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The impact of metabolic syndrome on carotid intima media thickness

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Abstract. – OBJECTIVES: Metabolic syndrome (MetS) is a cluster of metabolic abnormalities involving several cardiovascular risk factors. Carotid intima media thickness (CIMT) is an important early screening tool to assess subclinical manifestation of cardiovascular and metabolic diseases. We aimed to investigate the impact of MetS on CIMT in a large scaled community based study.

METHODS: The study was conducted on 2102 participants. Carotid intima media thickness was measured in all of the participants. The study sample was divided into 4 groups; Group 1 subjects with a body mass index (BMI) < 25.0 kg/m² [n = 499 (MetS- = 488, MetS+ = 11)], Group 2 BMI between 25.0 and 29.9 kg/m² [n = 693 (MetS- = 559, MetS+ = 134)], Group 3 BMI between ≥ 30 kg/m² and 39.9 kg/m² [n = 822 (MetS- = 375, MetS+ = 477)], and Group 4 BMI ≥ 40 kg/m² [n = 88 (MetS- = 27, MetS+ = 61)].

RESULTS: Carotid intima media thickness was higher in the individuals with MetS compared to their normal counterparts. Furthermore, the subgroup analysis showed that CIMT values in Group 1 (0.55±0.18 vs 0.82±0.70; $p < 0.001$), Group 2 (0.59±0.20 vs 0.68±0.18; $p < 0.001$) and Group 3 (0.61±0.15 vs 0.65±0.18; $p < 0.001$) were significantly higher in subjects with MetS compared to their normal counterparts, whereas the values were similar in Group 4 (0.62±0.13 vs 0.65±0.17; $p = 0.363$).

CONCLUSIONS: Carotid intima media thickness of overweight, obese and normal weight individuals without MetS were lower than their counterparts with MetS. MetS had no impact on CIMT in morbid obese individuals possibly due to established insulin resistance earlier than MetS.

Key Words:
Metabolic Syndrome, Carotid intima media thickness.

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities involving several cardiovascular risk factors. These include visceral obesity, hypertension, hypertriglyceridemia, a low level of high density lipoprotein cholesterol, and impaired glucose tolerance[1]. Insulin resistance is the most accepted unifying theory explaining the pathophysiology of the metabolic syndrome[2]. The scientific community has accepted the MetS as a predictor of cardiovascular diseases[3,4]. The prevalence increases with age and body mass index (BMI)[5]. Although the MetS is associated with obesity, it has been highlighted that not every obese subject has a deranged metabolic profile, and the term metabolically healthy obese (MHO) has been coined[6-8]. Some obese subjects only show one or two of the MetS components, others have none at all[9]. There were conflicting reports whether or not MHO subjects shows an increased risk for CV disease or mortality compared with normal weight subjects without the MetS[10-13].

Measurement of carotid intima media thickness (CIMT) is assessed by a noninvasive ultrasound imaging technique that can measure the extent of generalized atherosclerosis detected in the arterial wall. CIMT is an important early screening tool to assess subclinical manifestation of cardiovascular and metabolic diseases[14]. We aimed to investigate the impact of MetS on CIMT in a large scaled community based study.

Methods

Study Population

The MELEN Study is a prospectively designed survey on the prevalence of cardio metabolic risk factors in Turkish adults. The baseline visits were carried out in May and June, 2010 and biennial follow-up visits were planned. The name of the study

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comes from the geographic valley in north-east of Duzce, Turkey which is inhabitant of 21000 people. There is a town centre (Yigilca) and 37 villages. Health Service of the region was supplied by six family physicians, each following up almost 2500 adults. The study was conducted in May and June, 2010 in the Social Health Center located in the town center. 400 subjects from each family physician representatively stratified for sex, age and for rural-urban distribution were randomly assigned and invited to participate the study. A total of 2298 subjects with a mean age of 50 (age range 18 to 92) were interviewed. The study protocol was approved by the Ethics Committee of Duzce University and every subject signed a consent form. Data were obtained by a validated questionnaire, physical examination of the cardiovascular system, sampling of blood, recording of a resting electrocardiogram, carotid-intima media thickness and visceral fat measurement. The participants who refused CIMT measurement and blood sampling were excluded.

