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Mediterranean diets are associated with a lower incidence of metabolic syndrome one year following renal transplantation

Mohsen Nafar[1], Nazanin Noori[2], Sara Jalali-Farahani[2], Farhad Hosseinpanah[2], Fatemeh Poorrezagholi[1], Pedram Ahmadpoor[1], Fariba Samadian[1], Ahmad Firouzan[1] and Behzad Einollahi[3]

[1]Department of Kidney Transplantation, Shahid Labbafinejad Medical Center, Shahid Beheshti University, MC, Tehran, Iran; [2]Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University, MC, Tehran, Iran; [3]Nephrology Research Center, Baqiyatallah Hospital, Shahid Beheshti University, MC, Tehran, Iran

Considering the high prevalence of metabolic syndrome and its association with cardiovascular mortality, we prospectively evaluated the role of diet in the incidence of metabolic syndrome in renal transplant recipients. Our prospective cohort of 160 adult renal allograft recipients was followed for 1 year and had no existing metabolic syndrome or diabetes mellitus. Routine dietary intakes were assessed with food-frequency questionnaires, and metabolic syndrome was defined according to the Adult Treatment Panel III guidelines. We identified 3 major patterns by factor analysis, consisting of those recipients predominantly consuming fats and sugars, those predominantly consuming whole grain, and the Mediterranean diet. When analyzed by multivariable logistic regression and after controlling for potential confounders, subjects in the highest tertile of scores for the Mediterranean diet had a significantly lower odds of metabolic syndrome than those in the lowest tertile. Subjects in the highest tertile of scores for consuming fats and sugars had significantly greater odds of metabolic syndrome compared with those in the lowest tertile. Our study shows that the Mediterranean dietary pattern is associated with a reduced risk of metabolic syndrome in renal transplant recipients.

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Correspondence: *Mohsen Nafar, Department of Kidney Transplantation, Shaheed Labbafinejad Medical Center, Shahid Beheshti University, MC, Tehran 1666694516, Islamic Republic of Iran.*
E-mail: nafar@sbmu.ac.ir

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Cardiovascular diseases (CVD) contribute to 47% of all deaths in renal transplant recipients.[1] Compared with the general population, renal transplant recipients aged 25–34 years have a 10-fold higher risk of death from CVD.[2,3] This may be due in part to the increased cardiovascular (CV) risk associated with immunosuppressive medications.[4] Central to the development of CVD in renal transplantation are weight gain, hyperlipidemia, hypertension (HTN), and glucose intolerance, which characterize the metabolic syndrome (MS).[5] Apart from contributing to post-transplantation cardiovascular mortality, and morbidity, detecting the MS has also been proposed as an underlying transplantation-related risk factor for chronic renal allograft dysfunction.[6] Although several studies have evaluated the adverse effect of immunosuppressive agents in transplant recipients,[7] few have assessed the effects of diet. For instance calcineurin inhibitors cause post-transplant diabetes mellitus (DM), hypercholesterolemia, and HTN.[8] Sirolimus has hyperlipidemic effects, accelerating both hypercholesterolemia, and hypertriglyceridemia and corticosteroids can cause the worst CV risk profile, as they induce many metabolic effects including HTN, new onset DM after transplantation, hypercholesterolemia, and weight gain.[4] Corticosteroids may also have an important role in the incidence of post-transplant MS. The incidence of MS in renal transplant recipients has been reported to be 57% 1-year post-transplant.[9] The MS is a multi-factorial disorder, and diet has an important role in its development.[10] Diet can be considered in terms of dietary patterns, an approach that has been used to investigate diet–disease relations.[11–13] Dietary patterns address the effect of the diet as a whole and thus may provide insight beyond the effects described for single nutrients or foods.[11]

As no study has evaluated the impact of food pattern on MS incidence in renal transplant recipients, considering high prevalence potential and the CVD mortality associated with MS, we prospectively evaluated the potential role of food pattern on the incidence of MS at 1 year after transplant.

RESULTS

A total of 160 renal transplant recipients (100 male and 60 female recipients) who completed the FFQ in 2004–2007,

participated in the final analysis. Mean age and body mass index (BMI) of our participants at baseline were 40 ± 13 years and 22 ± 4 kg/m^2, respectively. The coefficient tau-b between waist circumference (WC) and BMI was also high (0.72) and statistically significant ($P<0.001$). During the 1-year follow-up period, we had 56 (35%) and 58 (36%) incident MS based on high BMI and high WC (including imputed WCs), respectively. With regard to factors associated with the MS, 101 patients (63%) presented with hypertriglyceridemia or required specific treatment for this lipid abnormality, 92 (58%) had low high-density lipoprotein (HDL) levels or required specific treatment for this lipid abnormality, 83 (52%) had HTN or required the use of antihypertensive medication, 29 (18%) had high BMI and 27 patients (17%) had high fasting glucose levels or required the use of anti-diabetic medication during the 1-year follow-up period. So a high triglyceride level was the most prevalent component.

