Observational study of metabolic syndrome among renal transplant recipients in Kasr Al-Aini School of Medicine: a single-center study

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Received 13 December 2015
Accepted 3 November 2016

Kasr Al Ainy Medical Journal
2017, 23:12–17

Introduction
The metabolic syndrome (MS) is a constellation of clinical abnormalities related to insulin resistance and inflammation. The syndrome is now recognized as a risk factor for diabetes and cardiovascular disease in the general population. Recent studies suggest that MS is common after kidney transplantation, also possibly being predictive of allograft loss and poor allograft function.
Objectives
We studied the prevalence of MS in Egyptian kidney transplant recipients (from Kasr Al-Aini School of Medicine) and its correlation with C-reactive protein (CRP), serum uric acid (UA), alkaline phosphatase (ALP), different immunosuppressive intakes, and hepatitis C virus (HCV) in these patients.
Patients and methods
The present cross-sectional study was conducted in 2012 on 100 renal transplant recipients, 68 male (68%) and 32 female (32%), with stable kidney function (serum creatinine=1.5±1 mg/dl) in King Fahd Unit, Cairo University. All clinical and laboratory data were recorded, including serum creatinine, UA, cholesterol, triglyceride (TGL), low-density lipoprotein, high-density lipoprotein (HDL), ALP, CRP, and HCV Abs. The presence of MS was determined using NCEP-ATP III criteria, with BMI used in place of waist circumference.
Results
Patients were divided into two groups – MS (group 1): 26 patients, 12 female (46.2%) and 14 male (53.8%), with a mean age of 34.46±9.69 years; and non-MS (group 2): 74 patients, 20 female (27%) and 54 male (73%), with a mean age of 27± 8.33 years. There was a highly significant correlation ($P \leq 0.001$) between CRP and MS, BMI and diabetes mellitus, whereas the correlation between CRP and hypertension, ALP, HCV Abs, alanine aminotransferase (ALT), TGLs level, and HDL was insignificant.
Conclusion
Metabolic syndrome is prevalent in post-renal transplant patients. Serum CRP concentration correlates positively with metabolic syndrome in kidney transplantation patients. The age, weight, BMI, systolic and diastolic BP, serum triglycerides, ALT of MS group were significantly higher than in non-MS group. The duration of hypertension in the MS cases was significantly longer than in non-MS cases.

Keywords:
BMI, cholesterol, C-reactive protein, metabolic syndrome, renal transplant recipient

Kasr Al Ainy Med J 23:12–17

1687-4625

Introduction

The association between obesity, metabolic abnormalities such as hyperglycemia, dyslipidemia, and cardiovascular disease (CVD) has been described almost 100 years ago and later on confirmed in the first reports from the Framingham study. In the late 80s of XX century, Reaven described a pathological link explaining the pathogenesis of CVD associated with obesity, metabolic abnormalities, and elevated blood pressure (BP), and indicated the central role of hyperinsulinemia and insulin resistance. The first name of this abnormality was syndrome X; the other names used were as follows: cardiometabolic syndrome, Reaven's syndrome, beer belly syndrome, cardiovascular dysmetabolic syndrome, insulin resistance syndrome, and, most commonly used nowadays, metabolic syndrome (MS) [1].

According to the few data available, MS increases every year following renal transplantation, and it may be an

 DOI: 10.4103/1687-4625.207189

independent risk factor for chronic allograft dysfunction. Immunosuppressant drugs, new-onset diabetes mellitus (DM) following renal transplantation, pretransplant hemodialysis, and post-transplant weight gain have been implicated in the contribution of MS [2]. Recent studies showed that C-reactive protein (CRP), hepatitis C virus (HCV), serum uric acid (UA), and serum alkaline phosphatase (ALP) have a direct association with MS in renal transplant recipients [3].

Aim of the work

The aim of this work was to study the prevalence of MS in Egyptian kidney transplant recipients from Kasr Al-Aini School of Medicine, as well as to study the correlation between MS and CRP, serum UA, ALP, different immunosuppressive intakes, and HCV in these patients.

Patients and methods

We included 100 stable renal transplant recipients attending the outpatient clinic in Kasr Al-Aini Hospitals (King-Fahd Unit). The patients met the following inclusion criteria:

(1) Absence of DM before transplantation.
(2) Stable renal function at 1 year after transplantation.

They were 68 male (68%) and 32 female (32%) patients.

The diagnosis of the MS was established using an adapted version of the US National Cholesterol Educational Program Definition (Adult Treatment Panel III) [4].

