

Regaining body weight after weight reduction further increases pulse wave velocity in obese men with metabolic syndrome

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Abstract

Subjects with metabolic syndrome (MetS) or obesity have worse arterial stiffness. However, there have been no studies addressing time-sequential changes in pulse wave velocity (PWV) after weight loss and then regaining weight in obese non-diabetic men with MetS.

We prospectively enrolled 40 obese, non-diabetic men with MetS undergoing a 3-month weight reduction program. Another 26 lean and healthy men were recruited for comparisons. Oral glucose tolerance test and brachial ankle (ba) PWV were assessed in study subjects. Eighteen obese non-diabetic MetS and 15 lean control subjects had follow-ups at the 60th month.

The body weight of obese MetS decreased from 94.8 ± 7.6 to 86.1 ± 9.0 (N = 18, $P < .001$) after a 3-month weight reduction program but regained gradually thereafter to 93.6 ± 11.6 kg at the 60th month ($P < .001$ versus 3rd month). baPWV decreased after weight loss slightly ($P = .240$) while weight regain significantly increased the baPWV (from 3rd month, 1358 ± 168 to 60th month 1539 ± 264 cm/sec, $P < .001$). Systolic and diastolic blood pressure increments correlated with the increment of baPWV after weight regain. At the 60th month, lean controls (N = 15) had increases in body weight while their baPWV increased non-significantly. The increments of baPWV after weight regain in obese MetS were significantly higher than the increment of baPWV in lean controls after weight gain.

In conclusion, regaining body weight after weight reduction worsened arterial stiffness with significant increase of baPWV in obese non-diabetic MetS.

Abbreviations: ABI = ankle-brachial index, DM = diabetes mellitus, hs-CRP = high-sensitivity C-reactive protein, IR = insulin resistance, MCP-1 = monocyte chemoattractant protein-1, MetS = metabolic syndrome, OGTT = oral glucose tolerance test, PWV = pulse wave velocity.

Keywords: arterial stiffness, metabolic syndrome, obesity, pulse wave velocity, weight reduction, weight regain

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1. Introduction

Progressive atherosclerotic disease with declined aortic elastin quality and content leads to increased aortic stiffness and, therefore, increased pulse wave velocity (PWV).^[1] PWV measures aortic and large vessel distensibility and increases with age, blood pressure, smoking, dyslipidemia and peripheral artery disease.^[1–4] Increased arterial stiffness or PWV has been shown to be a useful surrogate marker for future cardiovascular events, cardiovascular death or even total mortality.^[5–7] Insulin resistance (IR) either manifested as impaired fasting glucose or impaired glucose tolerance or diabetes mellitus (DM) is associated with worse arterial stiffness.^[2,8] Subjects with metabolic syndrome (MetS) or obesity have a higher PWV, too.^[3,9]

Ankle-brachial index (ABI) is a useful noninvasive examination for diagnosis of lower extremity arterial disease and a surrogate marker for future cardiovascular events.^[10] According to previous studies, an ABI value <0.9 is an independent risk factor for cardiovascular disease and mortality.^[10,11]

Few studies have investigated the time sequential change of arterial stiffness in obese non-diabetic men with MetS, who had undergone weight reduction but regained body weight in the long term follow-up.^[12,13] Weight loss could induce significant reduction in blood pressure and large arterial stiffness.^[12,14] In patients with type 2 DM, weight loss significantly improves the aortic PWV.^[15] However, it is unknown whether the reduction in arterial stiffness is due to weight reduction per se or whether it is correlated with changes of adipokines, IR or inflammatory markers accompanying weight loss.^[14] Moreover, the effect of regaining body weight after weight reduction on PWV and ABI is

not investigated in obese non-diabetic men yet. The aim of the present study was to record and analyze time-sequential changes of PWV, ABI, IR index, adipokines, inflammatory markers, and anthropometric profiles after weight loss and regained weight in obese non-diabetic men with MetS.

