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Large Artery Stiffening With Weight Gain in Humans

Role of Visceral Fat Accumulation

Jeb S. Orr, Christopher L. Gentile, Brenda M. Davy, Kevin P. Davy

Abstract—We tested the hypothesis that weight gain would increase arterial stiffness in healthy nonobese adults. To address this, we overfed 14 nonobese men (age: 23 ± 1 years) ≈ 1000 kcal/d for 6 to 8 weeks until a 5-kg weight gain was achieved. Carotid diameters (high-resolution ultrasound) and pressures (applanation tonometry), body composition (dual energy x-ray absorptiometry), and abdominal fat distribution (computed tomography) were measured at baseline and following 4 weeks of weight stability at each individual's elevated body weight. Overfeeding increased body weight 5.1 ± 0.1 kg and body fat 3.4 ± 0.4 kg (both $P < 0.001$) in 45 ± 7 days. Total abdominal fat increased 46 ± 7 cm² with weight gain due to increases in both subcutaneous (30 ± 6 cm²) and visceral fat (15 ± 4 cm²; all $P < 0.01$). As hypothesized, weight gain increased arterial stiffness $13 \pm 6\%$ and decreased arterial compliance $21 \pm 4\%$ (both $P < 0.05$). Furthermore, those individuals above the median increase in abdominal visceral fat demonstrated a significantly greater increase in arterial stiffness (0.97 ± 0.29 versus 0.06 ± 0.36 U; $P < 0.05$) compared with those below the median. Consistent with these observations, the only correlates of the changes in arterial stiffness with weight gain were the increases in total abdominal fat ($r = 0.794$), abdominal visceral fat ($r = 0.651$), and waist circumference ($r = 0.470$; all $P < 0.05$). Taken together, these findings suggest that modest weight gain is associated with increases arterial stiffness in nonobese men. The degree of large artery stiffening with weight gain seems to be determined, in part, by the amount of abdominal visceral fat gain. Importantly, this relation is independent of the amount of total body fat gained. (*Hypertension*. 2008;51:1519-1524.)

Key Words: arterial distensibility ■ adiposity ■ obesity ■ pulse pressure ■ hypertension

Approximately 65% of the US population¹ and >1 billion people worldwide² are overweight or obese and, thus, at increased risk for cardiovascular diseases.³ There is considerable heterogeneity in the risks associated with excess adiposity; the accumulation of abdominal visceral fat seems to be particularly deleterious.^{4,5} Importantly, elevated abdominal visceral fat, independent of total body adiposity, is associated with the development of cardiovascular diseases.^{4,5}

One mechanism by which the cardiovascular complications associated with obesity may be advanced is through remodeling of the vasculature. The results of numerous studies suggest that obesity is associated with the stiffening of arteries in the cardiathoracic region.⁶⁻¹² Importantly, large artery stiffness is associated with adverse cardiovascular outcomes,¹³⁻¹⁶ which occur more frequently in obese individuals.^{3,4} The relation between adiposity and arterial stiffness is evident even in young children,^{17,18} suggesting that long-duration obesity is not a prerequisite for arterial stiffening. Unfortunately, the available data, from observational studies of weight gain, are inconsistent.^{19,20} In addition, measure-

ments of body composition were not included in these previous studies. Furthermore, it is currently unknown whether increases in abdominal visceral fat with weight gain are associated with larger artery stiffening, independent of increases in total body fat. Therefore, we tested the hypothesis that modest weight gain would increase arterial stiffness in healthy nonobese adults. We further sought to determine whether those individuals who demonstrate the largest increases in abdominal visceral fat, independent of total body fat gain, would also demonstrate the largest increases in arterial stiffness.

Materials and Methods

Subjects

Fourteen young (age: 23 ± 1 years), nonobese (body mass index: < 30 kg/m²) men included in previous publications^{21,22} were studied. Subjects were normotensive, free from overt chronic disease, non-smokers, and not taking any medications. All of the subjects were weight stable (± 2 kg) for ≥ 6 months before entry into the study. The Virginia Tech Human Subjects Committee approved all of the experimental protocols. The nature, purpose, risks, and benefits of

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From the Human Integrative Physiology Laboratory, Department of Human Nutrition, Foods and Exercise, Virginia Polytechnic Institute and State University, Blacksburg.

