Abdominal Adiposity Is Associated With Elevated C-Reactive Protein Independent of BMI in Healthy Nonobese People

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OBJECTIVE — There is debate over the most appropriate adiposity markers of obesity-associated health risks. We evaluated the relationship between fat distribution and high-sensitivity C-reactive protein (hs-CRP), independent of total adiposity.

RESEARCH DESIGN AND METHODS — We studied 350 people with abdominal adiposity (waist-to-hip ratio [WHR] ≥0.9 in male and ≥0.85 in female subjects) and 199 control subjects (WHR <0.9 in male and <0.85 in female subjects) matched for BMI and age. We measured hs-CRP and major cardiovascular risk factors.

RESULTS — Participants with abdominal adiposity had BMI similar to that in control subjects (24.8 ± 2.5 vs. 24.7 ± 2.2 kg/m^2, respectively), but significantly higher waist circumference (96.4 ± 6.0 vs. 83.3 ± 6.7 cm; $P < 0.01$) and WHR (1.07 ± 0.08 vs. 0.85 ± 0.05; $P < 0.001$). Compared with the control subjects, participants with abdominal adiposity had an adverse cardiovascular risk factor profile, significantly higher hs-CRP (1.96 ± 2.60 vs. 1.53 ± 1.74 mg/dl; $P < 0.01$), and a twofold prevalence of elevated CRP values (>3 mg/dl).

CONCLUSIONS — In nonobese people, moderate abdominal adiposity is associated with markers of subclinical inflammation independent of BMI.

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There is debate over the most appropriate adiposity markers of obesity-associated health risks. Large studies have shown that measures of abdominal adiposity, such as waist circumference and waist-to-hip ratio (WHR), are more closely associated with the risk of diabetes, cardiovascular disease, and death than BMI, which is a measure of general adiposity (1,2). The excess cardiometabolic risk associated with abdominal adiposity is only partly explained by established risk factors; additional less extensively explored mechanisms may include systemic low-grade inflammation (3). Indeed, high-sensitivity C-reactive protein (hs-CRP) is a powerful marker of cardiovascular risk despite normal cholesterol levels, thus expanding the indication for use of statins beyond hyperlipidemia, because these drugs lower both cholesterol and CRP levels (4). To assess the impact of abdominal adiposity on low-grade inflammation independent of BMI, we compared hs-CRP in people with or without abdominal adiposity but with the same BMI.

RESEARCH DESIGN AND METHODS

— The analysis is based on a case-control design. Among 1,252 subjects undergoing health screenings (5), we selected 350 consecutive people with abdominal adiposity (WHR ≥0.9 in male and ≥0.85 in female subjects) and 199 control subjects (WHR <0.9 in male and <0.85 in female subjects) (6) matched for BMI (± 1 kg/m^2) and age (± 5 years) within sex strata. Exclusion criteria were diabetes, BMI >35 or <20 kg/m^2, use of statins or nonsteroidal anti-inflammatory drugs, acute or chronic infections (assessed by history, use of drugs, and clinical examination), and previous cardiovascular disease. We measured anthropometry, supine blood pressure, fasting plasma glucose levels, uric acid, triglycerides, total and HDL cholesterol levels (standard methods), insulin (radioimmunoassay), fibrinogen (immunonephelometry), and hs-CRP (Tina-Quant; Roche). Insulin resistance was also calculated using homeostasis model assessment of insulin resistance (HOMA-IR). Detailed study procedures have previously been published (5). The local ethics committee approved the study, and participants gave informed consent. Data were analyzed by unpaired Student's *t* test, χ^2, Pearson correlation, and multivariate regression.

RESULTS

— Participants with abdominal adiposity had age and BMI similar to that in control subjects (24.8 ± 2.5 vs. 24.7 ± 2.2 kg/m^2), but significantly higher waist circumference and WHR (Table 1). CRP was significantly higher in participants with abdominal adiposity than in control subjects; accordingly, in the group with abdominal adiposity, the proportion of people with elevated CRP (>3 mg/dl) was twice that in the control subjects (Table 1). Nine case subjects (1.9%) and one control subject (0.5%) had CRP >10 mg/dl, and removing these people from analysis quantitatively attenuated the differences between case and control subjects (mean ± SD CRP 1.66 ± 1.50 vs. 1.43 ± 1.26 mg/dl, $P = 0.07$, and 19.5 vs. 9.6%, $P = 0.04$, with CRP >3 mg/dl). The male sex was more prevalent among case subjects; however, CRP was similar for male and female subjects (1.78 ± 2.16 vs. 1.87 ± 2.11 mg/dl; $P < 0.65$). Furthermore, a two-way analysis of variance did not show a significant sex effect or the interaction between sex and abdominal adiposity on CRP. People with abdominal adiposity showed an adverse cardiometabolic risk profile compared with that in control subjects (Table 1) (i.e., significantly higher triglycerides, blood pressure, HOMA-IR, lower HDL