A patient was classified as having MS if at least three of the following criteria were present:

(1) BMI greater than 30 kg/m^2.
(2) Serum triglyceride (TGL) greater than 150 mg/dl.
(3) High-density lipoprotein (HDL) cholesterol levels below 40 mg/dl in men and below 50 mg/dl in women.
(4) BP greater than 130/85 mmHg.
(5) Fasting glucose level greater than 110 mg/dl.

Patients included in the study were classified into two groups:

MS group (group 1): This group fulfilled the criteria of MS, and it included 26 patients, 12 female (46.2%) and 14 male (53.8%). Their ages ranged between 23 and 51 years. The mean age for the MS group was 34.46±9.69 years.

Non-MS group (group 2): This group included 74 patients, 20 female (27%) and 54 male (73%). Their ages ranged between 12 and 54 years. The mean age for non-MS group was 27±8.33 years.

Relevant information about recipients and transplant characteristics was taken directly from patients and patients' files.

Informed consent was obtained from every patient.

The study was conducted in accordance with local ethical committee regulations and to standards set by faculty of medicine, Cairo University.

Methods

A full clinical history was taken and a complete clinical examination was performed for every patient.

Fasting blood samples were taken from patients for the following tests:

Blood urea nitrogen, serum creatinine, UA, fasting blood sugar, CRP, ALP, serum TGL, serum cholesterol, HDL, low-density lipoprotein (LDL), aspartate amino-transferase (AST), alanine aminotransferase (ALT), serum albumin, and HCV (Ab) by enzyme-linked immunosorbent assay.

Anthropometric data

All anthropometric measurements were made by a single investigator. Height was documented for each participant. Waist circumference (at the umbilicus) and hip circumference (at the level of the greater trochanter) were measured using a standard tape measure. BMI was calculated.

Statistical methods

Data were statistically described in terms of minimum, maximum, mean, and SD for quantitative variables and frequencies (number of cases) and relative frequencies (percentages for categorical variables). Comparison of quantitative variables was done using Mann–Whitney test. For comparing categorical data, χ^2-test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation was performed to test for linear relations between variables by Spearman's correlation coefficient. A probability value (P value less than 0.05 was considered statistically significant. All statistical calculations were performed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA version 16).

Results

The age, weight, BMI, and systolic and diastolic BP of the MS group were significantly higher (*P*=0.011, 0.001, 0.002, 0.046, 0.003) than in the non-MS group. The duration of hypertension in the MS cases was significantly longer than in non-MS cases (*P*=0.013). CRP, serum TGL, and ALT were significantly higher in the MS group cases (*P*=0.001, 0.006, 0.006, 0.047) respectively, whereas HDL was significantly lower compared with non-MS-group cases (*P*=0.006) (Table 1).

Table 2 shows the comparison between MS and non-MS regarding the presence of DM. There was a significant difference regarding the presence of DM between the non-MS group and the MS group. In the non-MS cases, DM was present in four of 74 cases (5.4%), whereas DM was present in eight of 26 MS cases (30.8%). The difference was significant (*P*=0.033).

Table 3 shows a highly significant correlation between CRP and MS (*P*=0.001), BMI (*P*=0.005) and DM (*P*=0.003), while the correlation between CRP and HTN (*P*=0.051), triglyceride level (*P*=0.248) and HDL (*P*=0.094) was insignificant. There was a highly significant correlation between uric acid and triglyceride level (*P*=0.001) and HDL (*P*=0.002), while the correlation between uric acid MS (*P*=0.451), BMI (*P*=0.267), HTN (*P*=0.756) and DM (*P*=0.368) was not significant. There was no correlation between alkaline phosphatase and MS (*P*=0.207), BMI (*P*=0.367), hypertension (*P*=0.914), TG (*P*=0.057), HDL (*P*=0.282) and DM (*P*=0.267). There was a significant correlation between HCV and TG level (*P*=0.033), while there was no correlation between HCV and MS (*P*=0.834), BMI (*P*=0.787), hypertension (*P*=0.666) and HDL (*P*=0.530).

Discussion

In the present cross-sectional study, the incidence of MS was 26% of recipients, which was lower compared with other studies (37.7%) [5].

