight, waist circumference, BMI, and body fat mass were positively correlated with fasting serum CRP levels in kidney transplantation patients. CRP concentration had no correlation with HDL cholesterol, triglycerides, fasting glucose, age, kidney transplantation duration, albumin, globulin or total cholesterol in our study. Multivariate forward stepwise linear regression analysis of the significant variables showed that BMI was an independent predictor of fasting serum CRP levels in our study.

Pharmacological interventions have been shown to influence serum CRP levels in humans. A meta-analysis showed that statins can reduce serum CRP levels,

Table 2 — Clinical characteristics and fasting serum C-reactive protein (CRP) levels of the 55 kidney transplantation patients

	n (%)	CRP (mg/dL)	*p*
Sex			
Male	27 (49.1)	0.23±0.32	0.852
Female	28 (50.9)	0.32±0.46	
Diabetes			
No	38 (69.1)	0.25±0.38	0.380
Yes	17 (30.9)	0.33±0.44	
Hypertension			
No	21 (38.2)	0.13±0.14	0.187
Yes	34 (61.8)	0.37±0.48	
Hyperlipidemia			
No	38 (69.1)	0.19±0.25	0.394
Yes	17 (30.9)	0.34±0.48	
Metabolic syndrome			
No	42 (76.4)	0.18±0.32	0.001*
Yes	13 (23.6)	0.58±0.49	
Angiotensin receptor blocker use			
No	33 (60.0)	0.18±0.26	0.141
Yes	22 (40.0)	0.43±0.53	
Calcium channel blocker use			
No	33 (60.0)	0.21±0.35	0.230
Yes	22 (40.0)	0.37±0.46	
β-blocker use			
No	49 (89.1)	0.24±0.32	0.553
Yes	6 (10.9)	0.54±0.79	
Statin use			
No	38 (69.1)	0.21±0.30	0.076
Yes	17 (30.9)	0.42±0.54	
Sulfaurea use			
No	45 (81.8)	0.27±0.39	0.403
Yes	10 (18.2)	0.32±0.43	
Metformin use			
No	49 (89.1)	0.27±0.38	0.948
Yes	6 (10.9)	0.33±0.54	
Insulin use			
No	48 (87.3)	0.27±0.39	0.757
Yes	7 (12.7)	0.33±0.49	
Cyclosporine use			
No	42 (76.4)	0.21±0.30	0.889
Yes	13 (23.6)	0.42±0.54	
Tacrolimus use			
No	19 (34.5)	0.31±0.45	0.741
Yes	36 (65.5)	0.26±0.37	
Mycophenolate mofetil use			
No	36 (65.5)	0.27±0.40	0.950
Yes	19 (34.5)	0.29±0.41	
Mycophenolic acid use			
No	34 (61.8)	0.34±0.47	0.237
Yes	21 (38.2)	0.17±0.22	
Steroid use			
No	17 (30.9)	0.25±0.34	0.732
Yes	38 (69.1)	0.29±0.43	
Rapamycin use			
No	48 (87.3)	0.26±0.37	0.861
Yes	7 (12.7)	0.37±0.58	
Hepatitis B			
No	47 (85.5)	0.31±0.42	0.206
Yes	8 (14.5)	0.10±0.11	
Hepatitis C			
No	52 (94.5)	0.29±0.41	0.087
Yes	3 (5.5)	0.04±0.02	

*$p<0.05$, Mann-Whitney U test.

Table 3 — Correlation between fasting serum C-reactive protein levels and clinical variables in the 55 kidney transplantation patients by univariate linear regression analysis

	β	*p*
Age (yr)	−0.200	0.143
Kidney transplantation duration (mo)	−0.127	0.355
Height (cm)	0.124	0.367
Body weight (kg)	0.421	0.001*
Waist circumference (cm)	0.355	0.008*
BMI (kg/m^2)	0.455	<0.001*
Body fat mass (%)	0.275	0.042*
Albumin (g/dL)	0.022	0.876
Globulin (g/dL)	0.120	0.397
GOT (IU/L)	−0.176	0.198
GPT (IU/L)	−0.174	0.204
Total cholesterol (mg/dL)	0.137	0.317
Triglyceride (mg/dL)	0.261	0.054
HDL cholesterol (mg/dL)	−0.100	0.466
Fasting glucose (mg/dL)	0.006	0.964
Creatinine (mg/dL)	0.108	0.434
WBC (×1000/μL)	0.166	0.225

*$p<0.05$. BMI=body mass index; GOT=glutamic oxaloacetic transaminase; GPT=glutamic pyruvic transaminase; HDL=high-density lipoprotein; WBC=white blood cell count.

Table 4 — Multivariate stepwise linear regression analysis of body weight, waist circumference, body mass index, and body fat mass: correlation with fasting serum C-reactive protein levels in the 55 kidney transplantation patients

	β	R^2	*p*
Body mass index (kg/m^2)	0.455	0.207	<0.001*

*$p<0.05$.

independent of the type and dose of statin used [28]. However, one study showed that atorvastatin 10 mg/day did not alter CRP levels after 3 months of treatment in kidney transplant recipients [29]. PPAR-α activation by fibrates also impairs proinflammatory cytokine-signaling pathways in the liver, resulting in the modulation of the acute phase response reaction via mechanisms independent of changes in lipoprotein levels [30]. PPAR-γ agonist treatment results in decreased plasma levels of CRP in both obese patients and patients with type 2 diabetes [31]. In one study, CRP level was significantly decreased in kidney transplantation patients who used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [32]. Mycophenolate mofetil use correlates inversely with CRP levels in renal transplant recipients [33]. None of our study patients used angiotensin-converting enzyme inhibitors, PPAR-γ agonists or fibrates. Our results did not show a relationship between any drug therapy and serum CRP concentration in kidney transplantation patients.

There were some limitations in our study. First, this study had a cross-sectional design. Therefore, our findings should be investigated in long-term prospective studies before a causal relationship between serum CRP and metabolic syndrome in kidney transplantation patients can be established. Second, there was a lack of serum insulin or insulin resistance in this study. Another limitation is that this study did not check other inflammatory markers such as tumor necrosis factor-α, interleukin-6 and interleukin-12. Further studies are needed to show the association between metabolic syndrome and serum CRP levels in kidney transplantation patients.

In conclusion, serum CRP concentration correlates positively with metabolic syndrome in kidney transplantation patients. BMI was an independent predictor of serum CRP levels in kidney transplantation patients.

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