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Table 1—*CRP values and cardiovascular risk factor profile in participants with or without visceral adiposity*

	Without visceral adiposity	With visceral adiposity	*P*
n	199	350	
Age (years)	44.9 ± 6.4	44.7 ± 6.2	NS
Male sex	76.4	85.7	0.01
BMI (kg/m^2)	24.8 ± 2.5	24.7 ± 2.2	NS
Waist circumference (cm)	83.3 ± 6.7	96.4 ± 6.0	0.01
WHR	0.85 ± 0.05	1.07 ± 0.08	0.01
CRP (mg/dl)	1.53 ± 1.74	1.96 ± 2.16	0.04
HDL cholesterol (mg/dl)	49.6 ± 12.8	45.29 ± 12.6	0.01
Triglycerides (mg/dl)	116 ± 59	149 ± 81	0.01
Uric acid (mg/dl)	4.5 ± 1.1	4.8 ± 1.6	0.01
Systolic blood pressure (mmHg)	132 ± 15	135 ± 16	0.02
Diastolic blood pressure (mmHg)	84 ± 9	87 ± 9	0.01
HOMA-IR	1.77 ± 0.90	1.99 ± 1.21	0.03
Fibrinogen (mg/dl)	302 ± 62	295 ± 61	NS
Proportion with CRP >3 mg/dl	10.1	21.4	0.01
Current smokers	50.8	52.0	NS
Former smokers	22.6	27.1	NS
Proportion with metabolic syndrome	10.1	25.9	0.01

Data are means ± SD or % unless otherwise indicated. NS, not significant.

cholesterol levels, and twice the prevalence of metabolic syndrome (Adult Treatment Panel III [ATPIII]). Smoking status and plasma fibrinogen were comparable in the two groups. hs-CRP was significantly correlated with BMI in both case ($r = 0.23$; $P < 0.01$) and control subjects ($r = 0.17$; $P < 0.02$); however, multivariate analyses confirmed a significant association of abdominal adiposity with either CRP (continuous variable) or elevated CRP (>3 mg/dl) independent of BMI, age, sex, and measured cardiovascular risk factors.

CONCLUSIONS — The study shows that in healthy nonobese people, abdominal adiposity is associated with hs-CRP, independent of age and BMI, which is a measure of total adiposity. hs-CRP values and the proportion of people with elevated hs-CRP [i.e., >3 mg/dl, a value associated with increased cardiovascular risk (7)] are significantly higher in those with abdominal adiposity than in control subjects, notwithstanding a superimposable BMI. A significant correlation between BMI and hs-CRP levels is observed in both groups, thus confirming expected findings and conferring internal consistency with our results. The excess cardiometabolic risk associated with abdominal adiposity is only partially explained by established risk factors; systemic low-grade inflammation may represent an additional less extensively explored mechanism (3,4). Indeed, hs-CRP predicts cardiovascular events in people with nonelevated LDL cholesterol levels (4,7). Because statins lower both cholesterol and CRP, measuring this biomarker helps to identify people who may benefit from statin treatment beyond its lipid-lowering effect.

Given the strong association we show between WHR and hs-CRP—independent of BMI—and considering the difficulty of routinely measuring hs-CRP in the general population, WHR (although a crude measure of abdominal adiposity) might be proposed in nonobese people as a surrogate marker for subclinical inflammation or, alternatively, as a simple means to select individuals in whom hs-CRP should be measured to further characterize their cardiovascular risk. CRP is the most widely measured marker of systemic inflammation; its interindividual variance is largely due to genetic factors (50%). However, adiposity is the other major determinant of hepatic CRP synthesis via production of proinflammatory cytokines (interleukin [IL]-6, IL-1, and tumor necrosis factor-α). There is evidence that IL-6, a key determinant of CRP production in hepatocytes, is secreted in an endocrine manner in proportion to the expansion of fat mass, particularly in the abdominal region (8,9). The relation of CRP with fat mass and fat distribution has been extensively explored with partially conflicting results (10–13). Most, but not all, studies focus on obese or morbidly obese people in whom a differential impact of total or abdominal adiposity may be difficult to evaluate. This is one of the very few population-based studies of nonobese people. Furthermore, unlike previous studies, we used a case-control design, which is particularly efficient in controlling for the confounding effect of BMI, allowing us to compare people with different fat distribution but the same BMI. The cross-sectional nature of the study, however, does not allow to determine whether abdominal adiposity is causally associated with CPR elevation or whether the association is mediated through other obesity-associated conditions such as insulin resistance or subclinical atherosclerosis.

In conclusion, the study shows that in healthy nonobese people, hs-CRP is associated with abdominal adiposity—evaluated as WHR—independent of BMI, thus supporting current recommendations that in people with BMI 25.0–34.9 kg/m^2, waist circumference or WHR should be measured to identify people at high cardiovascular and metabolic risk. The relative contribution of general adiposity may, however, be more relevant in severe obesity.

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