A study by Cheung *et al.* [6] in 121 Chinese renal transplant patients reported a 26% prevalence of MS (using the International Diabetes Federation, IDF criteria), which was similar to our findings. Another

Table 1 Comparison between quantitative data in both groups

	Metabolic syndrome		Nonmetabolic syndrome		
	Mean	SD	Mean	SD	*P* value
Age (years)	34.46	9.69	27	8.33	0.011
Height (cm)	163.46	3.1	161.19	8.43	0.373
Weight (kg)	78.62	14.91	62.73	12.78	0.001
BMI (kg/m^2)	29.46	5.11	24.08	4.32	0.002
DM duration (years)	3.75	1.71	0.04	0.06	0.064
HTN duration (years)	10.54	7.04	4.85	3.21	0.013
Systolic BP (mmHg)	139.17	13.11	130	13.61	0.046
Diastolic BP (mmHg)	83.33	6.51	77.04	4.65	0.003
Transplantation duration (months)	67.31	57.22	54.49	38.11	0.328
CRP (mg%)	16.46	18.14	5.78	3.19	0.001
ALP (U/l)	89.77	32.99	110.38	64.87	0.203
Uric acid (mg/dl)	5.79	1.7	6.28	1.73	0.445
FBS (mg/dl)	80.23	9.64	81.65	14.79	0.938
TGL (mg/dl)	210.08	125.01	145.84	91.81	0.006
HDL (mg/dl)	35.08	12.55	45.95	12.54	0.006
LDL (mg/dl)	120.15	43.4	111.19	39.55	0.507
Cholesterol (mg/dl)	198.15	55.38	186.78	54.62	0.558
Urea (mg/dl)	57.62	27.33	49.3	23.15	0.232
Creatinine (mg/dl)	1.5	0.53	1.35	0.5	0.314
AST (U/l)	22.77	10.51	25.38	17.73	0.458
ALT (U/l)	15.62	5.82	12.23	2.52	0.047
Albumin (g/dl)	3.93	0.64	4.24	0.48	0.146
Steroids (mg/day)	10.58	6.78	7.03	2.69	0.211
Hemodialysis before transplantation (months)	8.92	8.58	14.41	15.77	0.204

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; DM, diabetes mellitus; FBS, fasting blood sugar; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; TGL, triglyceride.

study by Naganuma *et al.* [7] in 101 Japanese renal transplant patients found that 15.8% of them had MS (using the IDF criteria).

The rate of incidence of recipients meeting each factor of the criteria for MS was also different from other reports. De Vries *et al.* [8] reported that the rate of prevalence of meeting MS criteria for waist circumference, TGL, HDL, BP, and fasting plasma glucose was 51, 60, 62, 88, and 10%, respectively. The incidence of obesity and hypertriglyceridemia and low HDL reported in that study was different from the results in our study (22, 40, 50%), whereas the incidence of hypertension and elevated fasting blood sugar was nearly similar (80 and 12%). We suggest that ethnicity differences might have contributed to those differences.

In our study, comparing non-MS cases and MS cases, there was a significant difference in age, weight, BMI, hypertension, hypertension duration, CRP, serum TGL, HDL, and ALT. However, there was no statistically significant difference between both groups with regard to sex, duration of DM, transplant duration, ALP, UA, LDL, serum cholesterol, blood urea, serum creatinine, AST, serum albumin, and dialysis duration before transplantation.

The age of MS cases was significantly higher than in non-MS cases (P=0.011). This is in agreement with the findings of Kishikawa *et al.* [9]. On the contrary, Faenza *et al.* [10] found no difference in age distribution between MS and non-MS cases. This may be because our study was a cross-sectional study.

Table 2 Diabetes mellitus cross-tabulation

	DM			
	No	Yes	Total	*P* value
Non-MS				
Count	70	4	74	0.033
% within metabolic	94.6%	5.4%	100.0%	
% within DM	79.5%	33.3%	74.0%	
Metabolic syndrome				
Count	18	8	26	
% within metabolic	69.2%	30.8%	100.0%	
% within DM	20.5%	66.7%	26.0%	
Total				
Count	88	12	100	
% within metabolic	88.0%	12.0%	100.0%	
% within DM	100.0%	100.0%	100.0%	

DM, diabetes mellitus; MS, metabolic syndrome.

Table 3 Correlation between CRP, uric acid, alkaline phosphatase and HCV with each of the following: MS, BMI, HTN, elevated triglyceride, low HDL and DM

			CRP	Uric acid	ALP	HCV
Spearman's rho	MS	R	.460**	-.109-	-.182-	.030
		P value	.001	.451	.207	.834
		N	50	50	50	50
	BMI	R	.392**	.160	-.130-	.039
		P value	.005	.267	.367	.787
		N	50	50	50	50
	Hypertension	R	.278	-.045-	-.016-	.062
		P value	.051	.756	.914	.666
		N	50	50	50	50
	TGL	R	.166	.449**	.271	.302*
		P value	.248	.001	.057	.033
		N	50	50	50	50
	HDL	R	-.240-	.436**	.155	.091
		P value	.094	.002	.282	.530
		N	50	50	50	50
	DM	R	.416**	-.130-	.160	-.277-
		P value	.003	.368	.267	.052
		N	50	50	50	50

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

No significant difference in sex distribution between MS and non-MS cases was observed, which is in agreement with the results of Faenza and colleagues. However, these results disagree with those of Landecho *et al.* [11], who found that MS was significantly higher in male patients than in female patients, in a study of 1498 patients.

