DOI 10.1002/mnfr.200500170 Mol. Nutr. Food Res. 2006, *50*, 858 – 868

Association of metabolic syndrome risk factors with selected markers of oxidative status and microinflammation in healthy omnivores and vegetarians

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Conditions predisposing to metabolic syndrome (MetS) are associated with increased oxidative stress and inflammation. We studied, in vegetarians ($n = 90$) and omnivores ($n = 46$), the impact of the dietary regimen on the occurrence of MetS risk factors (RFs: BMI, blood pressure, glucose metabolism and lipid profile) in relation to oxidative status (advanced glycation end products (AGEs), advanced oxidation protein products (AOPPs), malondialdehyde, ferric reducing ability of plasma, vitamins A, E, C, β-carotene and superoxide dismutase activity) and microinflammation (C-reactive protein, leukocytes and neopterin). The proportion of subjects without/positive for one or two MetS RFs was comparable between the groups. From the components of MetS only immunoreactive insulin levels differed significantly (95% CI: omnivores: 5.0 – 7.1 μU/mL, vegetarians: 4.5 – 5.4, $p = 0.03$). Omnivores had lower AOPP (omnivores: 0.29 – 0.36 μmol/g albumin, vegetarians: 0.36 – 0.52, $p = 0.01$) and β-carotene levels than vegetarians, they consumed more calories, proteins, fat and saturated fatty acids, and less fibres, β-carotene and vitamin C. Multiple regression analysis revealed vitamin E and AOPP levels as the most important independent determinants of MetS RFs. The vegetarian diet seems to exert beneficial effects on MetS RFs associated microinflammation. Whether the vegetarian diet may counteract the deleterious effects of elevated AOPPs and AGEs, remains to be elucidated.

Keywords: Advanced glycation end products / Advanced oxidation protein products / Inflammation / Metabolic syndrome risk factors / Oxidative status

Received: September 29, 2005; revised: April 21, 2006; accepted: May 9, 2006

1 Introduction

Metabolic syndrome (MetS) represents a cluster of anthropometric and pathophysiological aberrations, characterized by obesity, glucose metabolism abnormality, hypertension, hypertriglyceridemia, hypo-HDL-cholesterolemia and microalbuminuria. It is associated with impaired fibrinolysis and coagulatory abnormalities, microinflammation and oxidative stress, which represent important risk factors (RFs) for the later development of type 2 diabetes and cardiovascular disease [1 – 3].

Oxidative stress and microinflammation are linked to conditions predisposing to MetS (dyslipidemia, insulin resistance/type 2 diabetes, obesity, hypertension and chronic renal disease). Inflammation is suggested as one manifestation of oxidative stress: the activation of transcription nuclear factor κB leading to expression of proinflammatory

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Abbreviations: ANOVA, one-way analysis of variance; **AGEs,** advanced glycation end products; **Alb,** albumin; **AOPPs,** advanced oxidation protein products; **BP,** blood pressure; **DBP,** diastolic blood pressure; **FRAP,** ferric reducing ability of plasma; **hsCRP,** highly sensitive C-reactive protein; **IRI,** immunoreactive insulin; **LDL-C,** low density lipoprotein cholesterol; **MDA,** malondialdehyde; **MetS,** metabolic syndrome; **MUFA,** monounsaturated fatty acids; **QUICKI,** quantitative insulin sensitivity check index; **SBP,** systolic blood pressure; **SFAs,** saturated fatty acids; **SOD,** superoxide dismutase; **TAG,** triacylglycerol

cytokines, adhesion molecules and acute phase reactants, is controlled by redox status [4, 5]. A relationship between microinflammation and individual components of MetS has been documented in several studies [6–8]. MetS is also characterized by an imbalance in natural antioxidants: lower plasma concentrations of vitamin C and β-carotene, but higher levels of vitamin E and A. The number of MetS RFs inversely correlates with vitamin C and β-carotene, and directly with vitamins E and A concentrations [9]. Dietary intervention is the first line combat in the treatment of MetS and its individual components, particularly obesity, dyslipidemia and glucose metabolism abnormality. In subjects with MetS, a diet rich in natural antioxidants combined with moderate physical activity markedly improves insulin resistance, microinflammation, oxidative stress and hypertension [10, 11]. Thus, the question arises whether the consumption of a vegetarian diet, rich in natural antioxidants, fibres, and carbohydrates with low glycemic index, affects the association of oxidative markers and microinflammation with the appearance of MetS RFs in healthy subjects without overt MetS.

Therefore we investigated the relationship between the manifestation of MetS RFs with markers of microinflammation and oxidative status in healthy vegetarians and subjects on a traditional Western mixed diet (omnivores).

2 Materials and methods

The study was carried out in accordance with the declaration of Helsinki and after approval by the Institutional Ethics Board of the Slovak Medical University in Bratislava. Written informed consent was obtained from all study participants.

Ninety healthy, normoglycemic lacto-ovo-vegetarians, who consumed plant food, diary products and eggs, and 46 omnivores, nonvegetarian family members of the vegetarians, or colleagues with comparable life style, were included. All subjects were nonsmokers and free of any medication, including intake of nutritional supplements (vitamins, trace elements or minerals) for at least 3 months prior to the study. Participants were comparable regarding physical activity (mental work, no active sportsmen) and educational level (high school, university level of education). The survey was carried out over a period of 1 wk in spring.

Venous blood was collected after overnight fasting. Blood cell count (Sysmex KX-21 analyser, Japan) and standard blood chemistry (Vitros 250, J&J, USA) were analysed immediately. Plasma was stored at $-80^{\circ}C$ for analyses of immunoreactive insulin (IRI; Immunotech, France), parameters characterizing oxidative status (advanced glycation end products (AGEs) [12], advanced oxidation protein products (AOPPs) [13], malondialdehyde (MDA) [14], ferric reducing ability of plasma (FRAP) [15], vitamins A, C, E and β-carotenes [16, 17], erythrocyte superoxide dismutase activity (SOD; Randox, GB), and microinflammation (highly sensitive C-reactive protein (hsCRP) Dade Behring, USA). Neopterin and cystatine C (Dade Behring) concentrations were determined.