2. Materials and methods

2.1. Study subjects

We prospectively enrolled 40 men in total, who were diagnosed with MetS using the ATP-III criteria, from outpatient clinics at Taichung Veterans General Hospital (Taichung, Taiwan) in April to September 2008. Parts of the results have been published previously.^[16–19] In brief, the study enrollment criteria included central obesity, which was defined as waist circumference ≥ 90 cm, in addition to at least 2 other ATP-III MetS criteria.^[20] Patients with DM requiring oral anti-diabetic agents or insulin shots were excluded from the study. The patients undertook a 3-month weight reduction program. The dietitian instructed the study subjects to consume a 1200 Kcal diet per day comprising 55% carbohydrate, 30% fat, and 15% protein. Patients were educated how to estimate the energy and nutritional components per unit amount of food.^[18,21,22] They all received an instruction brochure, which stated all the nutritional facts and energy per unit amount of food for instant check. The patients were asked to keep a very detailed record of each meal. A dietitian would estimate the energy based on the record in order to keep the daily requirement of 1200Kcal per day. In addition, the dietitian closely followed them with phone-call consultations. We encouraged peer competition for weight loss and showed weight and waist circumference changes in bar graphs at each gathering, which was held once every week in the first month, then biweekly in the 2nd and 3rd month. The patients were encouraged to have at least 2 to 3 light physical exercise periods per week. We provided a 60-minute fitness program with a physical trainer at the biweekly gatherings. The study subjects underwent anthropometric data check, blood sampling and arterial stiffness examinations again at the 3rd and 60th month after the beginning of weight loss program if they were compliant with our recalls. Among the study participants, 18 obese non-diabetic MetS and 15 lean control subjects had follow-ups at the 60th month. All subjects provided written informed consent. The authors confirm that all ongoing and related trials for this study/intervention are registered. The study protocol was approved by the Human Research Ethics Review Committee of Taichung Veterans General Hospital (Taichung, Taiwan). The protocol and case enrollment were conducted after getting the ethics committee approval; however, the registration at www.clinicaltrials.gov (Multi-faceted Evaluations Following Weight Reduction in Subjects with MetS NCT 01065753) was delayed till Feb 8, 2010 because clinical trial registration was not compulsory in our country back then.

2.2. Biochemical analysis, inflammatory markers, adipokines, and oral glucose tolerance tests (OGTTs)

All obese MetS subjects underwent blood tests and OGTT after an overnight fast to exclude those with unknown diabetes. After a fasting blood sample was collected, glucose load of 75 g was ingested over 5 minutes. Blood samples were collected at 30 minutes, 60 minutes, 90 minutes, and 120 minutes after the test load. Blood glucose and insulin concentrations were measured in

each sample. Serum insulin was determined by a commercially available assay kit (IMMULITE, I-2000, EURO/Diagnostic Products Corporation, Gwynedd, UK). The inter- and intra-assay coefficients of variation for insulin (range 10.7 to 439 μ U/mL) were 4.3% and 5.4%, respectively. Insulin-resistance was estimated using the homeostasis model assessment of IR (HOMA-IR), defined as fasting glucose mg/dl \times fasting insulin μ U/mL/405.^[23,24] Serum high-sensitivity C-reactive protein (hs-CRP) was determined by particle-enhanced immunoturbidimetry (Latex microparticles sensitized with duck anti-CRP IgY kit, provided by Good Biotech Corp., Taichung, Taiwan). The intra- and inter-assay coefficients of variance were 1.4% and 1.42%, respectively.^[25] Serum monocyte chemotactic protein-1 (MCP-1) was determined by enzyme-linked immunosorbent assays (R&D Systems, Inc., Minneapolis, MN).^[26,27] The intra- and inter-assay coefficients of variation for MCP-1 were 5.80% and 5.70%, respectively, with a minimum detectable concentration of <5.0 pg/mL. Serum adiponectin and leptin were determined by enzyme-linked immunosorbent assays (R&D Systems, Inc., Minneapolis, MN). The intra- and inter-assay coefficients of variation for adiponectin were 3.53% and 6.50%, respectively, with a minimum detectable concentration of 0.079 to 0.891 ng/mL. The intra- and inter-assay coefficients of variation for leptin were 3.17% and 4.37%, respectively, with a minimum detectable concentration of <7.8 pg/mL.