The weight and BMI of MS cases in our study were significantly higher (P=0.001 and 0.002) than in non-MS cases, which agrees with the results of Kishikawa *et al.* [9] and Landecho *et al.* [11], yet it does not agree with the results of Faenza *et al.* [10], who did not find any significant difference in BMI between both groups.

The duration of hypertension in MS cases was significantly longer than in non-MS cases (P=0.0013). The systolic and diastolic BP were significantly higher in the metabolic group cases (P=0.046 and 0.003) than in nonmetabolic group cases, which is in agreement with the study of Landecho *et al.* [11]. However, Kishikawa *et al.* [9] and Faenza *et al.* [10] found no significant difference in systolic and diastolic BP between MS and non-MS cases.

There was no significant difference between MS cases and non-MS cases as regards duration of dialysis before transplantation (P=0.204). Similar findings were found by Faenza *et al.* [10].

In our results, we had contradictory findings to that of Naganuma *et al.* [7], with higher BMI, BP, and TGL levels in the MS group compared with his findings with lower BMI, BP, and TGL levels in his group of MS patients. We both had similar results in finding lower HDL levels in the MS group. Although insignificant and not included in the criteria of diagnosing MS, serum LDL was higher in our MS cases compared with non-MS cases.

The effects of immunosuppressive agents on adiposity, which have not been included in this study, may have played a role in the results of this study.

We noted significantly higher CRP level with positive correlation in the MS group cases compared with non-MS group cases (P=0.001).

A higher BMI and central obesity were independently associated with higher levels of CRP in a study conducted in Taiwan by Kao *et al.* [12]. Ewers *et al.* [13] noted that BMI, body weight, and fat mass also correlated positively with serum CRP in kidney transplant patients. Another study by Van Ree *et al.* [14] noted that waist circumference was an independent determinant of CRP in renal transplant recipients.

In our cases, BMI was positively correlated with serum CRP levels (P=0.005) and DM in kidney transplant patients (P=0.003). However, CRP concentration had no correlation with HDL, cholesterol, and TGLs.

Pharmacological interventions have been shown to influence serum CRP levels in humans. A meta-analysis by Genser *et al.* [15] showed that statins can reduce serum CRP levels, independent of the type and dose of statin used. PPAR-γ activation by fibrates also impairs proinflammatory cytokine-signaling pathways in the liver, resulting in the modulation of the acute-phase response reaction through mechanisms independent of changes in lipoprotein levels [16]. PPAR-γ agonist treatment results in decreased plasma levels of CRP in both obese and type 2 DM patients [17]. In one study by Argani *et al.* [18], CRP level was significantly decreased in kidney transplantation patients who used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Wong *et al.* [19] showed that mycophenolate mofetil use correlates inversely with CRP levels in renal transplant recipients. However, in our study, there was no significant difference between MS and non-MS cases as regards the use of mycofenolate mofetil (MMF), β-blockers, steroids, and calcium-channel blockers. None of our study patients used Angiotensin Converting Enzyme (ACE) inhibitors, PPAR-γ agonists, or fibrates.

Kerner *et al.* [20] found that elevation of liver enzymes was associated with higher CRP concentrations. We compared MS cases and non-MS cases as regards AST and ALT where we noted a statistically insignificant difference in the former, whereas the latter was statistically significantly higher in the MS group (P=047).

Hepatic inflammation secondary to liver steatosis associated with obesity is a potential contributor to the low-grade inflammation associated with the MS. Our MS cases had a significantly higher BMI and body weight. This may explain the elevated ALT level in the MS cases and the relation between CRP and AST/ALT. The difference in ALT between MS cases and non-MS cases cannot be attributed to HCV positivity, as the difference between both groups as regards HCV positivity was insignificant (P=1.00).

As it was reported that MS in transplant recipients has numerous detrimental effects such as the increased risk

of new-onset diabetes, CVD events and patient death, accelerated loss of graft function, proteinuria, and ultimately graft loss [21], randomized clinical trials should be conducted to define whether interventions on each MS component would result in better outcomes after transplantation [22].