As people do not eat isolated nutrients but foods with combinations of nutrients and because of the high level of intercorrelation among some nutrients makes it difficult to examine their separate effects and 'single nutrient' analysis may potentially be confounded by the effect of dietary patterns, it has recently been proposed to study overall dietary patterns by factor analysis which would parallel more closely the real world.[14] Factor analysis is a multivariate statistical technique, which uses information reported on food-frequency questionnaires[14] to identify patterns of food consumption. It aggregates specific food items on the basis of the degree to which food items in the dataset are correlated with one another (Table 1) to characterize the eating behavior. Three major dietary patterns were identified and labeled; the fats and sugars, the whole grain, and the Mediterranean dietary patterns on the basis of food groups with high factor loadings. The factor-loading matrixes for these dietary patterns are shown in Table 2. Other minor

Table 2 | Factor-loading matrix for major dietary patterns[a]

	Dietary pattern		
Food group	Fats and sugars	Whole grain	Mediterranean
High-fat dairy	0.57	—	—
Rice	0.56	—	—
Soft drinks	0.55	—	—
Confectionary	0.53	—	—
Salty snacks	0.50	−0.41	—
Saturated fats	0.47	—	—
Pizza	0.42	—	—
Poultry	0.39	0.30	0.22
Refined grain	0.38	−0.27	—
Tea and coffee	0.32	—	—
Processed meat	0.31	—	—
Potatoes	0.31	—	—
Eggs	—	−0.67	—
Salt	—	−0.60	—
Polyunsaturated fats	—	−0.48	—
Whole grain	—	0.48	0.24
Red meat	—	−0.43	—
Legumes	0.27	−0.39	0.29
Nuts	—	−0.30	0.27
Vegetables	—	—	0.80
Fruits	0.26	—	0.60
Olives	−0.32	—	0.48
Fish	—	—	0.34
Low-fat dairy	—	—	0.25

[a]Values <0.20 were excluded for simplicity.

Table 1 | Food grouping used in the dietary pattern analyses

Food group	Food items and food preparations
High-fat dairy	High-fat milk, whole milk, chocolate milk, cream, high-fat yogurt, cream yogurt, cream cheese, other cheeses, ice cream, doogh (an Iranian yogurt drink with a composition similar to that of whole milk)
Low-fat dairy	Skim or low-fat milk, low-fat yogurt
Saturated fats	Butter, margarine, mayonnaise, animal oil
Polyunsaturated fats	Vegetable oils (except for olive oil)
Red meat	Beef, lamb, beef liver
Processed meat	Sausages, hamburgers
Poultry	Chicken with or without skin
Fish	Canned tunafish, other fish
Fruits	All types
Vegetables	All types (except for potato)
Potatoes	Boiled potato
Whole grain	Dark Iranian breads (barbari, taftoon, sangak), barley bread, popcorn, cornflakes, wheat germ, bulgur
Refined grain	White breads (lavash, baguettes), noodles, pasta, toasted bread, milled barley, sweet bread, white flour, starch, biscuits, cake
Rice	White rice
Olives	Olives, olive oils
Legumes	Beans, peas, lima beans, broad beans, lentils, soy
Nuts	All types
Soft drinks	Coke, Pepsi, other soft drinks, cordial, low-calorie colas, other low-calorie soft drinks
Confectionary	Chocolates, hard candy, jam, jelly, sugar, honey, gaz (an Iranian confectionery made of sugar, nuts, and tamarisk), confections
Salty snacks	Fried potatoes, chips
Pizza	Pizza
Eggs	Eggs
Salt	Salt
Tea and coffee	Tea and coffee

Table 3 | Descriptive characteristics and dietary intake of participants at baseline: ANOVA for quantitative variables and χ^2 test for qualitative variables