Measurements

Blood pressure was measured in the sitting position on the right arm, and the mean of two recordings at least 3 min apart was recorded. Weight and visceral body composition was measured without shoes in light indoor clothes using a bio-impedance meter (Omron BF 510; Omron Corp. Kyoto, Japan). Waist circumference was measured with a tape, the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The study sample was divided into 4 groups; Group 1) subjects with a BMI < 25.0 kg/m^2 [normal weight group, n = 499 (MetS– = 488, MetS+ = 11)], Group 2) subjects with a BMI between 25.0 and 29.9 kg/m^2 [overweight group, n = 693 (MetS– = 559, MetS+ = 134)], Group 3) subjects with a BMI between ≥ 30 kg/m^2 and 39.9 kg/m^2 [obese group, n = 822 (MetS– = 375, MetS+ = 477)], and Group 4) subjects with a BMI ≥ 40 kg/m^2 [morbid obese group, n = 88 (MetS– = 27, MetS+ = 61)][15].

The participants underwent a Doppler Ultrasound examination (M Turbo, SonoSite Inc., Bothell, WA, USA) with a 5-12 MHz linear-array transducer. Ultrasonography was performed with the subject in the supine position. A careful search was performed to obtain optimal visualization of the vessel wall demonstrating the typical double lines representing the intima media layer. At least three consecutive longitudinal images of the common carotid artery were obtained. Measurements involved common carotid artery, bifurcation and origin (first 2 cm) of the internal carotid arteries. Carotid intima media thickness was measured from the thickest point on the far wall between the lumen–intima interface and the media–adventitia interface, using visual assessment[14]. Measurements were done 3 times at a site free of plaque and the mean of the three measurements was recorded. No software analysis was used during and after the measurement process. All measurements were made by two experienced radiologists (F.H.B. and O.Y.). The interobserver coefficient of variation was 4.1%.

Sample Collection

Ten milliliters of blood were drawn from the antecubital vein of each subject by applying minimal tourniquet force. Eight ml of blood was drawn into a vacutainer tube without anticoagulant. These blood samples were allowed to clot for 20 minutes prior to centrifugation. The blood tubes were centrifuged for 10 min at 1500 × g and were processed within 30 minutes in place. Sera were shipped within a few hours on cooled gel packs at 2-5°C, reached to the Duzce University Central Laboratory and were kept at –80°C until the final analyses.

Biochemical Analysis

Serum concentrations of cholesterol, fasting triglycerides, HDL-cholesterol, glucose, electrolytes, liver function tests and other biochemical variables were measured by a Cobas 6000 auto analyzer using commercially available kits (Roche Diagnostics GmbH, Mannheim, Germany). LDL-cholesterol values were computed according to the Friedewald formula.

Definitions

Individuals with diabetes mellitus were diagnosed with criteria of the American Diabetes Association[16] namely when fasting plasma glucose level was > 126 mg/dl, or a Hemoglobin A1C was > 6.5%, or a casual plasma glucose was > 200 mg/dl with classic symptoms of hyperglycemia and/or the current use of diabetes medication. Individuals with metabolic syndrome were identified when 3 out of the 5 criteria of the National Cholesterol Education Program (ATP III)[17] were met, modified for impaired fasting glucose (fasting glucose 100-125 mg/dl[18] and further for abdominal obesity using as cut point 95 cm in men and 90 cm in women, as assessed

in the Turkish Adult Risk Factor study[19]. Hypertension was defined as a blood pressure of > 140 mm Hg and/or 90 mmHg, and/or use of antihypertensive medication. Diagnosis of nonfatal coronary artery disease (CAD) was based on the presence of angina pectoris, history of myocardial infarction with or without accompanying Minnesota codes of the ECG, or history of myocardial revascularization.

Statistical Analysis

Statistical Package for Social Sciences software 12 (SPSS Inc., Chicago, IL, USA) was used for analysis. Descriptive parameters were shown as mean ± standard deviation or in percentages. Two-sided *t*-tests and Pearson's chi-square tests were used to analyze the differences in means and proportions between groups. Abnormally distributed variables were compared using Mann-Whitney U test. Multiple group comparisons were performed with analysis of variance (ANOVA). Linear regression analysis was applied to identify independent correlates of CIMT. Thickened CIMT was defined as mean ± 1SD (> 0.8 mm). Spearmen's correlation test was used to assess correlations between CIMT and MetS. A *p* value of < 0.05 was considered significant.

Results

The final cohort included 2102 participants. Metabolic syndrome was presented in 658 persons (464 women, 189 men with a mean age of 50). Characteristics and demographic findings of the study population were shown in Table I. Mean CIMT was significantly higher in patients with MetS (Figure 1). Hypertension was signifi-

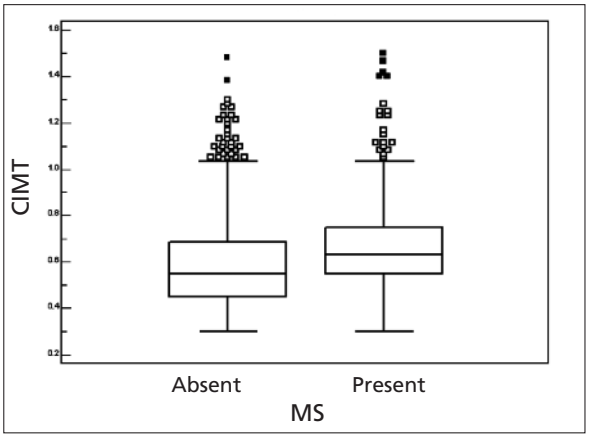

Figure 1. CIMT values compared with MetS– and MetS+.

