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Levels of physical activity are correlated with intima media ratio in subjects without but not with metabolic syndrome: A study of Iranians without a history of cardiovascular events

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We aimed to investigate the relationship between carotid Intima Media Thickness (CIMT) and physical activity levels (PAL), in subjects with and without metabolic syndrome (MetS) and in individuals with and without carotid artery plaque (CAP) defined using high-resolution ultrasound. Method: A sample of 506 subjects [215 (42.5%) males], aged 35–64 years was recruited from an urban population in Mashhad, Iran, using a stratified-cluster method as part of the Mashhad Stroke Heart Atherosclerosis Disorder (MASHAD) study cohort. This sub-sample was selected randomly from a cohort of 9765 individuals for carotid duplex ultrasound. Comparisons were made between individuals with and without CAP on the one hand, and between participants with and without MetS on the other hand with regard to physical activity and cardiometabolic risk level, as well as their correlation with CIMT. Result: PAL was positively and significantly correlated with CIMT in the total sample ($r = 0.132$, $p < 0.001$). The correlation coefficient was 0.132 ($p = 0.426$) in the MetS+ participants and 0.440 ($p < 0.001$) in the MetS- participants. The correlation of PAL with CIMT was also positive and significant in CAP+ participants ($r = 0.150$, $p < 0.001$), but not in the CAP- participants (r = _0.001, $p = 0.621$), with however a non-significant difference between the two estimates ($p = 0.374$). Hip circumference was correlated with CIMT in MetS- but not MetS+ participants. Conclusion: physical activity in the current study appeared to be a correlate of infraclinical CVD risk in participants without metabolic syndrome, but not in those without.

In a previous study we reported that physical activity (PA) was negatively associated with weight, systolic blood pressure, triglyceride concentration and fat free mass in an Iranian population [1]. The impact of levels of physical activity on peripheral arterial vascular wall structure and function in people with metabolic syndrome is still debated. Carotid intima–media thickness (CIMT) and the presence of carotid plaques are markers of clinically

important atherosclerosis [2], and CIMT has been proposed for assessing cardiovascular risk [2]. We aimed to investigate the relationship between CIMT and physical activity levels, in subjects with and without metabolic syndrome (MetS) and in individuals with and without carotid artery plaque (CAP) defined using high-resolution ultrasound. We also assessed the relationship between CIMT with cardiometabolic risk profile and in relationship to the presence vs. absence of MetS or CAP. We have previously reported that physical activity (PA) was negatively associated with weight, systolic blood pressure, triglyceride concentration and fat free mass in an Iranian population (1). However, the impact of physical activity on peripheral artery wall structure and function in people with metabolic syndrome is a matter of debate. Carotid intima–media thickness (CIMT) and the presence of carotid plaques by ultrasound are markers of sub-clinical atherosclerosis (2), and measurement of CIMT has been proposed for assessing cardiovascular risk (2). The objective of this study was to investigate whether there was a relationship between CIMT, or the presence of carotid artery plaque (CAP), both determined by carotid ultrasound, and levels of physical activity in an Iranian population with, or without metabolic syndrome (MetS). We also assessed the relationship between CIMT and elements of the cardiometabolic risk profile overall and according to the presence vs. absence of MetS or CAP.

A sample of 506 subjects [215 (42.5%) males], aged 35–64 years, was recruited from an urban population in Mashhad, Iran, using a stratified-cluster method as part of the Mashhad Stroke Heart Atherosclerosis Disorder (MASHAD) study cohort [3]. This subsample was selected randomly from a cohort of 9765 individuals for carotid duplex ultrasound. The key characteristics of the subsample were similar to those of the overall cohort. None of the subjects had a history of a cardiovascular event. CAP and CIMT were measured for both common and internal carotid arteries using a high-resolution ultrasound scanner (Medison, SA8000 Ex, Seoul, South Korea) equipped with a linear-array transducer. The maximum