	Fats and sugars dietary pattern				Whole grain dietary pattern				Mediterranean dietary pattern			
	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P*-value	T1 (*n*=54)	T2 (*n*=53)	T3 (*n*=53)	*P*-value	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P*-value
Age (years)	42 ± 14[a]	41 ± 12	36 ± 12	NS	41 ± 12	38 ± 12	40 ± 15	NS	37 ± 13	42 ± 12	41 ± 14	NS
Men (%)	63	63	63	NS	63	63	63	NS	63	63	63	NS
Menopause (%)	38	33	16	NS	33	27	27	NS	33	33	22	NS
Current smoking (%)	2	0	8	NS	4	4	2	NS	2	6	2	NS
Heavy PA (%)	2	0	0	NS	0	2	0	NS	0	2	0	NS
Duration on dialysis (months)	12 ± 4	8 ± 2	10 ± 3	NS	10 ± 2	11 ± 3	11 ± 3	NS	13 ± 4	12 ± 2	7 ± 1	<0.05
Prednisolone dose (mg per year)	4089 ± 1736	3717 ± 1910	3536 ± 1957	NS	3394 ± 2125	3804 ± 1755	4129 ± 1677	NS	3681 ± 1952	3592 ± 1994	4061 ± 1660	NS
Family history of DM (%)	6	2	6	NS	0	6	8	<0.05	4	4	6	NS
TE (kcal/d)	2359 ± 668[b]	3136 ± 774[c]	4460 ± 1040	<0.01	3780 ± 1129[b]	3131 ± 1103	3072 ± 1275	<0.01	2588 ± 910[b]	3459 ± 1165	3912 ± 1149	<0.01
CHO (% of TE)	57 ± 7	58 ± 7	56 ± 8	NS	56 ± 6	57 ± 8	58 ± 7	NS	56 ± 7	58 ± 7	57 ± 7	NS
Pr (% of TE)	16 ± 2	16 ± 3	16 ± 3	NS	15 ± 2[b]	17 ± 3	17 ± 3	<0.01	17 ± 3	16 ± 3	17 ± 3	NS
Fat (% of TE)	26 ± 7	24 ± 6[d]	28 ± 8	<0.05	28 ± 8[d]	26 ± 6	24 ± 7	<0.05	26 ± 7	26 ± 8	26 ± 7	NS
Fiber (g/d)[e]	34 ± 13[b]	23 ± 9	20 ± 10	<0.01	23 ± 13	23 ± 12	29 ± 11[f]	<0.05	15 ± 5[b]	24 ± 8[c]	36 ± 12	<0.01
Cholesterol (mg/d)[e]	182 ± 83	201 ± 83	302 ± 119[b]	<0.01	279 ± 121[b]	216 ± 101	193 ± 88	<0.01	280 ± 122[c]	227 ± 106[g]	179 ± 73	<0.01

ANOVA, analysis of variance; CHO, carbohydrate intake; DM, diabetes mellitus; PA, physical activity; Pr, protein intake; T, tertile; TE, total energy intake.
[a]X ± s.d. (all such values).
[b]Significantly different from the other tertiles, $P<0.01$.
[c]Significantly different from the third tertile, $P<0.01$.
[d]Significantly different from the third tertile, $P<0.05$.
[e]Adjusted for age and energy intake.
[f]Significantly different from the other tertiles, $P<0.05$.
[g]Significantly different from the first tertile, $P<0.05$.

Table 4 | BMI, blood pressure, and biochemical characteristics of participants at baseline

	Fats and sugars dietary pattern				Whole grain dietary pattern				Mediterranean dietary pattern			
	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P*-value[a]	T1 (*n*=54)	T2 (*n*=53)	T3 (*n*=53)	*P*-value	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P*-value
BMI (Kg/m^2)	23.4 ± 3.4	22.4 ± 6.1	21.1 ± 3.6	NS	22.0 ± 2.1	23.5 ± 5.5	21.4 ± 3.3	NS	22.2 ± 2.4	21.2 ± 3.7	22.4 ± 4.2	NS
SBP (mm Hg)	117 ± 22	123 ± 26	115 ± 19	NS	116 ± 18	120 ± 25	116 ± 20	NS	109 ± 15	114 ± 15	129 ± 28	NS
DBP (mm Hg)	70 ± 12	70 ± 14	69 ± 11	NS	68 ± 13	73 ± 10	67 ± 13	NS	66 ± 13	68 ± 9	74 ± 12	NS
Cholesterol (mg/dl)	213 ± 50	258 ± 62	240 ± 86	NS	227 ± 28	240 ± 74	230 ± 74	NS	269 ± 84	208 ± 35	225 ± 63	NS
LDL.c (mg/dl)	110 ± 27	137 ± 29	123 ± 38	NS	141 ± 32	126 ± 27	109 ± 34	NS	112 ± 36	122 ± 27	129 ± 33	NS
HDL.c (mg/dl)	60 ± 24	59 ± 24	55 ± 16	NS	60 ± 16	58 ± 23	57 ± 20	NS	58 ± 23	53 ± 21	63 ± 19	NS
TG (mg/dl)	217 ± 102	173 ± 62	350 ± 311[b]	<0.01	220 ± 72	193 ± 101	315 ± 280	NS	323 ± 320	232 ± 102	196 ± 90	NS
FBS (mg/dl)	106 ± 46	86 ± 10	81 ± 6	NS	78 ± 6	85 ± 9	106 ± 46[b]	<0.01	88 ± 8	91 ± 25	100 ± 49	NS
Creatinine (mg/dl)	1.4 ± 0.4	1.2 ± 0.1	1.4 ± 0.3	NS	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.3	NS	1.4 ± 0.3	1.4 ± 0.5	1.2 ± 0.1	NS

BMI, body mass index; DBP, diastolic blood pressure; HDL.c, high-density lipoprotein cholesterol; LDL.c, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
[a]Analysis of covariance with Bonferroni correction. All values adjusted for age, sex, physical activity, smoking, menopausal status, total energy intake.
[b]Significantly different from the other tertiles, $P<0.01$.