Table I. Characteristics and demographic findings of the study population.

	Group 1			Group 2			Group 3			Group 4		
	MS(–) (n: 488)	MS(+) (n: 11)	*p*	MS(–) (n: 559)	MS(+) (n: 134)	*p*	MS(–) (n: 375)	MS(+) (n:447)	*p*	MS(–) (n:27)	MS(+) (n:61)	*p*
Gender (Female)	252 (52%)	4 (36%)	0.226	324 (58%)	64 (48%)	0.032	300 (80%)	338 (76%)	0.141	25 (93%)	58 (95%)	0.311
HT	95 (19%)	8 (73%)	< 0.001	176 (31%)	84 (63%)	< 0.001	160 (43%)	321 (72%)	< 0.001	18 (67%)	52 (85%)	0.025
Smoker	152 (31%)	1 (9%)	0.095	119 (21%)	23 (17%)	0.284	26 (7%)	46 (10%)	0.09	1 (4%)	5 (8%)	0.419

cantly more frequent in patients with MetS among all the BMI groups. There was also a male predominance with MetS among overweight cohort (Table I).

Linear regression analysis revealed that age and smoking were the significant correlates of CIMT in participants without MetS, whereas in subjects with MetS, the significant correlates were age, systolic blood pressure and HDL cholesterol (Table II)

Age, systolic blood pressure, waist circumference neck circumference, visceral adiposity, fasting glucose, triglyceride, HDL cholesterol, creatinine and HOMA-IR levels were significantly higher in individuals with MetS in the overweight, obese and morbid obese groups with respect to the normal weight group (Table III. Mean CIMT values according to the BMI groups were shown in Table II. CIMT values in groups 1, 2 and 3 were significantly higher in subjects with MS whereas there was no difference in mean CIMT according to the presence of MetS in morbid obese participants (Table III).

Correlation analysis revealed that BMI of patients with MetS does not have a significant correlation with CIMT ($r = –0.05$; $p = 0.234$) whereas BMI of subjects without MetS has a positive significant correlation with CIMT ($r = 0.12$; $p = < 0.001$).

Discussion

The present study showed that mean CIMT values of individuals with MetS, except morbid obese, were significantly higher compared to individuals without MetS. This association was significant in normal weight, overweigh and obese groups. There was no difference between CIMT values of morbid obese subjects according to co-existence of MetS. Our data agreed with the previous reports which have shown that the presence of MetS increases the CIMT in young, middle and elderly population[20,21].

The physiological mechanisms for the relationships between CIMT and metabolic risk may relate to insulin levels acting on the arterial wall, resulting in cellular remodeling, or through insulin's association with clustering of multiple cardiovascular disease risk factors[22].

Several reports have shown that insulin resistance which is the main component of MetS is the most enhancing factor that increases CIMT but there is no difference between CIMT values in individuals without insulin resistance even if they are obese. Cremona Study[10] demonstrated that obese insulin-sensitive individuals, also known as metabolically healthy obese (MHO) individuals have less features of the metabolic syndrome, when compared with their insulin-resistant counterparts; and have similar risk of cardiovascular disease, compared with the normal-weight insulin-sensitive subjects. St-Pierre et al[13] showed that obesity is an important risk factor for ischemic heart disease but variations in BMI alone poorly reflect the risk of ischemic heart disease associated with features of insulin resistance syndrome. In addition, in another study found greater CIMT in obese individuals with insulin resistance when compared to their counterparts with no insulin resistance[23].

The other studies have shown that obesity is not so harmless and caused an increase in cardiovascular risk and mortality even if they do not have any metabolic abnormalities[11,24]. Although Montalcini et al[25] and Camhi et al[26] have not detected a relationship between BMI and carotid atherosclerosis in their study; we have shown that CIMT increases even in individuals without MetS according to their normal-weight counterparts. We also found that the presence of MetS has a more important role in carotid intima media thickening, and BMI has no effect on CIMT in subjects without MetS.

Table II. Significant correlates of CIMT in linear regression analysis.