intima-media thickness was measured on frozen B mode images. CIMT was measured between the leading edge of the first echogenic line (lumen– intima interface) and the second echogenic line (upper layer of the adventitia) in the far (deeper) artery wall [4]. All measurements were made on frozen, enlarged images at the end of diastole, with the transducer in the Medio lateral position [4]. Similarly, CAP was assessed by duplex-ultrasound of both common and internal carotid arteries. CIMT values were calculated as the average of three areas on both the right and left carotid artery: right common carotid artery (RCCA), right bulb (bifurcation) (RB), right internal carotid artery (RICA), left common carotid artery (LCCA), left bulb (left bifurcation) (LB) and left internal carotid artery (LICA) measurements. The presence of one or more CIMT 0.8 mm in one major area (RCCA, RB, RICA, LCCA, LB and LICA) was considered to be evidence of significant CIMT atherosclerosis (CIMT [+]) [4]. Patients in whom CIMT was <0.8 mm were considered to have a normal duplex ultrasound-defined by CIMT [4]. Physical activity was assessed as previously described [5], using the James and Schofield human energy requirements equations [6]. Physical activity level was calculated as the total energy expenditure (TEE) and ratio of the BMR (Basal Metabolic Rate) over a twenty-four hour period. Questions on physical activity were based on the James and Schofield equations, and were selected from those used in the Scottish Heart Health Study (SHHS)/ MONICA questionnaire [6]. Questions assessed the time spent on activities during work (including housework), outside work, and in bed (resting and sleeping) [6]. Cardiometabolic profile was assessed for all participants as previously described [7]. MetS was defined according to the modified NCEP ATP III criteria for Iranian adults [8]. Framingham Risk Score was used to estimate the 10-year cardiovascular risk [9]. Comparisons were made between individuals with and without CAP on the one hand, and between participants with and without MetS on the other hand with regard to physical activity and the level of cardio-metabolic risk, as well as their

correlation with CIMT. Correlation coefficients were comparison were compared using the Steiger test. Five hundred and six subjects [215 (42.5%) males], aged 35 to 64 years, were recruited from an urban population in Mashhad, Iran, using a stratified-cluster method as part of the Mashhad Stroke Heart Atherosclerosis Disorder (MASHAD) study cohort (3). This sub-sample was selected randomly from a cohort of 9765 individuals for carotid duplex ultrasound. The key characteristics of the sub-sample were similar to those of the overall cohort. None of the subjects had a history of a cardiovascular event. Carotid artery plaque (CAP) and Carotid intima-media thickness (CIMT) were measured by examining both common and internal carotid arteries using a high-resolution ultrasound scanner (Medison, SA8000 Ex, Seoul, South Korea) equipped with a linear-array transducer. CAP was defined by the presence of plaque regardless of the number and size. CIMT was based on the average of three areas on both the right and left carotid artery: right common carotid artery (RCCA), right bulb (bifurcation) (RB), right internal carotid artery (RICA), left common carotid artery (LCCA), left bulb (left bifurcation) (LB) and left internal carotid artery (LICA) measurements. Physical activity (PAL) was assessed as previously described (4), and was calculated as the total energy expenditure (TEE) and ratio of the BMR (basal metabolic rate) over a twenty-four hour period (4). Cardiometabolic profile was assessed for all participants as previously described (5). MetS was defined according to the modified NCEP ATP III for Iranian adults (6). Framingham Wilson Risk Score was used to estimate the 10-year cardiovascular risk (7). Comparisons were made between individuals with and without CAP, and between participants with and without MetS, with respect to physical activity and cardiometabolic risk factors, as well as their correlation with CIMT. Correlation coefficient comparisons were based on the Steiger test.

A total of 138 participants were positive for CAP. Their characteristics including physical activity levels were similar to those without CAP with the exception of waist circumference

(CAP + vs. CAP-: 89 vs. 95 cm, $p < 0.001$), CIMT (0.54 vs. 0.50 mm, $p = 0.022$), and Framingham score (11.6 vs. 9.4%, $p = 0.036$). In all, 122 participants had metabolic syndrome. Total serum cholesterol, HDL-cholesterol, LDL-cholesterol and current smoking habit, did not differ significant between MetS+ and MetS- participants, while all other characteristics were significantly different ($p < 0.05$). Physical activity level (Mets+ vs. MetS-) was 0.66 vs. 0.97 ($p = 0.001$), and CIMT level was 0.56 vs. 0.49 mm ($p = 0.031$). PAL was positively and significantly correlated with CIMT in the total sample ($r = 0.132$, $p < 0.001$). The correlation coefficient was 0.132 ($p = 0.426$) in the MetS+ participants and 0.440 ($p < 0.001$) in the MetS- participants, with comparisons indicating a significant difference between the two groups ($p < 0.001$ for correlation coefficients comparison). The correlation of PAL with CIMT was also positive and significant in CAP+ participants ($r = 0.150$, $p < 0.001$), but not in the CAP- participants (r = _0.001, $p = 0.621$), with however a non-significant difference between the two estimates ($p = 0.374$). In the overall sample, CIMT was also significantly correlated with age ($r = 0.560$, p = < 0.001), body mass index (r = _0.105, $p = 0.031$), systolic ($r = 0.218$, p = < 0.001) and diastolic blood pressure ($r = 0.186$, $p < 0.001$), total cholesterol ($r = 0.142$, $p < 0.001$), fasting glucose ($r = 0.152$, $p < 0.001$) and total haemoglobin ($r = 0.219$, $p < 0.001$). These correlations appeared to be mostly similar between MetS+ and MetS- participants (all $p > 0.05$), but significantly different between CAP+ and CAP- participants for the correlation of CIMT with age ($p < 0.001$), SBP ($p = 0.035$) and total haemoglobin ($p < 0.001$). Furthermore, hip circumference was correlated with CIMT in MetS- but not MetS + participants, while LDL-cholesterol was significantly associated with CIMT in both CAP+ and CAP- participants, but in the opposite directions ($p < 0.001$ for comparison of the correlation coefficients) (Tables 1, 2).

