Inflammation-Sensitive Plasma Proteins Are Associated With Future Weight Gain

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Cross-sectional studies have associated obesity and other components of the so-called metabolic syndrome with low-grade inflammation. The temporal and causal relations of this association have not been fully explored. This study explored whether elevated levels of inflammation-sensitive plasma proteins (ISPs) (fibrinogen, orosomucoid, α1-antitrypsin, haptoglobin, and ceruloplasmin) are associated with future weight gain. Five ISPs were measured in 2,821 nondiabetic healthy men (38–50 years of age) who were reexamined after a mean follow-up of 6.1 years. Future weight gain was studied in relation to the number of elevated ISPs (i.e., in the top quartile). The proportion with a large weight gain (75th percentile ≥3.8 kg) was 21.0, 25.9, 26.8, and 28.3%, respectively, among men with none, one, two, and three or more ISPs in the top quartile (*P* for trend 0.0005). This relation remained significant after adjustments for weight at baseline, follow-up time, height (at baseline and follow-up), physical inactivity (at baseline and follow-up), smoking (at baseline and follow-up), high alcohol consumption, and insulin resistance. The relations were largely similar for all individual ISPs. Elevated ISP levels predict a large weight gain in middle-aged men. This relation could contribute to the relation between inflammation, the metabolic syndrome, and cardiovascular disease. *Diabetes* 52: 2097–2101, 2003

Several cross-sectional studies have reported positive correlations between body fatness and inflammation-sensitive plasma proteins (ISPs) and other inflammatory markers (1–4). Weight reduction in obese subjects has been associated with reduced inflammation (5–7). It has been proposed that proinflammatory cytokines formed in the adipose tissue, e.g., interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), increase the hepatic synthesis of ISPs (4,8–10). However, the temporal and causal relations between obesity and elevated ISPs are incompletely understood. Even though inflammation is mainly considered an effect of obesity or weight increase, it also has been suggested that there could be a reverse relation, i.e., that inflammation could promote weight gain (11). A 3-year follow-up of the Atherosclerosis Risk in Communities (ARIC) study reported that a large weight gain was more common in subjects with elevated fibrinogen, white blood cells, von Willebrand factor, or factor VIII, i.e., four putative markers of inflammation (12).

The Malmö Preventive Study cohort includes ~6,000 men with data on five ISPs (fibrinogen, haptoglobin, α1-antitrypsin, orosomucoid, and ceruloplasmin). Previous studies from this cohort have shown cross-sectional relations between ISP levels and BMI, blood pressure, and insulin resistance (1,13,14). Follow-up studies have shown that these proteins are associated with an increased incidence of cardiovascular diseases and an increased incidence of high blood pressure (15,16). The present study sought to explore whether these proteins predicted weight gain over a mean follow-up of 6 years.

RESEARCH DESIGN AND METHODS

Between 1974 and 1983, 22,444 men participated in a screening program for the detection of individuals with high risk for cardiovascular diseases (15,17). The participation rate was 71%. Determination of five plasma proteins was part of the program for 6,193 men selected at random. After the exclusion of men with diabetes or a history of myocardial infarction, stroke, or cancer (according to questionnaire), 5,729 men remained.

A follow-up examination was performed after a mean follow-up of 6.1 ± 0.93 years (range 3.0–9.0). Only men born in 1926–1931 and 1938 were invited to the follow-up. Of the 3,482 men in these age cohorts who were alive in 1982 when the reexamination started, 2,821 (81%) participated. The sample of the present study thus consists of 2,821 healthy men, 38–50 years of age at baseline, who were reexamined after a mean period of 6.1 years. The proportions with two or more elevated ISPs at baseline were similar in dropouts (n = 661) and men who participated in the follow-up examination. However, nonparticipants had higher BMI at baseline than the study sample (25.4 vs. 24.7, $P < 0.001$). The health service authority of Malmö approved the screening program. All participants gave informed consent.

Baseline examinations. Men with diabetes at baseline were excluded (fasting whole blood glucose ≥6.1 mmol/l, 2-h post–glucose load ≥10.0, or self-reported diabetes) (14). Subjects were categorized into smokers and nonsmokers. Insulin was measured with a nonspecific radioimmunoassay (18). The homeostasis model formula according to Matthews et al. (19), i.e., fasting insulin × fasting glucose/22.5, was used to calculate a score for insulin resistance (homeostasis model assessment for insulin resistance).

Physical inactivity was assessed in a questionnaire at baseline and at follow-up. Men who reported that they were mostly sedentary in spare time were categorized as physically inactive. Some items of the questionnaire were changed before the end of the follow-up period. At the follow-up examination, physical inactivity was therefore defined as either those who were mostly sedentary in spare time or those who reported that they did not perform physical activity in spare time (e.g., walking or cycling) regularly every week.