Blood pressure (BP) was measured at forearm after 15 min resting in sitting position. BMI and quantitative insulin sensitivity check index (QUICKI) [18] were calculated. Subjects were classified as insulin resistant if QUICKI < 0.357 [19]. The manifestation of MetS RFs was classified according to World Health Organization (WHO) criteria [20].

The nutritional regimen was assessed by means of a food frequency questionnaire on the intake of 114 food items. Trained dieticians checked the completeness of the questionnaire. Information from the questionnaire (almost never, times *per* day/week/month, depending on food item) was used to determine the intake of proteins (of animal or plant origin), carbohydrates, fat, cholesterol, saturated fatty acids (SFA, sum of butyric, capronic, caprylic, caprinic, lauric, myristic, stearic, palmitic and arachic acids), poly- and monounsaturated fatty acids (PUFA and MUFA, respectively) (sum of oleic and palmito-oleic acids, and linolic, linolenic, arachidonic, eicosapentaenoic and docosahexaenoic acids, respectively), fibres and vitamins (vitamins A, E, C and β-carotene) employing a software based on the Slovak food consumption database [21].

SPSS v. 9 statistical programme was used for data evaluation. Normality of data distribution was tested. Data are given as mean and 95% confidence interval of the mean. Between-group comparisons were performed employing Student's *t*-test, or one-way analysis of variance (ANOVA) with *posthoc* Scheffe's test; and Mann-Whitney *U*-test or Kruskal-Wallis test, as appropriate. Chi-square was used to compare categorical data. Simple and multiple regression analyses were performed. $p < 0.05$ was considered as significant.

3 Results

3.1 Comparison between vegetarians and subjects on a traditional Western mixed diet

3.1.1 Group characteristics

Both groups were comparable with regard to age, gender ($\chi^2 = 0.184$, NS), mean plasma albumin (Alb) concentration and BMI. Vegetarians adhered to their dietary regimen between 2 and 25 years (Tables 1 and 2).

Table 1. Group characteristics of subjects on a standard Western mixed diet and after subdivision according to the number of MetS RFs

Omnivores	All	Number of MetS RFs			*ANOVA*/K-W *p*
		0	1	2	
n	46	29	11	6	
Age (years)	37.1	35.6	34.4	49.3	0.021
	33.5–40.7	30.8–41.8	27.0–41.8	43.2–55.5[a, b, c)]	
Gender (Male/Female)	19/27	10/19	6/5	3/3	NA
BMI (kg/m^2)	23.8	22.3	25.7	27.5	*0.001*
	22.7–24.9	21.2–23.4	23.3–28.1[a,c)]	24.2–30.8[a)]	
SBP (mm Hg)	115.0	108.5	119.6	130.8	*0.001*
	110.0–117.9	104.6–112.3	110.7–128.4[d, c)]	122.4–139.2[a, c)]	
DBP (mm Hg)	71.9	69.3	73.2	81.7	0.006
	69.4–74.3	66.9–71.7	66.9–79.4	74.5–88.8[a)]	
Glucose (μmol/L)	4.4	4.2	4.6	4.4	*0.012*
	4.3–4.5	4.1–4.4	4.4–4.9[d)]	4.3–4.6[c)]	
IRI (μU/mL)	6.1	4.3	9.6	7.5	0.001
	5.0–7.1[c)]	3.7–4.9	7.0–12.3[a, e)]	3.3–11.8[d)]	
QUICKI	0.386	0.404	0.348	0.370	*0.001*
	0.374–0.398	0.391–0.417	0.334–0.363[a, e)]	0.331–0.409[d)]	
Cholesterol (μmol/L)	4.6	4.4	5.0	5.2	0.046
	4.3–4.9	4.0–4.7	4.3–5.7	4.3–6.0	
HDL-C (μmol/L)	1.7	1.8	1.6	1.3	*0.024*
	1.5–1.7	1.6–2.05	1.4–1.8	1.0–1.6[d)]	
LDL-C (μmol/L)	2.4	2.2	2.8	2.8	0.038
	2.1–2.7	1.8–2.5	2.2–3.3[d)]	2.3–3.4[d)]	
TAG (μmol/L)	1.2	0.	1.5	2.3	0.001
	1.0–1.4	0.8–1.02	1.1–1.9[a)]	1.5–3.1[a,e,f)]	
Alb (g/L)	43.9	44.3	44.5	41.0	*0.078*
	42.9–44.9	42.9–45.6	42.9–46.2	36.8–45.1	
Cystatin C (mg/dL)	0.85	0.84	0.86	0.87	0.877
	0.81–0.88	0.80–0.88	0.76–0.96	0.73–1.00	

HDL-C, high density lipoprotein cholesterol; NA, not applicable; K-W, Kruskal–Wallis test.
a) $p < 0.01$ *vs.* omnivores without RFs for MetS.
b) $p < 0.01$ *vs.* omnivores with one RF for MetS.
c) $p < 0.05$ *vs.* vegetarians.
d) $p < 0.05$ *vs.* omnivores without RFs for MetS.
e) $p < 0.01$ *vs.* vegetarians.
f) $p < 0.05$ *vs.* omnivores with one RF for MetS.

3.1.2 BP and renal function

Mean BP values were insignificantly higher in the omnivores. All subjects had normal renal function, as evaluated by plasma cystatin C concentration (Tables 1 and 2).