dietary patterns were identified by factor analysis, but because of the small variances they explained, we did not consider them in subsequent analyses. The fats and sugars dietary pattern featured high consumption of high-fat dairy, rice, soft drinks, confectionary, salty snacks, saturated fats, pizza, poultry, refined grain, tea and coffee, processed meat, and potatoes. The whole grain dietary pattern was characterized by high consumption of whole grain products and Mediterranean dietary patterns by the higher consumption of legumes, nuts, vegetables, fruits, olives, fish, and low-fat dairy. On average, participants who more often followed the fats and sugars dietary pattern (highest tertile) compared with less often (lowest tertile) were more likely to report high intakes of total energy, percentage of fat, total cholesterol, and less fiber (Table 3). Conversely, participants who more often followed the whole grain diet (highest tertile) compared with less often (lowest tertile) were more likely to report lower dietary intake of total calories, percentage of fat, total cholesterol and a higher intake of protein and fiber (Table 3). Compared with participants in the lowest tertile, those in the highest tertile of the Mediterranean dietary pattern had significantly higher intakes of energy (ET) and fiber and lower intake of cholesterol. No significant differences were found in age, cumulative dose of steroid, and the distribution of menopause, current smoking, and heavy physical activity across tertile categories of dietary patterns. Blood pressure, BMI, and biochemical characteristics of study participants by tertiles of food patterns at baseline are shown in Table 4. In comparison with participants in the lowest tertile, those in the highest tertile of the fats and sugars and whole grain

Table 5 | Multivariate adjusted odds ratios (95% CIs) for metabolic syndrome (MS) across tertile (T) categories of dietary pattern scores

	Fats and sugars dietary pattern				Whole grain dietary pattern				Mediterranean dietary pattern			
	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P* for trend	T1 (*n*=54)	T2 (*n*=53)	T3 (*n*=53)	*P* for trend	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P* for trend
Odds ratios[a]												
Model 1	1.00	0.99 (0.42–2.32)	1.29 (0.54–3.06)	0.57	1.00	0.95 (0.40–2.20)	0.88 (0.38–2.04)	0.93	1.00	0.63 (0.27–1.48)	0.52 (0.21–1.24)	0.14
Model 2	1.00	1.00 (0.42–2.42)	1.21 (0.89–2.97)	0.18	1.00	0.85 (0.35–2.06)	0.80 (0.33–1.95)	0.63	1.00	0.58 (0.24–1.41)	0.45 (0.17–1.14)	0.09
Model 3	1.00	1.39 (0.53–3.62)	2.96 (1.10–7.85)	<0.05	1.00	0.76 (0.30–1.89)	0.70 (0.27–1.79)	0.46	1.00	0.57 (0.22–1.26)	0.44 (0.15-0.98)	<0.05
Model 4	1.00	2.66 (0.90–7.86)	6.38 (1.38–8.87)	<0.01	1.00	0.95 (0.35–2.54)	0.94 (0.35–2.52)	0.91	1.00	0.48 (0.17–1.31)	0.29 (0.11–0.90)	<0.05
Odds ratios[b]												
Model 1	1.00	0.82 (0.35–1.95)	1.35 (0.56–3.21)	0.50	1.00	0.88 (0.38–2.05)	0.79 (0.34–1.87)	0.60	1.00	0.61 (0.26–1.44)	0.55 (0.23–1.32)	0.18
Model 2	1.00	0.82 (0.34–1.99)	1.26 (0.51–3.09)	0.63	1.00	0.79 (0.33–1.91)	0.75 (0.31–1.82)	0.53	1.00	0.57 (0.23–1.38)	0.52 (0.21–1.10)	0.10
Model 3	1.00	1.11 (0.59–2.62)	2.26 (1.03–6.92)	<0.05	1.00	0.74 (0.30–1.86)	0.70 (0.28–1.78)	0.47	1.00	0.52 (0.21–1.24)	0.45 (0.16–0.97)	<0.05
Model 4	1.00	1.70 (0.60–4.78)	5.27 (2.11–9.75)	<0.01	1.00	0.91 (0.34–2.41)	0.90 (0.34–2.36)	0.84	1.00	0.44 (0.16–1.18)	0.30 (0.10–0.89)	<0.01

[a]Odds ratio of MS, defined as the presence of ⩾3 of the following components: Obesity (BMI⩾30 kg/m^2); low serum HDL cholesterol (<40 for men and <50 mg/dl for women) or specific treatment for this lipid abnormality; high serum triacylglycerol concentrations (⩾150 mg/dl) or specific treatment for this lipid abnormality; elevated blood pressure (⩾130/85 mm Hg) or use of antihypertensive medication; and abnormal glucose homeostasis (fasting plasma glucose ⩾110 mg/dl) or use of antidiabetic medication.
[b]Odds ratio of MS based on waist or imputed waist >102 cm for men and >88 cm for women.
Model 1, age and sex adjusted. Model 2, further adjusted for cigarette smoking (yes or no), physical activity, dialysis mode and its duration before transplantation, the cumulative dose of steroids at 1 year after transplant, menopausal status, and family history of diabetes and stroke. Model 3, additionally adjusted for energy intake. Model 4, additionally adjusted for baseline BMI.