Discussion

In this study, we found a significant correlation between CIMT and PA in this population-based cohort of Iranians without prior CVD, which was primarily driven by a strong and significant correlation in participants without metabolic syndrome, and no correlation in those with metabolic syndrome. Other investigators have reported an association between PA and CIMT [10]. The significant correlation of CIMT and other markers of subclinical CVD with PA has been reported in several other studies [11–16]. Other studies have revealed incident metabolic syndrome to be a predictor of progression of CIMT [17,18]. It appears that insulin resistance, which is an important feature of MetS, is the most important determinant of the increased CIMT in MetS; no differences were found in CIMT values in individuals without insulin resistance even if they were obese [17,19,20]. Furthermore, it has been reported that the CIMT of overweight, obese and normal weight individuals without MetS were lower than their counter- parts without MetS [17,21]. It is therefore likely that insulin resistance blunts the effects of physical activity on CIMT and explains the lack of association between physical activity and CIMT in our MetS+ participants. The overall burden of CVD risk factors in individuals with MetS may enhance the CIMT so that this is uniformly high in this group, while a gradient of CVD risk factors among individual without MetS could lead to a larger spectrum of CMIT levels, that hence allows the relationship with physical activity to be revealed. In conclusion, physical activity appeared to be a correlate of sub-clinical CVD risk in participants without metabolic syndrome, but not in those without. This differential association suggests that in strategies aiming to screen population's risk of CVD, consider-ation should be given to the possible added value of lifestyle factors such as physical activity level in people with low burden of cardiometabolic risk factors.

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Table1: characteristics of the population overall, by status for CVD and by status for metabolic syndrome

variables	Overall	Carotid artery plaque			Metabolic syndrome		
		Present	Absent	p	Present	Absent	p
n		138	384		122	400	
Age (y)	48.78±8.00	50.77±8.32	48.54±7.94	0.077	50.71±7.53	48.30±8.05	0.013
Body mass index (kg/m^2)	27.19±4.55	27.42±4.42	27.16±4.57	0.745	31.61±5.31	26.11±3.60	<0.00
Waist Circumference (cm)	94.85±10.71	89.55±10.55	95.43±10.58	<0.00	98.47±10.38	93.93±10.61	<0.00
Hip Circumference (cm)	102.56±8.96	100.73±9.32	102.77±8.91	0.161	104.66±9.33	102.04±80.80	0.016
Demispan (cm)	77.42±16.36	76.42±4.86	77.52±17.14	0.685	74.09±5.24	78.25±18.01	0.037
Systolic BP (mmHg)	120.75±15.03	122.09±14.35	120.59±15.13	0.536	131.62±16.10	118.10±13.52	<0.00
Diastolic BP (mmHg)	80.47±10.72	79.02±10.44	80.64±10.76	0.691	85.07±11.60	79.34±10.20	<0.00
Total cholesterol (mg/dl)	191.74±35.18	193.42±33.98	191.54±35.35	0.742	197.20±37.41	190.42±34.55	0.112
HDL-cholesterol (mg/dl)	43.00±8.10	43.36±8.34	42.95±8.08	0.761	42.82±8.58	43.04±7.99	0.863
LDL-cholesterol (mg/dl)	118.74±25.30	125.26±25.90	118.07±25.18	0.109	115.32±26.95	119.63±24.82	0.356
Triglycerides (mg/dl)	125.65±47.10	134.58±49.11	124.65±46.85	0.231	113.19±38.10	128.46±48.52	0.017
Fasting glucose (mg/dl)	89.66±22.55	87.85±23.69	89.88±22.44	0.583	109.42±35.93	84.97±14.52	<0.00
Hs-CRP (mg/L)	5.08±13.96	7.03±13.26	4.86±14.04	0.321	7.47±20.69	4.50±11.71	0.079
White cells (cells/ml)	6.02±1.31	6.05±1.74	6.01±1.26	0.884	6.32±1.33	5.94±1.30	0.023
Haemoglobin (g/dl)	13.81±1.55	14.05±1.23	13.78±1.58	0.315	13.51±1.28	13.88±1.61	0.042
Platelet (10^3/microliter)	231.18±58.57	225.59±59.10	231.84±58.55	0.504	250.72±25.82	226.32±58.98	<0.00
Physical activity level	0.91±0.77	0.92±0.70	0.90±0.78	0.625	0.66±0.63	0.97±0.79	<0.00
CIMT (mm)	0.50±0.10	0.54±0.12	0.50±0.10	0.022	0.56±0.11	0.49±0.10	0.031
Framingham Score	9.60±6.74	11.60±7.46	9.37±6.62	0.036	11.68±6.52	9.34±6.77	0.024
Current Smoking (%)	23.2	25.1	23.1	0.361	26.7	23.2	0.231
Hypertension (%)	21.4	22.4	21.8	0.412	40	20	<0.00
Diabetes mellitus (%)	8.8	10.2	9.3	0.652	32.1	2.9	<0.00
Dyslipidemia (%)	17.4	23.6	19.7	0.521	25.4	17.1	<0.00