Alcohol consumption was assessed by means of the modified shortened version of the Michigan Alcoholism Screening Test (20). Men with more than two (of nine) affirmative answers were considered to be high consumers of alcohol.

Weight. Trained nurses measured weight and height in the morning after an overnight fast. Weight increase was calculated as weight at baseline sub-

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HPA, hypothalamic-pituitary-adrenal; IL, interleukin; ISP, inflammation-sensitive plasma protein; TNF-α, tumor necrosis factor-α.

TABLE 1
Description of the study cohort at baseline and follow-up in relation to number of ISPs in the top quartile

	ISPs in the top quartile				
	None	One	Two	Three or more	*P* for trend
n	1,201	738	395	487	
Baseline characteristics					
Age at baseline (years)	47.3 ± 2.6	47.3 ± 2.5	47.4 ± 2.5	47.6 ± 2.0	0.03
Smokers (%)	30	47	61	76	<0.001
High alcohol consumption (%)	6.2	9.2	10.1	12.5	<0.001
Physical inactivity (%)	53	58	55	59	0.02
BMI (kg/m^2)	24.6 ± 3.0	24.8 ± 3.2	25.0 ± 3.4	24.7 ± 3.5	0.34
Height (cm)	176.7 ± 6.6	176.5 ± 6.6	175.4 ± 6.5	176.1 ± 6.3	0.006
Weight (kg)	76.9 ± 10.8	77.4 ± 11.1	76.9 ± 11.4	76.5 ± 11.4	0.51
Follow-up characteristics					
Follow-up (years)	6.2 ± 0.9	6.1 ± 0.9	6.1 ± 0.9	6.2 ± 0.9	0.67
Smokers (%)	23	36	50	62	<0.001
Physical inactivity (%)	48	52	52	53	0.02
BMI (kg/m^2)	25.0 ± 2.9	25.4 ± 3.2	25.6 ± 3.7	25.2 ± 3.8	0.08
Height (cm)	176.5 ± 6.6	176.3 ± 6.6	175.3 ± 6.6	175.8 ± 6.3	0.004
Weight (kg)	78.1 ± 10.6	78.8 ± 11.0	78.6 ± 12.4	78.0 ± 11.9	0.99

Data are means ± SD unless otherwise indicated.

tracted from the follow-up value. A large weight increase was defined as the 75th percentile of the distribution, i.e., a weight increase of ≥3.8 kg. BMI was calculated as weight in kilograms divided by height in meters squared.

The question "Has your weight increased >10 kg since the age of 30?" was used to estimate whether a large weight gain had occurred before the baseline examination.

ISPs. Electroimmunoassay was used to assess the plasma levels of five ISPs (21). The analysis was performed consecutively at the study entry. We have previously shown that the correlation coefficients between the individual proteins range between 0.31 and 0.56 (1). We have also reported that all five ISPs are associated with cardiovascular disease and that the cardiovascular risk increases with the number of ISPs in the top quartile (13–15). In accordance with the previous studies, the number of elevated ISPs was used. The top quartiles were as follows: fibrinogen >4.0 g/l, orosomucoid (α1-glucoprotein) >0.93 g/l, α1-antitrypsin >1.42 g/l, haptoglobin >1.76 g/l, and ceruloplasmin >0.36 g/l.

Statistics. Logistic regression was used to study the proportion with a large weight gain in relation to number of elevated ISPs. A general linear model was used to study weight increase (in kilograms) in relation to ISPs and to compute the adjusted means.

RESULTS

The baseline characteristics of the study cohort are presented in Table 1. Smoking, alcohol consumption, and physical inactivity were positively associated with the number of elevated ISPs. The proportion of smokers decreased from 47 to 37% during the follow-up period.

Weight change in relation to ISP levels. The proportion with a large weight gain (75th percentile ≥3.8 kg) increased from 21.0% among those with no ISP in the top quartile to 28.3% in those with three or more elevated ISPs (Table 2). This relation remained significant after adjustments for several potential confounders. Information on insulin levels at baseline was available in a subgroup of 1,966 men. The results were virtually identical ($P = 0.001$) when further adjusted for insulin sensitivity (log-transformed homeostasis model assessment values).

The relation between weight increase and ISP levels did not reach significance when weight increase was used as a continuous variable (Table 2). This was explained by the heterogeneity in weight change among men with three or more elevated ISPs. Particularly in smokers, the proportion with a low weight gain (25th percentile, a weight reduction ≥1.2 kg) also tended to be higher in men with three elevated ISPs.