Table 6 | Multivariate-adjusted odds ratios (95% CIs) for components of metabolic syndrome across tertile (T) categories of dietary pattern scores

	Fats and sugars dietary pattern				Whole grain dietary pattern				Mediterranean dietary pattern			
	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P* for trend	T1 (*n*=54)	T2 (*n*=53)	T3 (*n*=53)	*P* for trend	T1 (*n*=53)	T2 (*n*=53)	T3 (*n*=54)	*P* for trend
High BMI	1.00	1.34 (0.19–6.47)	3.28 (0.83–9.79)	0.40	1.00	0.19 (0.02–1.47)	1.34 (0.25–7.66)	0.61	1.00	1.27 (0.20–8.07)	0.98 (0.12–7.53)	0.95
High TG	1.00	1.28 (0.50–3.29)	4.52 (1.90–8.46)	<0.01	1.00	1.05 (0.42–2.01)	1.11 (0.45–2.72)	0.81	1.00	0.78 (0.31–1.99)	0.69 (0.25–1.93)	0.49
High BP	1.00	2.87 (1.06–6.75)	7.23 (1.64–8.87)	<0.01	1.00	1.04 (0.41–2.45)	0.72 (0.29–1.76)	0.46	1.00	0.68 (0.27–1.51)	0.48 (0.17–1.05)	<0.05
High FBS	1.00	2.65 (0.49–6.60)	1.67 (0.20–8.90)	0.54	1.00	1.05 (0.22–5.11)	3.13 (0.73–7.38)	0.09	1.00	0.63 (0.16–1.44)	0.36 (0.10–1.08)	<0.05
Low HDL	1.00	1.82 (0.69–3.79)	3.79 (1.08–7.43)	<0.05	1.00	1.90 (0.35–2.30)	0.51 (0.20–1.29)	0.14	1.00	0.57 (0.22–1.46)	0.63 (0.23–1.80)	0.81

High BMI defined as BMI⩾30 kg/m^2; low HDL cholesterol defined as serum HDL<40 for men and <50 mg/dl for women or specific treatment for this lipid abnormality; high-serum triacylglycerol concentrations defined as ⩾150 mg/dl or specific treatment for this lipid abnormality; high blood pressure defined as ⩾130/85 mm Hg or use of antihypertensive medication; and high FBS defined as fasting plasma glucose ⩾110 mg/dl or use of antidiabetic medication. All values adjusted for age, sex, cigarette smoking, physical activity, dialysis mode and its duration before transplantation, the cumulative dose of steroids at 1 year after transplant, menopausal status, family history of diabetes and stroke, energy intake, and baseline BMI.

dietary patterns had significantly higher TG and FBS, respectively at baseline.

Odds Ratio (OR)s for the MS across tertile categories of dietary pattern scores are presented in Table 5. After control for age and sex participants in the highest tertile of the Mediterranean dietary pattern score had lower odds of the MS (OR: 0.52; 95% CI: 0.21, 1.24) than those in the lowest tertile, whereas those in the highest tertile of the fats and sugars dietary pattern score had greater odds of the MS (OR: 1.29; 0.54, 3.06) than did those in the lowest tertile. Further adjustment for other potentially confounding variables even enhanced these associations. After additional control for total energy intake and baseline BMI, the inverse association of the Mediterranean dietary pattern score and the positive association of fats and sugars dietary pattern score with the MS based on either high BMI or high WC became stronger. However, either before or after adjustment for confounders, there was no significant overall association between the whole grain dietary pattern and MS. In the multivariate models, participants in the highest tertile of the Mediterranean dietary pattern score had lower odds for two of five components of the MS (0.36 (0.10–1.08) and 0.48 (0.17–1.05) for abnormal glucose homeostasis and high BP, respectively) (Table 6). In contrast, those in the highest tertile of the fats and sugars dietary pattern score had significantly higher odds for high TG, blood pressure and low HDL. However, the association was not significant for other components of MS. When we considered BMI changes during follow up according to tertiles of dietary patterns (Figure 1), we found that in comparison with those in the lowest tertile of fats and sugars dietary pattern, subjects in the highest tertile had significantly higher increase in BMI than other categories. Higher adherence to whole grain or Mediterranean dietary patterns was not associated with BMI change.

DISCUSSION

The major novel findings of our analysis are as follows: (1) regarding MS definition of the National Cholesterol Educational Expert Panel in our patients, we observed a 35% incidence of the MS at 12 months after renal transplantation.