Correspondence to Kevin P. Davy, Human Integrative Physiology Laboratory, Department of Human Nutrition, Foods and Exercise, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061. E-mail kdavy@vt.edu

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the study were explained to all of the subjects before obtaining informed consent.

Experimental Design and Protocol

After baseline measurements, subjects were overfed ≈ 1000 kcal/d for 6 to 8 weeks until a 5-kg weight gain was achieved. Subjects were provided with a liquid meal replacement supplement (Boost Plus, Novartis Nutrition Corp; 35% fat, 50% carbohydrates, and 15% protein) to meet their excess energy requirements. To avoid the potential effects of acute energy imbalance on the primary outcome variables, baseline measurements were repeated on each subject after a 4-week period of weight stability at their elevated body weight. Subjects underwent weekly assessment by a research dietician (B.M.D) throughout weight gain and weight stability phases to ensure adequate progress and compliance. Subjects reported to the Virginia Tech Human Integrative Physiology Laboratory between 7 and 11 AM after a 12-hour fast and having refrained from caffeine and exercise for 24-hours before each testing session. After post testing, subjects were provided with dietary counseling, physical activity recommendations, and, if desired, meal replacement products to facilitate return to their baseline body weight.

Measurements

Body mass and height were measured with a digital scale and stadiometer (Scale-Tronix model 5002), respectively. Dual-energy x-ray absorptiometry (GE Lunar Prodigy Advance, software version 8.10e) was used to determine body composition. Computed tomography scans (HiSpeed CT/i, GE Medical) were taken between the L3-L4 vertebra, and abdominal fat distribution was quantified using commercially available analysis software (Slice-O-Matic 4.3 Rev-4, Tomovision Inc). Maximal oxygen consumption was measured during a graded treadmill exercise to volitional exhaustion using open-circuit spirometry (TrueMax 2400, ParvoMedics). Standard criteria for the achievement of valid maximal oxygen consumption were met.²³ Casual blood pressure was measured over a brachial artery via mercury sphygmomanometry after 15 minutes of seated rest in a quiet room. Measurements were repeated until within-session stability was achieved (± 6 mm Hg on 3 sequential measurements) and on ≥ 3 separate occasions over a 2-week period until between-session stability was reached. Resting heart rate was determined from lead II of an ECG. Plasma lipid and lipoprotein concentrations were measured via nuclear magnetic resonance spectroscopy (LipoScience, Inc), as described previously.²⁴

β -Stiffness index²⁵ and arterial compliance were assessed by combining simultaneous measurements of carotid artery diameter and blood pressure over 3 consecutive cardiac cycles via B-mode ultrasonography and applanation tonometry, respectively. After 10 minutes of quiet rest in a supine position, arterial blood pressure was measured over a brachial artery via automated sphygmomanometry (Pilot 9200, Colin Medical Instruments) until stability was achieved (3 consecutive readings: ± 6 mm Hg). Subsequently, common carotid artery diameters were obtained with an ultrasound unit (Sonos 7500, Philips Medical Systems) equipped with a high-resolution linear array transducer (3 to 11 MHz). Longitudinal B-mode images of the cephalic portion of the common carotid artery were obtained 1 to 2 cm proximal to the carotid bulb. The transducer was placed 90° to the vessel so that near and far walls were clearly visible. The images were stored to optical disk for quantification of carotid artery diameters offline using commercially available analysis software (Vascular Research Tools 5, Medical Imaging Applications, LLC). The distance between the near and far wall vessel boundaries were measured at time points that corresponded with the maximal systolic and minimal diastolic diameters. Throughout the imaging process, pressure waveforms were obtained from the contralateral carotid artery using a high-fidelity noninvasive pulse tonometer (SPT-301, Millar Instruments) and digitized at 500 Hz for subsequent analysis using signal processing software (Windaq, Dataq Instruments). Carotid pressure waveforms were corrected for hold-down pressure by calibration to brachial diastolic and mean arterial pressures.²⁶ The reproducibility of measurements of the β -stiffness index in our laboratory is excellent ($r=0.90$; $P<0.05$).