Table 3 presents the relations between ISPs and a large

TABLE 2
Weight gain in relation to number of ISPs in the top quartile

	ISPs in the top quartile				
	None	One	Two	Three or more	*P* for trend
n	1,201	738	395	487	
Large weight gain (≥3.8 kg) (%)	21.0	25.9	26.8	28.3	0.0005
Adjusted OR, model 1*	1.00	1.38†	1.45†	1.55†	0.0001
Adjusted OR, model 2‡	1.00	1.34†	1.42†	1.51†	0.001
Mean weight gain (kg)	1.17 ± 4.3	1.41 ± 4.6	1.69 ± 4.7	1.43 ± 5.0	0.11
Adjusted means, model 1*	1.12	1.45	1.74†	1.44	0.10
Adjusted means, model 2‡	1.13	1.43	1.75†	1.46	0.10
Low weight gain (%) (weight loss >1.2 kg)	24.6	25.2	25.3	26.9	0.36
Adjusted OR, model 1*	1.00	0.99	0.97	1.08	0.67
Adjusted OR, model 2‡	1.00	0.98	0.95	1.05	0.88

Data are means ± SD unless otherwise indicated. *Adjusted for age, follow-up time, weight at baseline, and height at baseline and follow-up. †$P < 0.05$ vs. no ISP in top quartile. ‡Additionally adjusted for physical inactivity at baseline and follow-up, high alcohol consumption, and smoking at baseline and follow-up.

TABLE 3
The proportion with a large weight gain in relation to ISPs by smoking and BMI at baseline

	ISPs in the top quartile				
	None	One	Two or more	*P* for trend*	*P* for trend†
BMI <28 kg/m^2 (*n*)	1061	618	743		
Large weight gain (%)	22.1	26.5	26.8	0.01	0.03
Nonsmokers	19.6 (143/729)	24.1 (77/319)	22.5 (49/218)	0.10	0.09
Smokers	27.4 (91/332)	29.1 (87/299)	28.6 (150/525)	0.69	0.21
BMI ≥28 kg/m^2 (*n*)	140	120	139		
Large weight gain (%)	12.9	22.5	32.4	<0.001	0.002
Nonsmokers	10.9 (12/110)	21.3 (16/75)	32.1 (17/53)	0.0008	0.01
Smokers	20.0 (6/30)	24.4 (11/45)	32.6 (28/86)	0.063	0.048

Data are % (*n* of *n*) unless otherwise indicated. **P* for trend adjusted for age, follow-up time, weight at baseline, and height at baseline and follow-up. †Additionally adjusted for physical inactivity at baseline and follow-up, high alcohol consumption, and smoking at baseline and follow-up.

weight gain in smokers and nonsmokers in relation to BMI at baseline. The relation between ISPs and weight increase was observed both among men with high and low baseline BMI. The relations were most pronounced among nonsmokers and men with high BMI.

The possibility that a large weight increase before the baseline examination could explain the relations between elevated ISPs and future weight gain was explored using the question "Has your weight increased >10 kg since the age of 30?" The proportion with a large weight gain since the age of 30 years was 23% among men with no elevated ISP compared with 28% in those with three or more elevated ISPs (*P* for trend 0.01). However, future weight gain was lower in men with a large weight gain before the baseline examination. The association between number of elevated ISPs and future weight gain (≥3.8 kg), as described in Table 2, was unchanged when the relations were further adjusted for history of a large weight gain. The results were also identical after the exclusion of 31 men who had myocardial infarction during the follow-up period (not shown).

The multivariate-adjusted relations between number of elevated ISPs and large weight gain were also significant for other definitions of large weight gain, e.g., the 67th percentile (weight gain >3.0 kg), the 80th percentile (>4.5 kg), or the 90th percentile (>6.6 kg) of the distribution (all $P < 0.01$).

Weight increase in relation to individual ISPs. Table 4 presents the adjusted odds ratios (ORs) comparing the proportion with a large weight gain in quartiles of individual ISPs. The relations with a large weight gain were largely similar for all ISPs.

DISCUSSION

Many cross-sectional studies have reported associations between BMI and various markers of inflammation (1–4). It has been suggested that proinflammatory cytokines formed in the adipose tissue increase the hepatic synthesis of ISPs (4,8–10). However, the temporal and causal relations between obesity and elevated ISPs have not been fully explored. Few have studied whether inflammation predicts future weight gain. In this longitudinal study, a large weight gain was significantly more common in men with elevated ISPs.