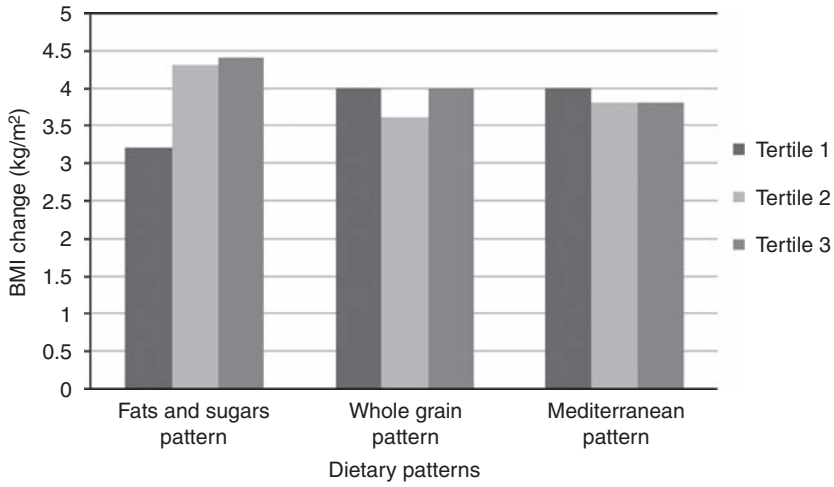

Figure 1 | BMI changes during follow-up across tertiles of dietary pattern scores.

(2) The Mediterranean dietary pattern was associated with lower risks of MS, whereas the fats and sugars dietary pattern was associated with higher risks of MS in renal transplant recipients.

Metabolic syndrome represents one of the major risks for the graft.[15] Moller and Kaufman[16] report an incidence of the metabolic syndrome in 20–30%, with the incidence in people >60 years of age rising to 40%. The MS therefore affects almost half of all transplant donors and recipients[16] and as the cluster of modifiable factors that early intervention can probably prevent more deleterious consequences cannot be ignored.[17] The increase in MS risk in renal transplant recipients compared with the normal population may be attributed to immunosuppressive medications that increase weight and body fat, reduced level of physical activity in these patients, appetite improvement, and some wasting metabolic processes associated with previous renal failure.[18] In particular, corticosteroids have long been implicated in increasing CV risk by causing multiple metabolic effects, including HTN, DM, dyslipidemia, and weight gain.[19] Teplan *et al.*[20] suggested that the metabolic syndrome can be effectively treated by the use of corticosteroid withdrawal and statins, but there is a high risk of acute rejection and adverse reactions to pharmacotherapy. Although lifestyle modification can be difficult to implement, it is a safer alternative. The incidence of the MS (35%) in our sample of the Iranian renal transplant population was higher than the incidence of the syndrome in many studies.[20–24] These differences underscore the importance of dietary modification in preventing the metabolic syndrome and can be attributed, partially, to the high frequency of the adoption of fats and sugars diet by our people, which showed significant increase on the odds of having the MS.

Data on the association of dietary patterns with MS are limited to healthy people. In the Malmo Diet and Cancer Cohort,[25] features of the MS were more prevalent in women with the 'white-bread' dietary pattern and less prevalent in women with the 'milk-fat' pattern. In a cross-sectional study in a British population,[26] a dietary pattern characterized by high consumption of fruit and vegetables and low consumption of processed meat and fried foods was inversely associated with features of the MS. However, that study was limited by the lack of control for physical activity, which tends to be associated with dietary patterns.[27]

To our knowledge, this is the first investigation in which major dietary patterns identified by factor analysis have been associated directly with the MS in a group of renal transplant recipients. We found in this study that the Mediterranean dietary pattern is associated with lower risk of metabolic abnormalities, whereas the fats and sugars dietary pattern is related to higher risk of adverse metabolic risk factors in renal transplant recipients. The main characteristics of this style diet include an abundance of plant food, olive oil as the principal source of fat, fish and poultry consumed in low-to-moderate amounts, relatively low consumption of red meat. It seems to be no individual component in this diet that is wholly responsible for the lower risk of MS and its components. Rather it is likely the interaction between many components of the diet or the overall diet quality offers protection against the MS.[28] Several mechanistic links offer potential explanations of the Mediterranean diet's protective effect on the MS. One of the most desirable features of the Mediterranean diet is its ability to improve CVD risk factors,[29–31] which account for the greater CV risk associated with metabolic diseases. Beyond this, epidemiological and interventional studies have revealed a protective effect of the Mediterranean diet against mild chronic inflammation and its metabolic complications.[29,30,32,33] More recent studies emphasize that inflammation and oxidative stress have a central role in atherosclerosis, and it is well-established that CRP is a cardiovascular risk marker in allograft recipients.[34] A Mediterranean dietary pattern, which is rich in nutrients with favorable anti-inflammatory properties and poor in pro-inflammatory nutrients may protect from autoimmune

or other chronic diseases that are related to chronic inflammation, including visceral obesity, type II DM, or the MS.[29,35] Moreover, people who eat a Mediterranean diet that includes virgin olive oil reduce their levels of oxidized LDL, as suggested by the results of a subgroup analysis of the PREDIMED study.[36]