3.1.3 Lipid profile and insulin sensitivity

No significant differences in lipid profile were observed between the groups (Tables 1 and 2). Fasting blood glucose concentration was comparable between the groups. IRI was significantly higher in the omnivores. This was not reflected by the significant difference in the mean index of insulin sensitivity ($p = 0.19$).

3.1.4 Enumeration of the frequency of MetS RFs

Insulin resistance was the most abundant MetS RF in the omnivores with one RF present, while hypertriacylglycerolemia was the leading event in the vegetarians, followed by glucose metabolism disturbance (Table 3). In spite of the low number of subjects with two MetS RFs present, combination of insulin resistance and elevated triacylglycerols (TAGs) seemed to dominate in both the cohorts.

3.1.5 Protein glycation (AGEs), protein oxidation (AOPPs), lipid peroxidation (MDA) and inflammatory markers

Mean plasma AGE-associated fluorescence corrected for plasma Alb was insignificantly, but plasma AOPP/Alb was significantly higher in vegetarians (Tables 4 and 5). In the omnivores, AGE-Fl/Alb and AOPPs/Alb correlated directly ($r = 0.369$, $p = 0.012$). Plasma hsCRP, MDA, neopterin, concentration and leukocyte count did not differ significantly.

Table 2. Group characteristics of vegetarians and after subdivision according to the number of MetS RFs

Vegetarians	All	Number of MetS RFs			*ANOVA*/K-W *p*
		0	1	2	
n	90	62	23	5	
Age (years)	37.7 35.1 – 40.3	37.0 34.0 – 40.1	39.0 32.9 – 45.0	39.4 26.0 – 52.9	0.833
Gender (Male/Female)	30/60	16/46	11/12	3/2	NA
Time veg. diet (years)	10.3 9.3 – 11.3	10.7 9.5 – 11.8	9.6 7.6 – 11.7	8.4 1.1 – 15.7	0.387
BMI (kg/m^2)	22.7 22.1 – 23.3	22.2 21.5 – 22.8	23.0 21.8 – 24.1	27.5 22.0 – 32.9[a,b)]	*0.001*
SBP (mm Hg)	110.9 108.7 – 113.2	110.6 107.9 – 113.2	110.0 104.9 – 115.1	119.6 105.5 – 133.7	0.168
DBP (mm Hg)	70.4 68.9 – 71.9	69.5 67.8 – 71.3	70.9 67.4 – 74.3	79.0 73.8 – 84.2[a,c)]	0.022
Glucose (μmol/L)	4.4 4.3 – 4.5	4.4 4.3 – 4.5	4.5 4.3 – 4.7	4.8 4.4 – 5.2	0.095
IRI (μU/mL)	4.9 4.5 – 5.4	4.3 3.9 – 4.7	5.9 4.9 – 7.0[a)]	7.6 1.7 – 13.6[a)]	*0.001*
QUICKI	0.396 0.387 – 0.405	0.404 0.393 – 0.414	0.381 0.367 – 0.395[d)]	0.369 0.315 – 0.422	0.003
Cholesterol (μmol/L)	4.5 4.3 – 4.7	4.3 4.0 – 4.5	5.0 4.6 – 5.4[a)]	5.1 4.2 – 5.9[d)]	0.003
HDL-C (μmol/L)	1.5 1.4 – 1.6	1.6 1.5 – 1.8	1.3 1.2 – 1.5[a)]	1.1 0.8 – 1.5[a)]	*0.007*
LDL-C (μmol/L)	2.5 2.3 – 2.7	2.3 2.1 – 2.6	2.7 2.4 – 3.1[d)]	3.0 1.8 – 4.20	0.025
TAG (μmol/L)	1.2 1.1 – 1.4	0.9 0.8 – 0.9	2.0 1.6 – 2.4[a)]	2.1 1.3 – 2.8[a)]	0.001
Alb (g/L)	43.3 42.6 – 44.0	43.8 43.0 – 44.6	42.3 40.6 – 44.1	42.6 40.0 – 46.2	*0.206*
Cystatin C (mg/dL)	0.86 0.84 – 0.89	0.84 0.82 – 0.87	0.90 0.83 – 0.97[d)]	0.95 0.85 – 1.04	0.049

a) $p < 0.01$ *vs.* vegetarians without RFs for MetS.
b) $p < 0.01$ *vs.* vegetarians with one RF for MetS.
c) $p < 0.05$ *vs.* vegetarians with one RF for MetS.
d) $p < 0.05$ *vs.* vegetarians without RFs for MetS.

3.1.6 Antioxidant status

Except for higher plasma β-carotene concentrations in vegetarians, plasma antioxidant vitamins (A, E and C), or the markers of antioxidant defence (FRAP and erythrocyte SOD activity), did not differ significantly between the groups (Tables 4 and 5). AGE/Alb levels were directly related to vitamin A concentrations in both cohorts (vegetarians: $r = 0.321$, $p = 0.002$; omnivores: $r = 0.527$, $p = 0.0002$) and to vitamin E in the omnivores ($r = 0.345$, $p = 0.018$). AOPPs/Alb showed a direct relationship to vitamin A (vegetarians: 0.359, $p = 0.0005$; omnivores: $r = 0.324$, $p = 0.028$) and in the omnivores to vitamin E ($r = 0.324$, $p = 0.028$), and an inverse relationship to vitamin C ($r = -0.432$, $p = 0.003$). In the vegetarians, the concentrations of vitamins E and A were directly related to MDA levels (vegetarians: $r = 0.413$, $p = 0.001$; omnivores: $r = -0.031$, $p = 0.839$; and vegetarians: $r = 0.256$, $p = 0.015$; omnivores: $r = -0.003$, $p = 0.986$, respectively).