2.3. Measurement of ankle-brachial index (ABI) and brachial ankle (ba) PWV

After seating and resting for 5 minutes, the study subjects' brachial and ankle blood pressure, PWV and ABI were measured by VP-2000 Vascular Profiling System (OMRON Healthcare Co., LTD, Kyoto, Japan), using simultaneous blood pressure and waveform measurements on all 4 limbs with electrocardiogram tracings. Brachial-ankle pulse wave velocity (baPWV) was calculated as the distance in centimeters between arterial sites of interest over time (in seconds) that the pressure waveforms travel from the heart to the respective arterial sites. Distance between peripheral sites was calculated using a height based algorithm as required by the Colin waveform analyzer.^[28] Time was calculated using the foot-to-foot velocity method of waveforms measured at various sites.^[29] The average of 2 runs was used in this analysis.

2.4. Statistical analysis

Continuous variables are expressed as mean \pm SD and categorical data as percentages. Differences in continuous variables between obese MetS and lean controls were measured by the independent Student *t* test. Differences in continuous variables at baseline and 60th month follow-up in lean controls were measured by the paired Student *t* test. Differences in continuous variables among different visits (baseline, the 3rd month and the 60th month) in obese MetS were measured by the repeated measure analysis of variance (ANOVA) test. Univariate correlation analysis between changes of body weight, blood pressure, IR indices, inflammatory marker and circulating adipokines versus increments of PWV in obese MetS after weight regain were analyzed using Pearson correlation analysis. The SPSS 17.0 statistical software package (SPSS, Inc., Chicago, IL) was used for all calculations. A 2-tailed *P* value less than .05 was considered statistically significant.

3. Results

3.1. Baseline clinical, biochemical and vascular stiffness data in obese non-diabetic men with MetS and lean controls

Parts of the results of the comparisons of obese MetS versus lean controls have been published previously.^[16-19] Obese non-diabetic men with MetS had a larger body weight, body mass index, worse IR profiles, and higher triglyceride and lower high-density lipoprotein cholesterol. Obese non-diabetic men with MetS had a higher baPWV (1365 ± 217 cm/sec, N=40) than the lean and healthy controls (1283 ± 119 cm/sec, N=26) but the difference did not reach statistical significance (P=.083). The ages (46 ± 10 versus 40 ± 13, P=.140) were similar between obese non-diabetic MetS (N=18) and the lean healthy controls (N=15) that complied with call-backs at 60th month.

3.2. Comparing anthropometric, biochemical and vascular stiffness data in lean healthy controls between baseline and 60th month (N=15)

Among the lean and healthy controls, 15 of them complied with call-back at 60th month. Average body weight increased from 67.1 ± 6.5 to 69.9 ± 9.7 (N=15, P=.032). Diastolic blood pressure and total cholesterol increased significantly after weight gain at 60th month (Table 1). Among the IR index, OGTT 2h glucose and insulin increased significantly after weight gain (Table 1). In terms of vascular stiffness indices, ABI values were similar and baPWV increased but the difference did not reach statistical significance (Table 1).