Regarding both strengths and limitations of our study, the main strength of our study is its novelty and prospective design; in this cohort, we clearly showed an independent protective role for Mediterranean diet in the development of MS. The several limitations of our analysis also deserve comments. Given the study's observational design we could not adjust some confounding variables such as socio-economic status. Limitations of the FFQ also apply to dietary pattern analyses that are based on dietary information collected by this method. Another limit is the absence of clinical outcomes: both the number of patients and the length of follow-up obviously preclude any possible conclusion on the future destiny of the graft. Renal function, however, remained stable in all recipients during the 12-month period and, although creatinine clearance may overestimate the true GFR, all recipients showed high values of creatinine clearance. Last but not the least we used BMI and imputed WC instead of direct measurement of abdominal obesity to define MS. Recipients with similar BMIs may have absolutely different amounts of visceral fat, the adipose tissue known to be associated with the greatest metabolic risk.[37]

In conclusion, the current findings indicate that a dietary pattern characterized by high consumption of fruit, vegetables, poultry, olives, fish, low-fat dairy, legumes, and nuts is associated with a reduced risk of MS in renal transplant recipients. In contrast, a dietary pattern with high amounts of refined grains, red meat, butter, processed meat, and high-fat dairy products and low amounts of vegetables and low-fat dairy products is associated with a greater risk of the MS.

MATERIALS AND METHODS

Study population

In this prospective cohort study patient and disease characteristic data were prospectively collected on recipients of a first or second living-donor kidney transplant recipients aged over 18 years in Labbafinejad hospital in Tehran, Iran, who underwent renal transplantation between 2004 and 2007 and were on the standard triple immunosuppressive regimen (cyclosporine (Sandimmune or neoral), prednisolone, and my–cophenolate mofetil (Cellcept) or azathioprine (Imuran)). Out of 382 recipients invited to participate in the study; 371 agreed to do so. Participants with a history of pretransplant DM ($n=53$) or cancer ($n=6$) (because of possible disease-related changes in diet), who were on immuno—suppressive therapy other than the standard triple regimen ($n=4$), who were on sirolimus (Rapamune) therapy ($n=31$), with missed variables ($n=46$), with missed $\geqslant 10\%$ food-consumption frequencies ($n=9$), with prevalent MS ($n=33$) and unstable renal function at 1 year after transplantation ($n=12$); defined as a serum creatinine level >1.5 mg/dl, were excluded. We also had 17 lost to follow up. These exclusions left 160 patients (100 male and 60 female patients) for this cohort who were followed for 1 year. Written informed consent was obtained from each participant. The study was approved by the research council of Urology and Nephrology Research Center, Shahid beheshti University, MC.

Assessment of dietary intake

Dietary intake was assessed by using a 168-item semi-quantitative FFQ at 2 months after transplant. All of the questionnaires were administered by a trained dietitian. The FFQ consisted of a list of foods with standard serving sizes commonly consumed by Iranians. Participants were asked to report their frequency of consumption of a given serving of each food item during the previous year on a daily, weekly, or monthly basis. The reported frequency for each food item was then converted to a daily intake. Portion sizes of consumed foods were converted to grams by using household measures.[38] Because of the large number of the food items relative to the number of participants, we assigned each food item into 1 of 24 defined food groups (Table 1). The basis for placing a food item in a certain food group was the similarity of nutrients. A previous validation study of this FFQ revealed good correlations between dietary intakes assessed by a similar FFQ and those from multiple days of 24-h dietary recalls completed during an earlier yearlong study.[39]

Assessment of anthropometric measures

Weight was measured while the subjects were minimally clothed and not wearing shoes; weight was measured with analog scales and recorded to the nearest 100 g. Height was measured by using a tape measure while the subjects were standing, were not wearing shoes, and had the shoulders in a normal position. BMI was calculated as weight (in kg) divided by height^2 (in m^2). WC was measured at the narrowest level over light clothing, by using an unstretched tape measure, without any pressure to the body surface; measurements were recorded to the nearest 0.1 cm.[40] To reduce errors, all measurements were taken by the same technician.

Assessment of biomarkers

A blood sample was drawn between 0700 and 0900 hours into evacuated tubes after an overnight (12 h) fast. Blood samples were taken while the subjects were sitting and according to a standard protocol; the samples were centrifuged for 10 min at 500 *g* and at 4°C within 30–45 min of collection. Samples were analyzed by using an autoanalyzer (Selectra 2; Vital Scientific, Spankeren, Netherlands). Fasting plasma glucose was measured on the day of blood collection by the enzymatic colorimetric method and using glucose oxidase. Serum triacylglycerol concentrations were assayed with triacylglycerol kits (Pars Azmoon, Tehran, Iran) by using enzymatic colorimetric tests with glycerol phosphate oxidase. HDL cholesterol was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungistic acid. The inter-assay and intraassay CVs of this method were $<10\%$.

Assessment of blood pressure

For blood pressure measurements, participants were first asked to rest for 15 min. Then, a trained physician measured blood pressure of the participants twice, in a sitting position, by using a standard mercury sphygmomanometer, and thereafter the mean of two measurements was considered as the participant's blood pressure. Systolic blood pressure was defined as the appearance of the first sound (Korotkoff phase-1), and diastolic blood pressure was defined as the disappearance of the sound (Korotkoff phase-5) during deflation of the cuff at a 2–3-mm/s rate of decrement of the mercury column.