3.1.7 Nutritional intake

Mean energy intake was significantly higher in the omnivores than vegetarians (Tables 6 and 7). This was on the account of higher fat and protein consumption, namely that of animal origin. The intake of the proteins of plant origin did not differ significantly (omnivores: 43.0; 37.3 – 48.7 g/day; vegetarians: 43.4; 23.5 – 30.4 g/day, $p = 0.892$). Omnivores consumed significantly more dietary cholesterol, but this was not reflected by higher cholesterolemia. Mean daily intake of saturated as well as unsaturated fatty acids was significantly higher in the omnivores, the latter one on the account of monounsaturated fatty acids, while that of PUFAs did not differ significantly between the groups (omnivores: 22.9, 20.9 – 24.9 g/day; vegetarians: 22.0, 20.6 – 23.3 g/day, $p = 0.467$). Groups did not differ significantly in the mean dietary intake of carbohydrates. Omnivores consumed less fibres, β-carotenes and vitamin C, while the intake of fat-soluble vitamins was comparable

Table 3. Occurrence of MetS RFs in the subjects on a Western mixed diet and vegetarians

One MetS RF	Omnivores $n = 11$	Vegetarians $n = 23$	Two MetS RFs	Omnivores $n = 6$	Vegetarians $n = 5$
G/IR	7	4	IRI + HDL-C	0	1
BMI	1	1	IRI + TAG	2	2
BP	1	1	BMI + TAG	2	1
TAG	2	15	HDL-C + TAG	1	0
HDL-C	0	2	BP + TAG	1	1

G, fasting glycemia > 6.1 μmol/L; IR, insulin resistance: QUICKI < 0.357; BMI, BMI > 30 kg/m^2; BP, blood pressure ≥140/≥90 mm Hg; TAG, triacylglycerols ≥1.7 μmol/L; HDL-C, HDL cholesterol – males < 0.9 μmol/L, females < 1.0 μmol/L.

Table 4. Parameters characterizing oxidative and inflammatory status in subjects on a standard Western mixed diet, and after subdivision according to the MetS RF

Omnivores	All	Number of MetS RFs			*ANOVA*/K-W *p*
		0	1	2	
n	46	29	11	6	
AGE-Fl/Alb (AU/g)	7.4 6.7–8.1	7.0 6.2–7.8	7.7 6.3–9.2	8.7 6.1–11.3	*0.216*
AOPPs/Alb (μmol/g)	0.33 0.29–0.36[a)]	0.28 0.26–0.31	0.37 0.30–0.44[b,c)]	0.46 0.30–0.62[b)]	0.002
Leukocytes (× 10^3/μL)	5.8 5.3–6.2	5.5 5.0–6.0	5.6 5.0–6.3	7.2 5.1–9.3[d)]	*0.025*
Neopterin (mg/dL)	5.6 5.2–6.0	5.5 5.0–6.0	5.9 4.8–6.9	5.8 5.0–6.5	0.330
hsCRP (mg/dL)	0.81 0.53–1.09	0.59 0.31–0.87	0.79 0.12–1.47[d)]	1.90 0.74–3.05[c,d)]	0.026
MDA (μmol/L)	1.36 1.22–1.50	1.40 1.18–1.61[c)]	1.34 1.11–1.56	1.22 0.97–1.466	0.877
FRAP (μmol/L)	1118 1017–1219	1034 919–1148	1271 1036–1505	1248 799–1696	*0.086*
SOD (U/Hb)	1317 1206–1427	1386 1238–1535	1160 971–1350	1266 849–1683	*0.221*
β-Carotene (μmol/L)	0.20 0.12–0.28[a)]	0.21 0.10–0.32[a)]	0.20 0.03–0.38[a)]	0.16 0.06–0.31[c)]	0.940
Vitamin A (μmol/L)	1.74 1.59–1.90	1.65 1.43–1.87	1.82 1.58–2.07	2.06 1.70–2.41	0.179
Vitamin E (μmol/L)	28.1 25.9–30.4	25.4 23.9–28.2	27.6 24.6–30.6[b)]	39.1 27.0–51.2[b)]	0.003
Vitamin C (μmol/L)	75.7 67.7–83.70	78.4 68.9–88.0	67.0 47.5–86.5	78.3 43.3–113.3	*0.486*

AGEs/Alb, advanced glycation end products associated fluorescence corrected for plasma albumin; AOPPs/Alb, advanced oxidation protein products corrected for albuminemia.
a) $p < 0.01$ *vs.* vegetarians.
b) $p < 0.01$ *vs.* omnivores without RFs for MetS.
c) $p < 0.05$ *vs.* vegetarians.
d) $p < 0.05$ *vs.* omnivores without RFs for MetS.

between the groups (vitamin A: omnivores: 2.2; 1.9–2.5 mg/day; vegetarians: 2.2; 2.0–2.5 mg/day, $p = 0.881$; and vitamin E: omnivores: 13.2; 11.9–14.5 mg/day; vegetarians: 13.6; 12.8–14.4 mg/day, $p = 0.617$). Lower dietary intake of β-carotene, but not vitamin C, was reflected by lower plasma values in the omnivores.