Table 1. Subject Characteristics at Baseline and After Weight Gain

Variable	Baseline	Weight Gain
Age, y	23 \pm 1	NA
Body weight, kg	75.3 \pm 2.9	80.3 \pm 3.0*
Body mass index, kg/m ²	24.0 \pm 0.7	25.7 \pm 0.7*
Body fat, %	21.3 \pm 1.2	24.6 \pm 1.1*
Total fat mass, kg	15.5 \pm 1.1	18.9 \pm 1.1*
FFM, kg	56.7 \pm 2.3	58.2 \pm 2.5*
Waist circumference, cm	84.9 \pm 1.9	90.5 \pm 1.7*
Total abdominal fat, cm ²	226 \pm 19	271 \pm 20*
Abdominal subcutaneous fat, cm ²	160 \pm 13	190 \pm 11*
Abdominal visceral fat, cm ²	66 \pm 8	81 \pm 11*
VO ₂ max, mL/kg/min	44.7 \pm 1.8	43.8 \pm 1.5*
VO ₂ max, L/min	3.4 \pm 0.2	3.5 \pm 0.2
VO ₂ max, mL/kg FFM/min	60.7 \pm 2.0	60.1 \pm 1.6
Heart rate, bpm	62 \pm 2	65 \pm 3
Systolic blood pressure, mm Hg	114 \pm 2	119 \pm 2*
Diastolic blood pressure, mm Hg	75 \pm 2	75 \pm 2
Triglycerides, mg/dL	92 \pm 17	135 \pm 31*
Total cholesterol, mg/dL	134 \pm 6	148 \pm 8*
HDL cholesterol, mg/dL	40 \pm 2	40 \pm 2
LDL cholesterol, mg/dL	80 \pm 6	89 \pm 8

All values are expressed as means \pm SEs. VO₂max indicates maximal oxygen consumption; FFM, fat-free mass; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.

* $P<0.05$ vs baseline.

Statistical Analysis

Differences in subject characteristics and dependent variables before and after weight gain were assessed with paired Student *t* tests. To gain better insight into the relation between abdominal fat distribution and arterial compliance and stiffness, subjects were subsequently divided into 2 groups (smaller increase in abdominal visceral fat [SVF] and larger increase in abdominal visceral fat [LVF]) based on the median split of abdominal visceral fat change with weight gain. Repeated-measures ANOVA was used to assess changes in subject characteristics and dependent variables in the SVF and LVF groups with weight gain. Differences in the magnitude of change in subject characteristics and dependent variables with weight gain between the 2 groups were assessed with independent-sample *t* tests. Comparisons performed using Wilcoxon signed-rank tests yielded similar outcomes. Relations among variables of interest were assessed using simple correlation analyses. All of the data are expressed as means \pm SEs. The significance level was set a priori at $P<0.05$.

Results

Subject characteristics at baseline and after weight gain are shown in Table 1. Overfeeding resulted in 5.1 \pm 0.1 kg (range: 4.2 to 5.8 kg) of body weight gain in 45 \pm 7 days. Body fat (3.4 \pm 0.4 kg), percent body fat (3.2 \pm 0.6%), lean body mass (1.5 \pm 0.4 kg), and waist circumference (5.6 \pm 0.6 cm) increased with weight gain (all $P<0.001$). Total abdominal fat (46 \pm 7 cm²) increased due to increases in both visceral (15 \pm 4 cm²) and subcutaneous fat (30 \pm 6 cm²) depots (all $P<0.01$). There was a small, but significant, reduction in maximal oxygen consumption expressed relative to body weight with weight gain. However, maximal oxygen consumption ex-