3.3. Anthropometric, biochemical and vascular stiffness data in obese non-diabetic men after 3-month weight reduction program and weight regain at 60th month (N=18)

Among the obese non-diabetic men with MetS, 18 of them had follow-ups after weight loss at 3rd month and weight regain at 60th month. Average body weight decreased from 94.8 ± 7.6 to 86.1 ± 9.0 (N=18, P<.001) after a 3-month diet and exercise weight reduction program. Weight regained gradually thereafter and increased to 93.6 ± 11.6 kg at 60th month (P<.001 versus 3rd month (after just finishing weight reduction program)) (Table 1). Systolic and diastolic blood pressure increased significantly but lipid profiles were similar after weight regain (Table 1). The inflammatory marker hs-CRP increased significantly after regaining body weight (Table 1). Among the OGTT derived IR index, only OGTT 2h glucose increased significantly after weight regain (Table 1). In terms of vascular stiffness indices, ABI did not change significantly throughout the weight loss and weight regain periods. baPWV decreased after weight loss (baseline 1414 ± 214 versus 1358 ± 168 cm/sec, P=.240, N=18) but the difference did not reach statistical significance. Weight regain significantly increased the baPWV (from 3rd month, 1358 ± 168 to 60th month 1539 ± 264 cm/sec, P<.001, N=18) (Table 1). In addition, baPWV at 60th month after weight regain was even worse than the baseline values in obese MetS (Table 1). Moreover, the increments of baPWV after weight regain in obese MetS were significantly higher than the increment of baPWV in lean healthy controls at 60th month (181 ± 146 versus 49 ± 100 cm/sec, P=.006).

Table 1
Comparing anthropometric, biochemical and vascular stiffness data in lean controls between baseline and 60th month (N = 15) and obese non-diabetic men with metabolic syndrome after 3-month weight reduction program and regained weight at 60th month (N = 18).

	BW (kg)	BMI (kg/m ²)	SBP (mmHg)	DBP (mmHg)	Chol (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	TG (mg/dl)	hsCRP (mg/dl)	APN (μg/ml)	Leptin (ng/ml)	Fasting glucose (mg/dl)	OGTT 2h glucose (mg/dl)	Fasting insulin (μIU/ml)	OGTT 2h insulin (μIU/ml)	HOMA-IR (mg/dl x μIU/ml)	baPWV (cm/sec)	ABI	
Lean controls (N=15)																			
baseline	67.1 ± 6.5	22.6 ± 1.5	119 ± 12	68 ± 9	187 ± 30	119 ± 29	56 ± 12	98 ± 31	0.17 ± 0.45	4.7 ± 2.6	3.1 ± 1.2	90 ± 7	108 ± 19	6.4 ± 3.0	37.4 ± 34.4	1.48 ± 0.77	1268 ± 107	1.14 ± 0.07	
60th month	69.9 ± 9.7	23.7 ± 2.1	117 ± 12	74 ± 8	226 ± 44	122 ± 27	64 ± 11	153 ± 141	0.10 ± 0.12	7.1 ± 4.4	4.7 ± 4.0	91 ± 9	151 ± 17	8.7 ± 4.3	67.0 ± 50.5	2.00 ± 1.16	1317 ± 131	1.14 ± 0.08	
P	.032	.014	.221	.035	.005	.783	.009	.119	.459	.010	.076	.871	<.001	.068	.026	.089	.081	.836	
Obese MetS (N=18)																			
baseline	94.8 ± 7.6	32.9 ± 3.0	139 ± 18	78 ± 13	210 ± 60	126 ± 33	40 ± 9	346 ± 629	0.23 ± 0.23	3.2 ± 1.6	15.5 ± 9.2	106 ± 16	148 ± 47	19.8 ± 14.8	100.0 ± 109.4	5.23 ± 3.93	1414 ± 214	1.10 ± 0.09	
3rd month	86.1 ± 9.0	29.9 ± 3.3	118 ± 17	73 ± 12	185 ± 37	109 ± 27	42 ± 9	214 ± 357	0.19 ± 0.07	3.2 ± 1.6	11.6 ± 10.4	99 ± 11	132 ± 42	14.2 ± 7.0	66.2 ± 60.0	3.52 ± 1.82	1359 ± 168	1.14 ± 0.08	
60th month	93.6 ± 11.6	32.6 ± 3.9	141 ± 16	84 ± 11	185 ± 55	102 ± 41	47 ± 11	169 ± 173	0.26 ± 0.16	4.5 ± 1.9	16.0 ± 11.4	100 ± 13	159 ± 48	17.2 ± 10.3	109.9 ± 90.9	4.31 ± 2.51	1539 ± 264	1.12 ± 0.07	
P	<.001	<.001	<.001	.082	.016	.008	.600	.184	.216	>.99	.289	.026	.125	.168	.614	.116	.240	.466	
P	>.99	>.99	>.99	.177	.659	.003	.119	.703	>.99	.006	>.99	.199	.743	.994	>.99	.674	.005	.450	
P	<.001	<.001	<.001	.002	>.99	>.99	.349	>.99	.001	.001	.088	>.99	.017	.563	.208	.551	<.001	>.99	