3.2 Comparison between vegetarians and subjects on a traditional Western-mixed diet after subdivision according to the number of MetS RFs

Twenty-nine (63%) omnivores and 62 (69%) vegetarians were free from MetS RFs (Tables 1, 2). One MetS RF was

Table 5. Parameters characterizing oxidative and inflammatory status in vegetarians and after subdivision according to MetS RFs

Vegetarians	All	Number of MetS RFs			*ANOVA*/K-W *p*
		0	1	2	
n	90	62	23	5	
AGE-Fl/Alb (AU/g)	7.6	7.3	8.2	8.6	*0.047*
	7.0 – 8.0	6.8 – 7.7	7.3 – 9.2[a)]	6.6 – 10.5	
AOPPs/Alb (μmol/g)	0.44	0.36	0.65	0.47	0.001
	0.36 – 0.52	0.27 – 0.44	0.44 – 0.85[a)]	0.33 – 0.61[b)]	
Leukocytes (× 10^3/μL)	5.5	5.4	5.6	6.1	0.278
	5.2 – 5.7	5.0 – 5.7	5.1 – 6.1	4.4 – 7.7	
Neopterin (mg/dL)	6.0	5.8	6.7	5.9	0.176
	5.6 – 6.5	5.4 – 6.2	5.3 – 8.2	5.1 – 6.8	
HsCRP (mg/dL)	0.87	0.82	0.94	1.10	0.144
	0.58 – 1.15	0.48 – 1.16	0.27 – 1.60	0.15 – 2.04	
MDA (μmol/L)	1.34	1.20	1.67	1.52	0.001
	1.24 – 1.44	1.11 – 1.30	1.39 – 1.95[b)]	1.04 – 2.00	
FRAP (μmol/L)	1104	1102	1107	1110	0.750
	1033 – 1174	1012 – 1191	963 – 1251	843 – 1377	
SOD (U/Hb)	1343	1342	1396	1100	*0.355*
	1256 – 1430	1236 – 1449	1230 – 1563	995 – 1705	
β-Carotene (μmol/L)	0.68	0.65	0.80	0.56	0.740
	0.52 – 0.85	0.46 – 0.84	0.38 – 1.23	0.12 – 1.00	
Vitamin A (μmol/L)	1.73	1.62	1.96	1.96	*0.016*
	1.62 – 1.84	1.49 – 1.75	1.74 – 2.19	1.69 – 2.23[b)]	
Vitamin E (μmol/L)	28.3	25.9	33.5	34.0	0.001
	26.4 – 30.2	24.1 – 27.6	28.3 – 38.8	28.0 – 39.9[b,c)]	
Vitamin C (μmol/L)	74.1	76.5	67.3	75.7	*0.339*
	68.8 – 79.4	68.8 – 83.3	60.2 – 74.5	31.6 – 119.8	

a) $p < 0.05$ *vs.* omnivores without RFs for MetS.
b) $p < 0.01$ *vs.* omnivores without RFs for MetS.
c) $p < 0.01$ *vs.* omnivores with one RF for MetS.

manifest in 11 (24%) omnivores and 23 (26%) vegetarians, while two MetS RFs were revealed in 6 (13%) omnivores and 5 (5%) vegetarians. The proportion of the subjects free from MetS RFs, and those positive for 1 or 2 of them, did not differ significantly between the cohorts ($\chi^2 = 2.299$, NS). Omnivores in whom two RFs were manifest were significantly older than the subgroups of omnivores without or with one RF present, as well as the corresponding group of vegetarians. Vegetarians in all three subgroups adhered to their diet for comparable time (Table 2).

3.2.1 MetS RFs (Tables 1, 2)

In the omnivores, BMI was significantly higher in the subjects with MetS RFs, while in the vegetarians only the subgroup with two RFs showed higher BMI. Comparison between the corresponding subgroups of omnivores and vegetarians revealed that omnivores with one MetS RFs had significantly higher BMI than vegetarians.

In the omnivores, both systolic and diastolic BP values rose with the manifestation of the RFs, but in the case of diastolic blood pressure (DBP) significance was reached only in subjects with two RFs. Both subgroups of omnivores with MetS RFs displayed higher systolic blood pressure (SBP) than the corresponding groups of vegetarians. In the vegetarians, higher BP values were observed in the subgroup with two RFs, while significance was reached only in the case of DBP.

Mean glycemia tended to increase by the manifestation of MetS RFs; however, significance was reached only in omnivores with one RF. Corresponding subgroups of omnivores and vegetarians did not differ significantly, except for the subgroup with two MetS RFs. These vegetarians had higher mean fasting glycemia when compared with omnivores, but statistical significance was reached within the normal range. In both cohorts, IRI levels were higher in the subgroups with RFs. Both subgroups of omnivores with manifest MetS RFs were more insulin resistant than the RF-free subjects. In the vegetarians, QUICKI decreased by increasing the manifestation of the RFs, but reached significance only in the subgroup with one RF, probably due to a high inter-individual variability and a relatively small number of the subjects in the group with two factors. Omnivores with one MetS RF had higher fasting IRI levels and were more insulin resistant than the corresponding subgroup of vegetarians.

Table 6. Daily nutritional intake of subjects on a standard Western mixed diet and after subdivision according to the number of MetS RFs

Omnivores	All	Number of MetS RFs			*ANOVA*/K-W *p*
		0	1	2	
n	46	29	11	6	
Energy (MJ)	10.20 9.15–11.25[a)]	9.98 8.79–11.17[a)]	9.69 7.17–12.21	13.61 6.98–17.00	*0.368*
Proteins (g)	102.4 90.7–114.0[a)]	99.6 86.6–112.6[a)]	101.2 67.5–134.9	116.2 68.1–164.3	*0.629*
Animal proteins (g)	58.1 49.5–66.7[a)]	54.4 45.3–63.5[a)]	64.7 36.0–93.3[b)]	63.1 35.6–90.5[b)]	0.748
Carbohydrates (g)	298.5 262.4–324.5	294.3 252.9–335.7	269.4 197.2–341.6	365.0 178.2–551.8	*0.272*
Fat (g)	92.1 83.3–100.8[a)]	89.9 79.6–100.2[a)]	91.8 69.1–114.5	102.0 65.5–138.4[b)]	*0.646*
UFA (g)	56.0 50.7–61.2[a)]	55.0 48.7–61.4[a)]	54.2 42.1–66.3	62.9 39.0–86.8[b)]	*0.564*
MUFA (g)	33.1 29.2–37.2[a)]	32.5 27.4–37.6[a)]	31.6 23.3–39.9	38.4 22.2–54.6[b)]	0.633
SFA (g)	29.3 25.5–33.2[a)]	28.3 23.8–32.8[a)]	30.7 20.2–41.2[a)]	31.6 16.6–46.6	0.855
Cholesterol (g)	0.30 0.25–0.34[a)]	0.28 0.23–0.34[a)]	0.31 0.20–0.42[a)]	0.33 0.16–0.513[b)]	*0.755*
Fibres (g)	29.4 26.6–32.1[a)]	30.1 26.1–34.0	25.8 21.1–30.6[b)]	31.2 25.0–39.2	*0.321*
β-Carotene (mg)	4.8 4.0–5.6[b)]	5.2 4.0–6.5	3.8 3.1–4.5[b)]	4.6 2.3–6.9	0.449
Vitamin C (mg)	103.6 94.3–113.0[a)]	105.7 94.6–116.9[a)]	100.3 80.0–120.5[a)]	100.0 52.1–147.9	*0.850*