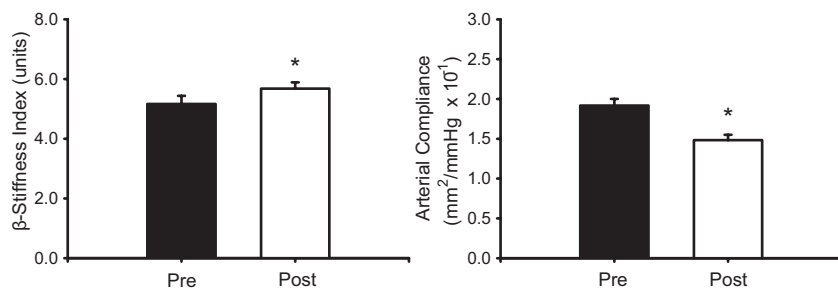


Figure 1. Left, β -Stiffness index at baseline and following weight gain. Right, Arterial compliance at baseline and after weight gain (* $P < 0.05$ vs baseline).

pressed in absolute terms and relative to fat-free mass did not change. Systolic blood pressure (5 ± 1 mm Hg; $P < 0.01$) but not diastolic blood pressure increased with weight gain, whereas resting heart rate tended to increase (3 ± 2 bpm; $P = 0.056$). Regarding traditional cardiovascular risk factors, only total cholesterol and triglyceride concentrations increased significantly after weight gain (15 ± 5 and 43 ± 16 mg/dL, respectively). As hypothesized, arterial stiffness increased (0.51 ± 0.26 U; $P < 0.05$; Figure 1, left), and arterial compliance decreased (0.43 ± 0.09 mm²/mm Hg $\times 10^{-1}$; $P < 0.001$; Figure 1, right) with weight gain. Relative to baseline values, this represents a change in arterial stiffness and arterial compliance of $+13 \pm 6$ and $-21 \pm 4\%$, respectively (both $P < 0.05$).

To gain further insight into the relation between abdominal fat distribution and arterial stiffness (and compliance), we divided the subjects into 2 groups (SVF and LVF) based on the median change in abdominal visceral fat with weight gain. Subject characteristics and arterial stiffness (and compliance) of the SVF and LVF groups at baseline and following weight gain are shown in Table 2. At baseline, the 2 groups did not differ with respect to age, body weight, body composition, abdominal fat distribution, maximal oxygen consumption, heart rate, blood pressure, arterial stiffness, or arterial compliance (all $P > 0.05$). In contrast, LVF had higher concentrations of total cholesterol, LDL-C, and triglycerides compared with SVF (all $P < 0.05$ for group effect). Despite gaining a slightly lesser amount of body weight (4.8 ± 0.2 versus