Conclusion

(1) MS is prevalent in post-renal-transplant patients.
(2) Serum CRP concentration correlates positively with MS in kidney transplantation patients.
(3) The age, weight, BMI, systolic and diastolic BP, serum TGLs, and ALT of MS group were significantly higher than in the non-MS group.
(4) The duration of hypertension in the MS cases was significantly longer than in non-MS cases.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Litwin M, Niemirska A. Metabolic syndrome in children with chronic kidney disease and after renal transplantation. Pediatr Nephrol 2014; 29:203–216.

2 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120:1640–1645.

3 Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001; 286:64–70.

4 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109:433–438.

5 Porrini E, Delgado P, Bigo C, Alvarez A, Cobo M, Checa MD, *et al.* Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. Am J Kidney Dis 2006; 48:134–142.

6 Cheung CY, Chan HW, Liu YL, Chan YH, Wong HS, Chak WL, *et al.* Prevalence of metabolic syndrome in Chinese renal transplant recipients. Hong Kong Med J 2008; 14:379–384.

7 Naganuma T, Uchida J, Kinoshita Y, Kuroki Y, Takemoto Y, Yoshimura R, *et al.* The prevalence of metabolic syndrome in Japanese renal transplant recipients. Nephrology (Carlton) 2007; 12:413–417.

8 De Vries AP, Bakker SJ, van son WJ, van der Heide JJ, Ploeg RJ, The TH, *et al.* Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. Am J Transplant 2004; 4:1675–1683.

9 Kishikawa H, Nishimura K, Kato T, Kobayashi Y, Arichi N, Okuno A, *et al.* Prevalence of the metabolic syndrome in kidney transplantation, Transplant Proc 2009; 41:181–183.

10 Faenza A, Fuga G, Nardo B, Donati G, Cianciolo G, Scolari MP, Stefoni S. Metabolic syndrome after kidney transplantation. Transplant Proc 2007; 39:1843–1846.

11 Landecho MF, Colina I, Huerta A, Fortuno A, Zalba G, Beloqui O. Connection between the early phases of kidney disease and the metabolic syndrome. Rev Esp Cardiol 2011; 64:373–378.

12 Kao TW, Lu IS, Liao KC, Lai HY, Loh CH, Kuo HK. Associations between body mass index and serum levels of C-reactive protein. S Afr Med J; 99:326–30. Semin Immunopathol 2009; 31:79–94.

13 Ewers B, Gasbjerg A, Zerahn B, Marckmann P. Impact of vitamin D status and obesity on C-reactive protein in kidney transplant patients. J Ren Nutr 2008; 18:294–300.

14 Van Ree RM, de Vries AP, Oterdoom LH, *et al.* Abdominal obesity and smoking are important determinants of C-reactive protein in renal transplant recipients. Nephrol Dial Transplant 2005; 20:2524–2531.

15 Genser B, Grammer TB, Stojakovic T, Siekmeier R, Murz W. Effect of HMG CoA reductase inhibitors on low-density lipoprotein cholesterol and C-reactive protein: systematic review and meta-analysis. Int J Clin Pharmacol Ther 2008; 46:497–510.

16 Zambon A, Gervois P, Pauletto P, Fruchart JC, Staels B. Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-alpha activators: clinical and experimental evidence. Arterioscler Thromb Vasc Biol; 2006; 26:977–986.

17 Consoli A, Devangelio E. Thiazolidinediones and inflammation. Lupus 2005; 14:794–797.

18 Argani H, Ghorbanihaghjo A, Aghaeishahsavari M, Noroozianavval M, Rashtchizadeh N, Veisi P, *et al.* Effects of losartan and enalapril on high-sensitivity C-reactive protein and total antioxidant in renal transplant recipients with renin-angiotensin system polymorphisms. Transplant Proc 2008; 40:16–21.

19 Wong BM, Huang M, Zaltzman JS, Prasad GV. Mycophenolate mofetil and C-reactive protein in renal transplant recipients. Transplantation 2007; 83:48–53.

20 Kerner A, Avizohar O, Sella R, Bartha P, Zinder O, Markiewicz W, *et al.* Association between elevated liver enzymes and C-reactive protein. Possible hepatic contribution to systemic inflammation in the metabolic syndrome. Arterioscler Thromb Vasc Biol 2005; 25:193–197.

21 Wissing KM, Pipeleers L. Obesity metabolic syndrome and diabetes mellitus after renal transplantation: prevention and treatment. Transplant Rev 2014; 28:37–46.

22 Pedrollo EF, Corea C, Nicoletto BB, Manfro RC, Leitao CB, Souza GC, Goncalves LF. Effects of metabolic syndrome on kidney transplantation outcomes: a systemic review and meta- analysis. Transpl Int 2016; 29:1059–1066.