UFA, unsaturated fatty acids.
a) $p < 0.01$ *vs.* vegetarians.
b) $p < 0.05$ *vs.* vegetarians.

HDL-cholesterol concentration decreased with the increase in the manifestation of MetS RFs in both cohorts, reaching significance in omnivores with two RFs and in both subgroups of vegetarians. TAG concentrations were higher in the subgroups with MetS RFs, and even higher in the omnivores with two RFs in comparison with vegetarians. Mean total cholesterol and low density lipoprotein cholesterol (LDL-C) concentrations increased with the manifestation of RFs in both cohorts.

3.2.2 Nutritional intake

Except for β-carotene intake, which decreased significantly in the vegetarians with the number of MetS RFs, no other variable differed significantly within either cohort according to MetS RFs manifestation (Tables 6 and 7). Consistently with the findings of comparison of two cohorts, significant differences in nutritional intake were confirmed even after the comparison of corresponding subgroups according to the manifestation of MetS RFs.

3.2.3 Albuminemia and renal function

Mean plasma Alb concentration did not differ significantly within the subgroups, or between the cohorts (Tables 1 and 2). Plasma cystatin levels tended to rise with the number of MetS RFs in the both cohorts. Statistical significance was revealed comparing the vegetarian subgroups (0 *vs.* 1 RF, within the normal range).

3.2.4 Protein glycation (AGEs), protein oxidation (AOPPs), lipid peroxidation (MDA) and inflammatory markers

AGE-associated fluorescence corrected for albuminemia tended to rise with the increasing manifestation of the MetS RFs in both cohorts, but was significant only in the vegetarians with one RF. AOPPs corrected for Alb were higher in the subgroups with MetS RFs (*vs.* corresponding RF-free subjects), both in omnivores and vegetarians (Tables 4 and 5). Vegetarians showed a tendency towards higher AOPP/Alb levels than omnivores, but significance was reached only in the subgroup with one RF. MDA concentration was higher in the omnivores without any RF when compared with vegetarians. In the vegetarians MDA, levels were significantly higher in the subgroup with one MetS RF when compared with RF-free subjects. In contrast to vegetarians, leukocyte count and hsCRP concentration increased with the manifestation of the RFs in the omnivores. Significance

Table 7. Daily nutritional intake of vegetarians and after subdivision according to the number of MetS RFs

Vegetarians	All	Number of MetS RFs			*ANOVA*/K-W *p*
		0	1	2	
n	90	62	23	5	
Energy (MJ)	8.14	7.94	8.43	9.10	0.411
	7.58 – 8.69	7.23 – 8.65	7.36 – 9.49	7.00 – 11.24	
Proteins (g)	72.6	70.5	76.0	82.0	*0.406*
	67.7 – 77.5	64.4 – 76.6	66.6 – 85.5	49.4 – 111.6	
Animal proteins (g)	27.0	26.0	28.5	30.9	*0.707*
	48.5 – 66.7	21.9 – 30.1	21.1 – 35.8	8.0 – 53.7	
Carbohydrates (g)	276.1	268.5	284.8	325.2	*0.391*
	255.9 – 296.2	242.6 – 294.3	246.8 – 322.9	266.1 – 384.3	
Fat (g)	70.1	69.7	71.7	66.4	0.975
	63.9 – 76.2	62.2 – 77.2	58.1 – 85.3	51.3 – 81.5	
UFA (g)	46.5	45.8	49.3	41.7	0.386
	43.7 – 49.2	42.5 – 49.1	43.3 – 55.0	27.6 – 55.8	
MUFA (g)	24.5	23.7	27.4	20.4	0.186
	22.6 – 26.4	21.6 – 25.8	23.0 – 31.8	10.5 – 30.5	
SFA (g)	20.0	20.4	18.9	20.3	0.765
	17.9 – 22.1	17.6 – 23.3	14.8 – 23.0	12.3 – 20.2	
Cholesterol (g)	0.13	0.12	0.14	0.15	0.632
	0.11 – 0.15	0.10 – 0.15	0.09 – 0.20	0.05 – 0.25	
Fibres (g)	34.8	33.8	36.1	39.3	*0.596*
	31.9 – 37.6	30.2 – 37.6	30.5 – 41.8	28.6 – 50.0	
β-Carotene (mg)	6.2	6.7	5.7	2.5	0.037
	5.2 – 7.3	5.2 – 8.2	4.5 – 7.0	1.2 – 3.9[a,b)]	
Vitamin C (mg)	141.8	137.9	157.9	111.7	0.133
	127.6 – 156.0	119.4 – 156.4	134.6 – 181.1	32.0 – 191.3	

a) $p < 0.05$ *vs.* vegetarians without RFs for MetS.
b) $p < 0.01$ *vs.* vegetarians with one RF for MetS.

was reached in the subgroup with two RFs in the case of white blood cell count and in both subgroups if hsCRP was considered. HsCRP levels in the subgroup of omnivores with two RFs were significantly higher than in the vegetarians. Plasma neopterin, a marker of leukocyte activation, tended to higher values in the positive subgroups, without reaching significance in comparison with RF-free subjects, in both cohorts.