Table 2. Subject Characteristics in Individuals With SVF Versus LVF

Variable	SVF (n=7)		LVF (n=7)	
	Baseline	Weight Gain	Baseline	Weight Gain
Age, y	21.3 \pm 1.0	NA	24.9 \pm 2.3	NA
Body weight, kg	78.2 \pm 3.9	83.5 \pm 4.0	72.3 \pm 4.4	77.1 \pm 4.5*
Body mass index, kg/m ²	23.9 \pm 0.9	25.5 \pm 0.9	24.2 \pm 1.0	25.9 \pm 1.0*
Body fat, %	20.0 \pm 1.4	23.0 \pm 1.6	22.7 \pm 1.9	26.1 \pm 1.4*
Fat mass, kg	15.1 \pm 1.5	18.4 \pm 1.7	15.9 \pm 1.8	19.4 \pm 1.6*
FFM, kg	59.8 \pm 2.9	61.5 \pm 3.2	53.5 \pm 3.3	54.8 \pm 3.5*
Waist circumference, cm	83.8 \pm 2.4	89.3 \pm 2.4	85.9 \pm 3.0	91.8 \pm 2.5*
Total abdominal fat, cm ²	200 \pm 21	233 \pm 24	251 \pm 31	310 \pm 24*
Abdominal subcutaneous fat, cm ²	143 \pm 14	173 \pm 16	177 \pm 21	207 \pm 13*
Abdominal visceral fat, cm ²	57 \pm 9	60 \pm 10	75 \pm 12	102 \pm 15*‡
VO ₂ max, mL/kg/min	45.9 \pm 3.0	43.9 \pm 2.3	43.6 \pm 2.1	43.6 \pm 2.2*
VO ₂ max, L/min	3.6 \pm 0.3	3.7 \pm 0.3	3.2 \pm 0.3	3.3 \pm 0.3
VO ₂ max, mL/kg FFM/min	61.3 \pm 3.9	59.4 \pm 2.5	60.3 \pm 1.7	60.7 \pm 2.4
Heart rate, bpm	62 \pm 3	63 \pm 5	62 \pm 3	67 \pm 4
Systolic blood pressure, mm Hg	115 \pm 3	120 \pm 3	114 \pm 4	118 \pm 4*
Diastolic blood pressure, mm Hg	73 \pm 3	74 \pm 4	76 \pm 2	77 \pm 3
Triglycerides, mg/dL	58 \pm 8	84 \pm 14	133 \pm 26	196 \pm 56*†
Total cholesterol, mg/dL	120 \pm 5	128 \pm 6	150 \pm 6	172 \pm 4*†
HDL cholesterol, mg/dL	41 \pm 1	42 \pm 4	38 \pm 3	37 \pm 1
LDL cholesterol, mg/dL	68 \pm 6	70 \pm 6	94 \pm 6	111 \pm 8†
Arterial compliance, mm ² /mm Hg $\times 10^{-1}$	1.85 \pm 0.12	1.57 \pm 0.09	1.98 \pm 0.12	1.39 \pm 0.09*§
β -Stiffness index, U	5.4 \pm 0.2	5.4 \pm 0.3	5.0 \pm 0.5	5.9 \pm 0.3*§

All values are expressed as means \pm SEs. VO₂max indicates maximal oxygen consumption; FFM, fat-free mass; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.

Effect of time (*), group (†), and time \times group interaction (‡), $P < 0.05$.

§ $P = 0.07$ to 0.10 for interaction effect.

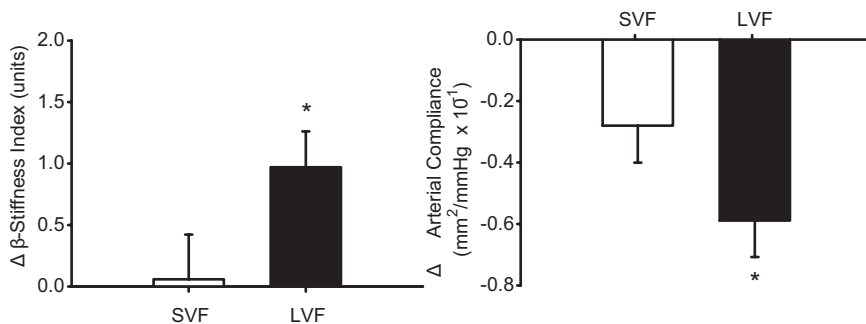


Figure 2. Left, Change in β -stiffness index following weight gain in subjects with smaller and larger increases in visceral fat. Right, Change in arterial compliance following weight gain in subjects with smaller and larger increases in visceral fat (* $P < 0.05$ vs SVF).

5.3 ± 0.2 kg, $P = 0.04$), the LVF group experienced a significantly greater increase in total abdominal fat (58 ± 10 versus 33 ± 7 cm²) due to greater visceral fat (28 ± 5 versus 3 ± 2 cm²) accumulation with weight gain (both $P < 0.05$). The increase in abdominal subcutaneous fat (30 ± 5 versus 30 ± 11 cm²; $P > 0.05$) with weight gain was not different in the 2 groups. Consistent with our hypothesized association between abdominal visceral fat and arterial stiffness, the LVF group experienced a significantly greater increase in arterial stiffness (0.97 ± 0.29 versus 0.06 ± 0.36 U; $P < 0.05$; Figure 2, left) and decrease in arterial compliance (-0.589 ± 0.119 versus -0.280 ± 0.120 mm²/mm Hg $\times 10^{-1}$; $P < 0.05$; Figure 2, right) compared with SVF. The magnitudes of change in body fat, fat-free mass, maximal oxygen consumption, systolic and diastolic blood pressure, and plasma lipid and lipoprotein concentrations did not differ between the 2 groups (all $P > 0.05$).