ABI = ankle-brachial index; APN = adiponectin; baPWV = brachial-ankle pulse wave velocity; BMI = body mass index = body weight (kg)/height² (m); BW = body weight; Chol = total cholesterol; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment (HOMA) index of insulin resistance = (fasting glucose mg/dl x fasting insulin μU/mL)/405; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MetS = obese non-diabetic men with metabolic syndrome; OGTT = oral glucose tolerance test; SBP = systolic blood pressure; TG = triglyceride.
 P = baseline versus 60th month (lean controls).
 * P = baseline versus 3rd month (obese MetS).
 † P = baseline versus 60th month (obese MetS).
 ‡ P = 3rd month versus 60th month (obese MetS).

3.4. Correlation analysis of increment of PWV after weight regain at 60th month (versus at 3rd month, just finishing weight reduction) in obese non-diabetic men with MetS (N=18)

Systolic blood pressure increment ($r=0.493$, $P=.038$) and diastolic blood pressure increment ($r=0.474$, $P=.047$) correlated with the increment of baPWV after weight regain (Table 2). However, body weight increment, hs-CRP increment and IR index changes did not correlate with the increment of baPWV after weight regain (Table 2).

4. Discussions:

Though, it is known that subjects with MetS or obesity have increased arterial stiffness and PWV.^[9,13,30] However, there is lack of longitudinal study investigating time-sequential changes of PWV following weight loss and weight regain. Moreover, it is worthwhile to investigate the underlying mechanism inside arterial stiffness change after weight loss and weight regain in obese MetS. In this study, we found that obese non-diabetic men with MetS had a trend toward higher baPWV than the healthy controls ($P=.083$). Weight reduction with diet and exercise for 3 months decreased body weight and improved IR but did not reduce baPWV significantly. However, weight regain at 60th month worsened arterial stiffness with significant increase of baPWV ($P<.001$ versus weight reduction at 3rd month). Systolic or diastolic blood pressure increment but not weight, hs-CRP or IR change correlated with the increment of baPWV after weight regain.

Weight loss improves IR, decreases circulating leptin and increases adiponectin in obesity or MetS.^[17,18,31] Weight reduction also improved arterial stiffness and decrease PWV.^[14] Previous study in the SAVE trial showed that the amount of weight loss and the decrease of circulating insulin

correlated with decrease of baPWV after weight loss in obese non-diabetic subjects.^[12] Another study by Cooper et al.^[32] showed that reductions in heart rate and C-reactive protein were associated with reduced baPWV in obese young adults after weight reduction. In our study, weight reduction with diet and exercise for 3 months in obese non-diabetic men with MetS decreased baPWV but the difference did not reach significance (Table 1). Report by Gjevestad et al.^[33] showed significant weight reduction by either gastric bypass surgery or intensive life style intervention but no decrease of PWV in morbidly obese men at 1 year. The discrepancy of these studies on PWV changes after weight loss is difficult to explain. We postulated that studies that recruited younger obese subjects who did not have many metabolic abnormalities tended to show improvement of arterial stiffness after weight reduction. In contrast, obese subjects with MetS had many factors that contributed to arterial stiffness, which could not be reversed by short-term weight reduction program.