3.2.5 Antioxidant status

In the omnivores, no significant differences in vitamin A concentrations were revealed within the subgroups, while in the vegetarians the two RF subgroups had significantly higher levels (Tables 4 and 5). Vitamin E concentration was significantly higher in the vegetarians with two RFs, and in both subgroups with RFs in omnivores. No significant differences in vitamin C and β-carotene levels were observed. Even after the subdivision according to number of manifest MetS RFs, β-carotene levels were significantly higher in the corresponding groups of vegetarians than in omnivores.

3.3 Relation between the number of MetS RFs and investigated parameters

3.3.1 Relation to BMI, BP, lipid profile and markers of glucose metabolism

If all subjects were evaluated together, BMI, DTK, concentrations of TAGs and IRI were selected in multiple regression analysis as contributing to 63.2% of variance if the number of MetS RFs was entered as a dependent variable ($F = 58.19$, $p = 0.0001$). If omnivores and vegetarians were evaluated separately, BMI, TAG and IRI concentrations contributed significantly (omnivores: $r^2 = 0.729$, $F = 40.41$, $p = 0.0001$; vegetarians: $r^2 = 0.542$, $F = 35.75$, $p = 0.0001$).

3.3.2 Relation to markers of oxidative and inflammatory status

If all subjects were evaluated together and the number of manifest metabolic RFs was entered as a dependent variable, the multiple regression model indicated that AOPP/Alb, AGE/Alb, white blood cell count, and vitamin E concentration contributed significantly ($r^2 = 0.228$, $F = 10.87$, $p = 0.0001$). In the omnivores AOPP/Alb, vitamin E and FRAP concentrations and SOD activity had the strongest

impact ($r^2 = 0.644$, $F = 20.87$, $p = 0.0001$), while in the vegetarians AOPP/Alb, AGEs/Alb and vitamin E concentration contributed significantly ($r^2 = 0.200$, $F = 8.42$, $p = 0.001$).

4 Discussion

The main findings of this study are as follows: (1) In the healthy, normoglycemic subjects, who were of comparable age, sex and BMI, the proportion of subjects free from MetS RFs and those with manifest one or two factors, was comparable between omnivores and vegetarians. (2) Regarding inflammatory markers and parameters characterizing oxidative status vegetarians differed from omnivores only by higher concentrations of AOPPs. (3) AOPPs and plasma vitamin E concentration had the strongest impact on MetS RFs occurrence.

In the studied cohorts of healthy omnivores and vegetarians, the proportion of the subjects free from MetS RFs was high, and the manifestation of the RFs was limited to 1 or 2. Since the distribution of MetS RFs was comparable in both cohorts, it could be misinterpreted that, in the absence of overt MetS, there is no direct evidence of the impact of dietary regimen on manifestation of MetS RFs. However, in the omnivores, the markers of MetS (namely BMI, TAG and IRI, as selected by the multiple regression model) showed higher impact on the number of manifest RFs (73 *vs.* 52%). This could be attributed particularly to the higher fasting IRI concentrations in the omnivores, albeit not reflected by overt increase in insulin resistance. Data in the literature consistently report higher insulin sensitivity in the vegetarians when compared with omnivores, although omnivores showed higher levels of fasting glucose [22] or steady-state plasma glucose [23]. Our data supports the beneficial effects of a vegetarian diet on insulin sensitivity: lower amounts of insulin are needed to maintain comparable glycemia. With regard to this data, the role of nutrition is to be considered. In spite of the comparable body weight and life-style, omnivores had a higher energy intake, on account of animal proteins and fat. Although carbohydrate intake did not differ significantly between the groups, higher intake of vitamin C and β-carotene reflects higher intake of fruit and vegetables, containing carbohydrates with low glycemic index. A vegetarian diet rich in fibres, with high content of PUFAs and low intake of SFAs may contribute to lower fasting IRI concentrations. It might be expected that in the presence of MetS, the protective role of a vegetarian diet becomes more evident.

Among the investigated markers of oxidative status, AOPPs/Alb levels were higher in the vegetarians. AOPPs represent an exquisite marker of phagocyte-derived oxidative stress *via* myeloperoxidase reaction [13]. They are considered inflammatory mediators, able to trigger the oxidative burst and synthesis of inflammatory cytokines [24]. Since neither the leukocyte count nor hsCRP concentrations pointed to the presence of microinflammation, the reason for potential phagocyte activation remains unclear. However, AOPP/Alb appeared consistently as an independent determinant of MetS RFs (the most significant in the omnivores and the second contributing one in vegetarians and the whole cohort), and if all subjects were evaluated together leukocyte count was shown to be an independent factor as well. In a larger clinical Japanese study leukocyte count – even within the normal range – showed a significantly independent association with the components of MetS [25]. These results raise the question on the potential involvement of myeloperoxidase axis in MetS.