Assessment of other variables

Physical activity level was determined using the Lipid Research Clinics[41] questionnaire, which is a simple and comprehensible measure including four questions; no special education is needed to complete this questionnaire. The individuals are divided into three groups of light, moderate, and heavy physical activity according to this questionnaire. Additional covariate information regarding age, menopausal status, medical history, and current use of medications was obtained with questionnaires. Smoking statuses were defined according to WHO guidelines; current smoker was defined as a person who smokes cigarettes daily or occasionally. Dialysis mode (none, hemodialysis, or peritoneal dialysis) and its duration before transplantation also were recorded. The cumulative dose of steroids at 1 year after transplant was considered as a potential covariate. As none of our subjects used tacrolimus, it was not considered as a potential covariate.

Definition of terms

The metabolic syndrome was defined as the presence of $\geqslant 3$ of the following components as recommended by Adult Treatment Panel III (ATP III):[42] Obesity (BMI $\geqslant 30\,kg/m^2$); low serum HDL cholesterol (<40 for male and <50 mg/dl for female patients) or specific treatment for this lipid abnormality; high serum triacylglycerol concentrations ($\geqslant 150$ mg/dl) or specific treatment for this lipid abnormality; elevated blood pressure ($\geqslant 130/85$ mm Hg) or use of antihypertensive medication; and abnormal glucose homeostasis (fasting plasma glucose $\geqslant 110$ mg/dl) or use of anti-diabetic medication. We utilized the BMI to define obesity because waist circumference was not obtained in all patients as from Meigs *et al.*[43] who showed that this change had little effect on the applicability of the definition. In addition in the National Health and Nutrition Examination Survey Study both variables were highly correlated. MS was also determined according to the NCEP-ATP-III criteria (WC or imputed WC >102 cm in men and >88 cm in women). The presence of the MS was assessed at 1 year after renal transplantation.

Statistical analysis

To identify major dietary patterns based on the 24 food groups, we used principal component analysis, and the factors were rotated by orthogonal transformation. The natural interpretation of the factors in conjunction with eigenvalues >1 and the Scree test[44] determined whether a factor should be retained. The Scree plot is a plot of the eigenvalues of derived factors. The eigenvalues of the factors dropped substantially after the third factor and remained more similar to each other after the fourth factor. The derived factors (dietary patterns) were labeled on the basis of our interpretation of the data and of a higher score suggests better adherence to a certain dietary pattern. The factor score for each pattern was calculated by summing intakes of food groups weighted by their factor loadings,[44] and each participant received a factor score for each identified pattern. We categorized participants by tertiles of dietary pattern scores. We used gender-specific tertiles as there are substantial gender differences in dietary consumption. Hence, we had three groups: first group – lowest tertile of men and lowest tertile of women, second group – mid tertile of men and mid-tertile of women, third group – highest tertile of men and highest tertile of women. One-way analysis of variance with Bonferroni *post hoc* comparisons was performed to evaluate significant differences in general characteristics across tertile categories of dietary pattern scores; the distribution of qualitative variables across tertiles was evaluated by using χ^2 tests. Age- and energy-adjusted means for dietary variables across tertiles of dietary pattern scores were calculated. We also calculated multivariate-adjusted (that is, age, sex, physical activity, smoking, menopausal status, total EI) means for features of the MS. Analysis of covariance with Bonferroni correction was used to compare these means. The analysis of concordance using the Kendall rank correlation was calculated to measure concordance between WC and BMI. Linear regression models were used to impute waist at 1 year. Models included age, sex, and BMI 1 year after transplant. Covariate data from those missing waists were then entered into the models to impute the missing waists. To determine the associations of dietary patterns with MS, we used multivariable logistic regression. First, we obtained age- and sex-adjusted ORs, and then we adjusted for cigarette smoking (yes or no), physical activity (mild, moderate, heavy), dialysis mode (none, hemodialysis, or peritoneal dialysis) and its duration before transplantation, the cumulative dose of steroids at 1 year after transplant, menopausal status (yes or no), and family history of DM and stroke (yes–no). We also adjusted for EI (kcal/d) in the third model, and finally we added baseline BMI (kg/m^2) to the logistic regression model to examine whether the relation was mediated by obesity in the time of transplant. In all multivariate models, the first tertile of dietary patterns score was considered as a reference. To determine the associations of dietary patterns with features of MS, we used multivariable logistic regression. All analyses were adjusted for age, sex, cigarette smoking, physical activity, dialysis mode, and its duration before transplantation, the cumulative dose of steroids at 1 year after transplant, menopausal status, family history of DM and stroke, EI and baseline BMI. Finally means for BMI changes from baseline across tertiles of dietary pattern scores were analyzed using ANOVA. We used SPSS software (version 15; SPSS, Chicago IL, USA) for all statistical analyses.

DISCLOSURE

All the authors declared no competing interests.

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