Table 2: correlation (p-value) of CIMT with characteristics overall and by status for carotid artery plaque (CAP) and metabolic syndrome (MetS)

variables	Overall	CAP (N=138)	No CAP (N=384)	P*	MetS +(122)	MetS –(400)	P*
Age	0.560 (<0.001)	0.774 (<0.001)	0.524 (<0.001)	<0.00	0.485 (<0.001)	0.578 (<0.001)	0.111
Body mass index	-0.105 (<0.031)	0.004 (0.231)	-0.123 (<0.012)	0.053	-0.123 (0.265)	0.132 (<0.016)	0.462
Waist Circumference	0.030 (0.328)	-0.087 (0.123)	0.064 (0.239)	0.234	0.134 (0.325)	0.049 (0.429)	0.193
Hip Circumference	-0.076 (0.145)	0.010 (0.062)	-0.082 (0.145)	0.236	0.070 (0.146)	0.123 (<0.038)	0.288
Demispan	-0.021 (0.625)	-0.010 (0.132)	-0.020 (0.628)	0.501	-0.113 (0.365)	0.011 (0.426)	0.125
Systolic BP	0.218 (<0.001)	0.126 (0.423)	0.229 (<0.001)	0.035	0.219 (0.125)	0.227 (<0.001)	0.463
Diastolic BP	0.186 (<0.001)	0.205 (0.268)	0.191 (<0.001)	0.365	0.207 (0.469)	0.183 (<0.001)	0.389
Total cholesterol	0.142 (<0.001)	0.152 (0.092)	0.140 (<0.001)	0.321	0.144 (0.324)	0.132 (<0.028)	0.465
HDL-cholesterol	0.080 (0.163)	0.262 (0.083)	0.053 (0.326)	<0.00	0.080 (0.476)	0.081 (0.637)	0.492
LDL-cholesterol	-0.042 (0.092)	0.390 (<0.022)	-0.109 (<0.019)	<0.00	-0.094 (0.624)	0.025 (0.924)	0.251
Triglycerides	-0.020 (0.237)	0.045 (0.235)	-0.039 (0.278)	<0.00	-0.100 (0.128)	0.038 (0.356)	0.251
Fasting glucose	0.152 (<0.001)	0.133 (0.923)	0.159 (<0.001)	0.052	0.289 (<0.035)	0.080 (0.124)	0.057
Hs-CRP	0.059 (0.429)	0.155 (0.145)	0.040 (0.426)	0.023	0.119 (0.426)	0.036 (0.436)	0.195
White cells	-0.018 (0.324)	-0.232 (0.095)	0.016 (0.062)	0.442	0.058 (0.092)	0.043 (0.351)	0.443
Haemoglobin	0.219 (<0.001)	0.046 (0.325)	0.233 (<0.001)	<0.00	0.330 (<0.001)	0.236 (<0.001)	0.148
Platelet	-0.071 (0.168)	-0.041 (0.712)	-0.072 (0.128)	<0.00	-0.217 (0.862)	0.042 (0.624)	0.005
Physical activity level	0.133 (<0.001)	-0.001 (0.621)	0.149 (<0.001)	0.374	0.132 (0.426)	0.449 (<0.001)	<0.001

***** p-value for the difference in correlation coefficients.