In the pooled sample, the magnitude of change in abdominal visceral fat with weight gain was correlated with the magnitude of change in arterial stiffness ($r = 0.651$; $P < 0.05$) and arterial compliance ($r = -0.589$; $P < 0.05$; Figure 3). The magnitude of increase in total abdominal fat and waist circumference with weight gain were also correlated with the increases in arterial stiffness ($r = 0.794$ and 0.470 , respectively; both $P < 0.05$) and the decreases in arterial compliance ($r = -0.765$ and -0.496 , respectively; all $P < 0.05$). Furthermore, baseline values of arterial stiffness and compliance correlated with the magnitude of their respective changes with weight gain ($r = 0.683$ and $r = -0.711$, respectively; both $P < 0.05$). There were no other significant correlations.

Discussion

The major new finding of the present study is that modest diet-induced weight gain results in increases in large artery stiffness in healthy young adult men. Those individuals with

relatively larger increases in abdominal visceral fat demonstrated correspondingly larger increases in arterial stiffness and greater reductions in arterial compliance. Importantly, the adverse effect of abdominal visceral fat accumulation on arterial stiffness and compliance occurred independent of the amount of total body fat gained.

The results of previous prospective studies regarding the determinants of arterial stiffening are inconsistent with respect to the role of weight gain. Wildman et al²⁰ found weight gain over a 2-year period to be associated with an increase in pulse-wave velocity among healthy young adults whereas Benetos et al¹⁹ failed to support such an association. The reasons for these disparate findings remain unclear, but may be explained, in part, by the inclusion of older subjects (> 50 years) by Benetos et al.¹⁹ Nonetheless, our current findings confirm and extend the findings of Wildman et al²⁰ by demonstrating that experimental weight and fat gain, particularly in the abdominal visceral region, are associated with an increase in arterial stiffness in healthy young men.

Numerous cross-sectional studies report associations between surrogate (ie, waist circumference) and direct measures of visceral adiposity and large artery stiffness across a variety of subject populations.^{6–12} Most notably, abdominal visceral fat (measured via computed tomography) appears to be the strongest predictor of aortic stiffness.^{10,11} Taken together with these previous cross-sectional studies, our findings implicate abdominal fat partitioning as an important mediator of the arterial stiffening that occurs with weight gain.

The mechanisms linking abdominal visceral fat and arterial stiffening are unclear, although numerous possibilities have been advanced.²⁷ Seals and Gates²⁸ hypothesized that the proinflammatory state and oxidative stress accompanying weight gain (and aging) alters vascular structure and function by disrupting the balance of key extracellular matrix proteins (ie, elastin and collagen) and vasoconstrictive and vasodila-

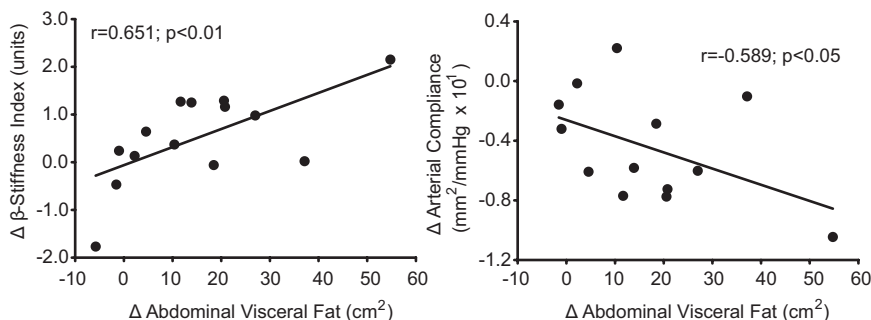


Figure 3. Left, Relation between changes in abdominal visceral fat and changes in β -stiffness index in the pooled sample. Right, Relation between change in abdominal visceral fat and magnitude of change in arterial compliance in the pooled sample.