The participation rates were high and the procedures were identical at both examinations. Body weight was measured by trained nurses and was not subject to self-report. As smoking is associated with elevated ISPs and smoking cessation is associated with weight gain, smoking is a potential confounder. However, the results were adjusted for smoking at baseline and follow-up. The relations were most pronounced among the nonsmokers, and it is unlikely that smoking explains the results. Physical activity is another factor that could reduce weight gain and inflammation (22). The results were adjusted for physical inactivity both at baseline and follow-up. However, only two categories of physical activity were used, and it is possible that the variables did not detect all of the effects of physical activity. We have no information on diet. It has been reported that macronutrient intake induces oxidative stress (6,23,24), which could increase inflammation (25,26). It is possible that the relations between ISPs and weight gain reflect dietary factors that increase both weight and ISPs. A limitation of the study is that we do not know whether the weight gain was due to increased abdominal fat. It can be assumed, however, that weight gain among men in this age-group is largely explained by increased body fat and not by increased muscle mass.

Obesity is an important component of the so-called metabolic syndrome and tends to cluster with hyperten-

TABLE 4
ORs comparing the proportion with a large future weight gain in quartiles (Q) of five ISPs

	Q2	Q3	Q4	*P* for trend
Model 1				
Fibrinogen	0.99	1.10	1.34*	0.01
Haptoglobin	0.98	1.11	1.25	0.06
Ceruloplasmin	1.07	1.33*	1.32*	0.01
Orosomucoid	1.03	0.96	1.36*	0.02
α1-antitrypsin	0.97	1.14	1.27	0.02
Model 2				
Fibrinogen	1.00	1.07	1.28	0.046
Haptoglobin	0.97	1.08	1.19	0.17
Ceruloplasmin	1.08	1.31*	1.28	0.03
Orosomucoid	1.02	0.93	1.29*	0.06
α1-antitrypsin	0.96	1.08	1.20	0.10

*$P < 0.05$ vs Q1. Reference quartile 1. Model 1, adjusted for age, follow-up time, weight at baseline, and height at baseline and follow-up; model 2, additionally adjusted for physical inactivity at baseline and follow-up, smoking at baseline and follow-up, and high alcohol consumption.

sion, dyslipidemia, insulin resistance, and type 2 diabetes. Increased levels of ISPs are also part of this syndrome (27). The knowledge on the adipose tissue has gradually turned in favor of an organ with endocrine functions. For example, TNF-α, IL-6, leptin, and other proinflammatory molecules are produced in the adipose tissue (8–10). An increased synthesis of cytokines in obese subjects could contribute to the relations between adiposity and diabetes (10,28–30), and it has been shown that obesity in combination with elevated ISPs substantially increases the risk of being diabetic or insulin resistant (14). It is reasonable to ask which component comes first: obesity, inflammation, or insulin resistance. Several studies have reported associations between inflammatory markers and an increased incidence of diabetes (29–31). It has also been shown that elevated ISP levels are associated with future blood pressure increase (16). The present results show that ISPs are associated with future weight gain. These results support the view that elevated levels of inflammatory markers occur early in the process, leading to obesity and the metabolic syndrome, and that inflammation could have a causal role for the development of the syndrome. However, this does not contradict the assumption that obesity increases ISP levels. Once obesity and/or insulin resistance has been established, this may further stimulate the production of proinflammatory cytokines, forming a vicious circle of inflammation and other elements of the metabolic syndrome.

We can only speculate about the reasons for the associations between ISPs and weight gain. It is obvious that very small alterations in metabolism or food intake can cause a weight increase of this magnitude. The hepatic synthesis of ISPs is regulated by various cytokines, e.g., IL-6, IL-1β, and TNF-α (32,33). These cytokines are, in many different ways, involved in the regulation of metabolism and food intake. For example, TNF-α regulates the actions of insulin in the adipose tissue (28) and has been shown to affect endothelial function (34). TNF-α and IL-1β modulate the release of leptin, an anorexogenic hormone formed in the adipose tissue (35). TNF-α and IL-1 have a role in the development of cancer anorexia (36). Studies of rodents have shown that these cytokines act directly on the hypothalamus by modulating the monoaminergic regulation of food intake (36). Polymorphism of the TNF-α receptor 2 gene has been associated with leptin resistance and obesity (37).

It has been suggested that activation of the hypothalamic-pituitary-adrenal (HPA) axis followed by hypercortisolemia and symphathetic activation cause obesity and other features of the metabolic syndrome (38). Elevated cortisol levels are associated with central obesity, resistance to leptin, and an increased food intake (38–40). As various proinflammatory cytokines stimulate the HPA axis (41), this is another possible link between elevated ISPs and weight gain. Chronic inflammation is also associated with inhibition of the growth hormone secretion, which could further increase abdominal obesity (42,43).

We conclude that elevated ISP levels predict weight gain in middle-aged men. This relation could contribute to the relations between inflammation, the metabolic syndrome, and cardiovascular disease.

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