Variable	MetS (–)		MetS (+)	
	Beta value	*p* value	Beta value	*p* value
Age (year)	0.571	< 0.001	0.574	< 0.001
Smoker	0.128	0.001	–	–
Systolic blood pressure (mmHg)	–	–	0.310	0.001
HDL cholesterol (mg/dl)	–	–	-0.179	0.031

Table III. Comparison of clinical variables according to the BMI groups.

	Group 1		Group 2		Group 3		Group 4	
	MS– (n:488)	MS+ (n:11)	MS– (n:559)	MS+ (n:134)	MS– (n:375)	MS+ (n:447)	MS– (n:27)	MS+ (n:61)
Age (year)	45 ± 18	61 ± 15**	48 ± 16	57 ± 13***	50 ± 13	54 ± 11***	51 ± 13	52 ± 11
SBP (mmHg)	114 ± 20	127 ± 16*	121 ± 21	134 ± 22***	128 ± 23	142 ± 24***	139 ± 27	142 ± 24
DPB (mmHg)	72 ± 11	75 ± 15	77 ± 12	83 ± 13***	81 ± 13	86 ± 12***	88 ± 14	87 ± 15
Waist circumference (cm)	79 ± 8	101 ± 5***	89 ± 8	101 ± 4***	101 ± 10	107 ± 7***	113 ± 12	119 ± 12
Visceral adiposity (%)	6 ± 2	9 ± 3***	9 ± 3	12 ± 3***	12 ± 3	13 ± 4***	13 ± 4	14 ± 3
Total Body Fat (%)	23 ± 9	24 ± 10	32 ± 9	32 ± 8	42 ± 8	42 ± 8	50 ± 6	51 ± 4
Muscle (%)	34 ± 7	34 ± 5	30 ± 5	30 ± 5	26 ± 4	26 ± 4	22 ± 3	23 ± 2
Neck circumference (cm)	34 ± 3	38 ± 2***	36 ± 3	38 ± 3***	37 ± 4	38 ± 3***	38 ± 6	40 ± 3
FBG (mg/dl)	105 ± 37	136 ± 29**	105 ± 29	140 ± 60***	109 ± 43	137 ± 66***	99 ± 19	138 ± 77**
Creatinine (mg/dl)	0.8 ± 0.2	0.9 ± 0.3*	0.8 ± 0.3	0.9 ± 0.3**	0.7 ± 0.2	0.8 ± 0.3***	0.8 ± 0.3	0.8 ± 0.2
Total Cholesterol (mg/dl)	168 ± 35	178 ± 25	178 ± 40	194 ± 37***	182 ± 35	195 ± 42***	176 ± 33	182 ± 37
Triglyceride (mg/dl)	128 ± 76	246 ± 118***	157 ± 107	255 ± 149***	148 ± 105	248 ± 129***	140 ± 85	201 ± 107**
LDL (mg/dl)	95 ± 28	96 ± 25	103 ± 35	109 ± 32	107 ± 30	109 ± 36	97 ± 25	107 ± 45
HDL(mg/dl)	48 ± 12	40 ± 10*	46 ± 12	38 ± 10***	48 ± 11	41 ± 10***	51 ± 15	41 ± 10***
HOMA	3.2 ± 3.8	9.4 ± 11.5***	3.9 ± 5.7	7.7 ± 9.9***	4.2 ± 6	7.9 ± 12***	2.9 ± 3	7.5 ± 12
Hemoglobin (g/dl)	13 ± 2	13 ± 2	13 ± 2	14 ± 1*	13 ± 1	13 ± 2	13 ± 2	13 ± 1
CIMT (mm)	0.55 ± 0.18	0.82 ± 0.70***	0.59 ± 0.20	0.68 ± 0.18***	0.61 ± 0.15	0.65 ± 0.18***	0.62 ± 0.13	0.65 ± 0.17

Present study has shown differently from other studies that MetS does not add additional risk in the increase of carotid intima media in morbid obese individuals. Examination of the cardio metabolic risk profiles of morbid obese individuals revealed that fasting glucose, HDL and TG levels, which all are required for the diagnosis of MetS, significantly diverge in existence of MetS as in the other groups; normal weight, overweight and obese groups; respectively. On the other hand, levels of HOMA which is the indicator of insulin resistance were similar only in the morbid obese groups. The reason of this similarity in CIMT and HOMA-IR can be explained with the assumption that morbid obese individuals establish insulin resistance earlier than MetS. Overweight, obese and normal weight individuals with MetS have earlier increase in CIMT. On the other hand, in morbid obese, this association could not be shown. They have thickened CIMT whether or not they have MetS.

Conclusions

Carotid intima media thickness of overweight, obese and normal weight individuals without MetS were lower than their counterparts without MetS. MetS had no impact on CIMT in morbid obese individuals possibly due to established insulin resistance earlier than MetS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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