In contrast to our previous report [26], in the present study plasma AGE levels were only insignificantly higher in vegetarians than in omnivores. In the former study, we assumed that increased AGEs may reflect a higher dietary intake of AGE precursors and foods with a higher content of Maillard reaction products, and/or lower metabolic activity of the kidney responsible for excretion of AGEs. A partial change in the diet of vegetarians might not be excluded. However, as a consequence of higher protein intake the postprandial glomerular filtration rate could be higher in the omnivores due to a protein-induced glomerular filtration [27]. Thus, the renal removal of dietary AGEs could be elevated for several hours after a meal, resulting in lower plasma AGE levels. Moreover, an alternative explanation of enhanced AGE levels was suggested by McCarty. She pointed out that the relatively poor taurine status of vegetarians may up-regulate the physiological role of myeloperoxidase-derived oxidants in the generation of AGEs [28]. Thus, higher AOPP levels and a tendency towards higher AGEs in the vegetarians, and the direct relationship between AGEs and AOPPs in the omnivores may reflect this mechanism. Potential involvement of an altered taurine metabolism is to be considered in further studies, since we did not determine its levels. Multiple regression implicated AGEs as contributing significantly to the number of MetS RFs in the omnivores, and all participants together. Experimental studies suggest that AGE-induced down-regulation of leptin production in adipocytes is linked to reduction of the insulin sensitivity in MetS [29]. This concept is similar to findings in healthy mice administered with an AGE-rich diet for 6 months: animals developed abdominal obesity and Type 2 diabetes [30]. Correspondingly, in healthy volunteers, consumption of high-AGE diet was associated with a rise in fasting IRI and body weight [31], and dietary AGE intake directly correlates with IRI and hsCRP levels [32]. In addition, AOPPs and AGEs play a pathophysiological role in the development of chronic renal failure and diabetes-related complications, in particular accelerated atherosclerosis [24, 33, 34]. However, in spite of higher AOPP

and a tendency towards higher AGE levels, vegetarians appear to be more insulin-sensitive than omnivores. Moreover, there is no evidence that a vegetarian diet represents a risk for accelerated atherosclerosis. Thus, it might be speculated that, a high intake of natural antioxidants may *in vivo* counteract these deleterious actions of mildly increased AGEs and AOPPs.

A number of population studies suggest that components of MetS are associated with elevated CRP levels in apparently healthy subjects [4 – 7]. Elevated CRP levels are considered to be an independent predictor of cardiovascular events in the general population [5]. In our study, the rising number of MetS RFs was associated with increase in markers of inflammation (white blood cell count, hsCRP) only in the omnivores. Subsequently, the impact of subclinical inflammation on the presence of MetS RFs, even in the absence of MetS itself, is to be considered. Our data suggest that a vegetarian diet may postpone microinflammation associated with the MetS RFs. This question remains to be elucidated, particularly since hsCRP was recently suggested as an additional clinical criterion for MetS and global cardiovascular risk prediction [35].

Plasma levels of vitamins with antioxidant properties pointed to a balanced diet in both cohorts, since they did not differ significantly, except for lower β-carotene levels in the omnivores. This fits to the data obtained from food frequency questionnaires, showing higher intake of β-carotene and vitamin C in vegetarians, confirming their higher consumption of fruits and vegetables. Surprisingly, and contrary to the results of our previous studies [36], plasma levels of the other vitamins were not lower in the omnivores. This may indicate some positive changes of dietary habits of the educated urban population after the fall of the iron curtain in Eastern Europe, reflecting the balance between demand and supply on the market. The comparable levels of vitamin C between the cohorts may be attributed to the time point of sampling – late spring – when vegetables and fruits of inland provenience are available for a sufficient duration of time to achieve saturation of the organism. This, in combination with the incomparably lower number of subjects studied, may account for the discrepancy to the HNANES study, in which the presence of MetS was associated with lower vitamin C levels and a decreasing trend of vitamin C concentration with the number of MetS RFs was observed [9].

Plasma vitamin A levels increased with appearance of MetS RFs significantly in vegetarians, and those of vitamin E in both cohorts. Multiple regression analyses showed that vitamin E concentration was the major factor determining the number of MetS RFs in the vegetarians and all subjects, while it was the third strongest and independent factor in the omnivores. These data correspond to the observation of Ford *et al.* [9], who showed a similar association among HNANES III participants. The positive relationship between vitamin E concentration and MetS RFs status supports the assumption that this antioxidant vitamin, at its physiological concentrations, is directly related to MetS, even in the general healthy normoglycemic population. Long-term administration of pharmacological doses of vitamin E improved insulin action both in clinical and experimental settings [37, 38]. In view of the mentioned facts, the clinical relevance and the mechanisms leading to increased vitamin E concentration with appearance of MetS RFs requires further investigation.

It is to be stressed that *in vivo* antioxidants operate concertedly to provide an effective antioxidant defence. The carotenoid molecule repairs the vitamin E radical, and, in turn is repaired by vitamin C [39]. Thus, the synergistic protection is dependent upon a balance between all the components, and an increase/decrease in the concentration of one might disturb the balance, reducing the antioxidant effectiveness of the system [40]. The observed relationship of vitamins A, E or C to markers of oxidation, such as MDA, AGEs and AOPPs, is to be viewed in this regard, and underlies the complexity of the system *in vivo*.

In conclusion, we found that in normoglycemic healthy subjects in a good nutritional state the manifestation of MetS RFs seems not to be directly influenced by dietary regimen, although the role of nutrition might not be definitively excluded. A balanced nutritional regimen (a traditional Western mixed diet or vegetarian) renders comparable antioxidant defence in prevention of plasma lipid peroxidation and advanced glycation. The surprising finding of higher levels of circulating AOPPs in vegetarians remains unclear and its clinical relevance is to be elucidated in controlled studies. However, our data suggest that vegetarian diet could render at least partial protection against toxic effects of mildly accumulated AOPPs and AGEs. Moreover, it ensures higher insulin sensitivity and seems to exert a protective effect in the development of microinflammation associated with MetS. However, the latter finding is to be confirmed in larger studies, particularly since hsCRP was recently suggested to be added to MetS and to the assessment of global cardiovascular risk.

We wish to acknowledge the support from the Verein zur Bekämpfung der Hochdruck- und Nierenkrankheiten e. V., Würzburg, Germany, and the excellent assistance of Andreé Klassen in preparing the manuscript.

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