tory molecules (eg, NO, prostacyclins, endothelin-1, and angiotensin II), and promoting vascular smooth muscle cell hypertrophy. Together these pathophysiological mechanisms lead to arterial stiffening. Given the short duration of the present study, it seems unlikely that structural modifications to the vasculature, as observed in age-associated arterial stiffening, can account for the increase in stiffness observed following weight gain. A more plausible explanation is that a multitude of interrelated factors sensitive to acute changes in body weight, including reductions in insulin sensitivity, dyslipidemia, activation of the sympathetic nervous and renin-angiotensin systems, and perhaps other factors conspire to impair endothelial function (ie, increase vascular smooth muscle tone) and, in turn, result in arterial stiffening.²⁷ However, we found no association between the changes in carotid stiffness or compliance and changes in estimates of insulin sensitivity (ie, fasting insulin and HOMA score), plasma renin activity, or muscle sympathetic nerve activity (data not shown).²² We should emphasize that our study was not designed to address potential mechanisms. As such, future studies will be necessary to address this important issue.

There are some limitations of the present study that should be discussed. First, we did not include a control group, and our sample size was relatively small. Thus, inclusion of a control group and/or a larger sample size may have yielded different results. However, that 11 of the 14 subjects demonstrated an increase in carotid artery stiffness after weight gain and, as hypothesized, the subjects with the largest increase in abdominal visceral fat (manipulated variable) also demonstrated the largest increase in arterial stiffness (the outcome variable) suggest that our results are unlikely to have been the result of random deviations over time.

Second, the subjects in the present study were limited to young, nonobese men. Women tend to accumulate fat in the gluteal-femoral region, and older adults are more susceptible to visceral fat accumulation. As such, the vascular responses to weight gain may be attenuated or amplified, respectively. For these reasons, caution should be taken in extrapolating our findings to women or beyond the age-range studied.

Third, the experimental weight gain produced in the present study may not be representative of the more gradual changes that occur over time in the general population. As such, our findings should be considered with this in mind.

Finally, we should emphasize that our findings do not preclude the possibility that the expansion of other fat depots, such as perivascular adipose tissue, may play an important role in mediating the effects of weight gain on arterial stiffness.²⁹

In conclusion, the results of the present study indicate that modest diet-induced weight gain results in large artery stiffening in young, nonobese men. Those individuals who demonstrated the largest increases in abdominal visceral fat also demonstrated the largest increases in arterial stiffness. Importantly, the increase in arterial stiffness associated with abdominal visceral fat accumulation occurred independent of the amount of total body fat gained.

Perspectives

Arterial stiffening has long been regarded as an indicator of disease³⁰ and is independently associated with an increased risk for developing hypertension.³¹ Arterial stiffening reduces the cushioning function of the aorta. As a consequence, systolic blood pressure rises, diastolic blood pressure falls, and the ability to convert pulsatile cardiac ejection to continuous flow at the level of the microcirculation is impaired.³⁰ As such, arterial stiffening may lead to left ventricular hypertrophy, cardiac dysfunction, and a reduction in myocardial perfusion in the face of increased demand. In addition, microvascular damage can occur in key target organs, such as the kidney and brain, as a result of the reduced cushioning function.³² Our current findings suggest that individuals who gain even modest amounts of weight may experience arterial stiffening even if they do not become obese. The accumulation of abdominal visceral fat appears to be particularly important in this regard. Taken together with the recent findings of an increasing prevalence of abdominal obesity,³³ our data highlight the importance of abdominal visceral fat as an important therapeutic target. Importantly, overfeeding-induced weight gain in humans may provide an insightful model to discern the mechanism(s) responsible for weight gain-induced arterial stiffening.

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Disclosures

None.

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