There were some studies addressing increase of PWV after weight gain in healthy subjects.^[34,35] One study showed that increase of PWV after weight gain was associated with visceral abdominal fat increase.^[34] Another study disclosed larger baseline body weight and greater annual weight gain were associated with larger annual pulse-wave velocity increases.^[35] Our study also showed increase of baPWV after weight gain in lean and healthy controls but the difference did not reach statistical significance (Table 1). However, studies on temporal changes of arterial stiffness after weight regain in obese non-diabetic MetS, who had undergone weight reduction are lacking. Our study is novel in showing a significant increase of baPWV after weight regain at 60th month in comparison with PWV at 3rd month after weight reduction. Moreover, baPWV at 60th month after weight regain was even worse than the baseline values in obese MetS (Table 1). In addition, we reported that the increment of baPWV after weight regain was only associated with systolic or diastolic blood pressure increments but not with body weight, hs-CRP or insulin-resistance changes (Table 2). Moreover, our study disclosed that the increment of baPWV after weight regain at 60th month was significantly higher than the increment of PWV after weight gain in healthy lean healthy controls in the same time frame. This implies that the increment of baPWV after weight regain in obese MetS was beyond the aging-process or weight gain related increase of arterial stiffness within a 5-year period.

There are several limitations in this study. Among the study participants, only 18 obese non-diabetic men with MetS and 15 lean controls complied with call-backs at 60th month. The smaller sample size would limit its statistic impact. The other arterial stiffness indices, such as carotid-femoral PWV, central pulse wave analysis, and local arterial stiffness were not investigated in this study.^[29] More studies on the other arterial stiffness indices are needed to corroborate our study findings on temporal changes of baPWV during weight reduction and weight regain. Finally, further cellular or animal studies are needed to address the molecular mechanism inside the changes of arterial stiffness after weight reduction and weight regain in obese MetS.

In conclusion, our study showed that a 3-month weight reduction program with diet and exercise in obese MetS decreased body weight and improved IR but did not reduce baPWV significantly. Weight regain at 60th month worsened arterial stiffness with significant increase of baPWV versus 3rd month after weight reduction program. Systolic or diastolic blood pressure increment but not weight, hs-CRP or IR change

Table 2

Correlation analysis of increment of pulse wave velocity after weight regain at 60th month (versus 3rd month, just finishing weight reduction) in obese non-diabetic men with metabolic syndrome (N=18).

Increment of baPWV after weight regain (60th month versus 3rd month) (N=18)	Correlation coefficient	P
Age (years)	0.161	.524
Increment of systolic blood pressure, mmHg	0.493	.038
Increment of diastolic blood pressure, mmHg	0.474	.047
Increment of body mass index, kg/m ²	-0.067	.792
Increment of body weight, kg	-0.141	.577
Increment of fasting glucose, mg/dL	-0.063	.803
Increment of fasting insulin, μ U/mL	-0.378	.135
Increment of HOMA-IR	-0.365	.150
Increment of OGTT 2h glucose, mg/dL	0.241	.351
Increment of OGTT 2h insulin, μ U/mL	0.152	.574
Increment of total cholesterol, mg/dL	-0.505	.033
Increment of LDL-C, mg/dL	-0.281	.258
Increment of triglycerides, mg/dL	-0.465	.052
Increment of hsCRP, mg/dL	-0.321	.194
Increment of adiponectin, μ g/mL	-0.208	.407
Increment of HDL-C, mg/dL	-0.222	.376
Increment of leptin, ng/mL	-0.354	.149

baPWV=brachial-ankle pulse wave velocity; HDL-C=high-density lipoprotein cholesterol; HOMA-IR=homeostasis model assessment (HOMA) index of insulin resistance=(fasting glucose mg/dL x fasting insulin μ U/mL)/405; hs-CRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; OGTT=oral glucose tolerance test.

correlated with the increment of baPWV after weight regain. The increments of baPWV after weight regain in obese MetS were more than changes of arterial stiffness in lean controls during a 5-year period.

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