Obesity and Weight Gain Are Associated with Increased Incidence of Hyperinsulinemia in Non-Diabetic Men

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Original Clinical

Abstract

We investigated the temporal relationships between obesity, weight change and hyperinsulinemia in a population-based 4-year follow-up study of 695 middle-aged, non-diabetic, and normoinsulinemic men. Thirty-eight men developed hyperinsulinemia during the follow-up (fasting serum insulin ≥ 12.0 mU/l). In logistic regression analysis adjusting for other risk factors, men with body mass index of ≥ 26.7 kg/m^2 (highest third) had a 6.6-fold (p = 0.001) risk of developing hyperinsulinemia, compared with men with body mass index of < 24.4 kg/m^2 (lowest third). Correspondingly, men with waist-to-hip ratio of ≥ 0.95 (highest third) had a 3.5-fold (p = 0.028) incidence of hyperinsulinemia compared with men with waist-to-hip ratio of < 0.90 (lowest third). Weight gain in middle age and weight gain from the age of 20 years to middle age were also associated with increased risk of hyperinsulinemia. Hyperinsulinemia at baseline was not associated with weight gain during the follow-up. This prospective population-based study emphasizes the importance of avoiding obesity and weight gain during adulthood in preventing hyperinsulinemia.

Key words
Obesity · Weight Gain · Hyperinsulinemia · Insulin Resistance · Population Studies · Cohort Study

Introduction

Overall and abdominal obesity have been associated with insulin resistance or compensatory hyperinsulinemia in numerous cross-sectional studies [1]. On the basis of cross-sectional data, however, it is impossible to conclude whether obesity precedes or follows hyperinsulinemia. Indeed, prospective evidence concerning the temporal relationships between obesity, change in body weight and hyperinsulinemia is inconsistent. Some prospective studies on non-diabetic individuals of different ethnic backgrounds have shown that insulin resistance and hyperinsulinemia are associated with lower rates of weight gain [2 – 8]. On the other hand, hyperinsulinemia has been found to promote weight gain in Pima Indian children [9] and in both black and white young adults [8]. In some population-based studies on non-diabetic subjects, obesity and weight gain have predicted increases in insulin levels or hyperinsulinemia [9 – 13]. For both temporal sequences, there are plausible physiological mechanisms that may explain the association [14 – 16]. The existing data are, however, derived from different ethnic populations, age groups, and often from special high-risk populations, which limits the generalizability of the results. In addition, it is not known whether obesity in early adulthood and change in body weight from early adulthood to middle age affect the development of hyperinsulinemia in middle age.

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Received 18 September 2001 · **Accepted after revision** 23 April 2002

Bibliography
Horm Metab Res 2002; 34: 492–498 © Georg Thieme Verlag Stuttgart · New York · ISSN 0018-5043

Due to the inconsistency of the existing data, more research is needed on the time order of obesity, weight gain and hyperinsulinemia. Therefore, we evaluated the associations of obesity and weight gain during adulthood and middle age with the incidence of hyperinsulinemia and also the relationship of hyperinsulinemia with the development of obesity during middle age in a prospective population-based study among non-diabetic men.

Materials and Methods

Study population

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) is an ongoing, population-based study designed to investigate risk factors for cardiovascular diseases and related outcomes in middle-aged men from the Kuopio region in eastern Finland [17]. The study was approved by the Research Ethics Committee of the University of Kuopio. All subjects gave their written informed consent. A total of 2682 participants (82.9% of those eligible) aged 42, 48, 54 and 60 years were enrolled in the study between March 1984 and December 1989. Four-year follow-up examinations were conducted between March 1991 and December 1993 on those men who had undergone ultrasound examination of the carotid arteries at baseline. A total of 1229 men were eligible for the follow-up study; of these, 107 refused, 52 could not participate due to death, severe illness or relocation, and 32 could not be contacted. Thus, the follow-up study included 1038 participants, 88.2% of those alive.

The present study sample included 926 men after the exclusion of men with diabetes (fasting blood glucose of ≥ 6.7 mmol/l or clinical diagnosis with either dietary, oral or insulin treatment) or missing serum insulin value at baseline or follow-up or missing values in any of the anthropometric measures used. Average time to follow-up was 4.2 years (range 3.6 – 5.2 years). In analyses of incident hyperinsulinemia, men with hyperinsulinemia at baseline defined as fasting serum insulin ≥ 12.0 mU/l (highest quarter) were excluded [18], leaving a sample of 695 initially non-diabetic, normoinsulinemic men. Correspondingly, a subject was defined as having incident hyperinsulinemia in the follow-up if he had fasting serum insulin ≥ 12.0 mU/l among the 695 men.

Anthropometric measurements

Body mass index (BMI) was computed by dividing body weight in kilograms by the square of the body height in meters. Waist circumference was calculated as the average of one measurement taken after inspiration and one taken after expiration at the level of mid-distance between the bottom of the rib cage and the top of the iliac crest. Hip circumference was measured at the level of trocanter major. Waist-to-hip ratio (WHR) was calculated as the ratio of the circumference of the waist to the hip. Body weight at the age of 20 years was obtained from a self-report questionnaire administered at baseline [19].

Blood sampling

The subjects gave blood specimens between 8 and 10 a. m. They were instructed to fast and to abstain from smoking for 12 hours, from drinking alcohol for 3 days, and from using analgesics for 7 days. After the subjects had rested in a supine position for 30 min, blood was drawn using Terumo Venoject vacuum tubes (Tokyo, Japan). No tourniquet was used.

Measurement of serum insulin

Fasting serum insulin was measured with RIA at baseline (Novo Biolabs; Novo Nordisk, Bagsvaerd, Denmark) [20]. The serum samples were stored frozen at – 80° C for 0.2 to 2.5 years. The between-batch coefficient of variation (CV) was 8.9% at 9.1 mU/l and 17.5% at 30.9 mU/l. In the follow-up, the serum samples were stored at – 80° C for a period of one week to six months, and insulin was determined by RIA (Pharmacia Diagnostics, Uppsala, Sweden). The between-batch CV was 6.7% at 14.5 mU/l and 5.4% at 40.3 mU/l.

Other biochemical analyses

Blood glucose was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany) after proteins had been precipitated with trichloroacetic acid. The measurement of serum lipids and lipoproteins has been described previously [21]. Plasma fibrinogen was determined based on clotting of diluted plasma with excess thrombin with a KC4 coagulometer (Heinrich Amelung, Lemgo, Germany). Blood leucocytes were assessed using a cell counter (Coulter Counter Electronics, Luton, U.K.). Serum uric acid was measured enzymatically (Kone Instruments, Espoo, Finland). Plasma α-tocopherol and ascorbate concentrations were determined by high-performance liquid chromatography. To separate the effect of α-tocopherol from that of serum lipids, lipid-standardized plasma α-tocopherol concentration was used in the statistical analyses [22].

Other assessments

Assessment of medical history and medications, family history of diseases, blood pressure, smoking, alcohol consumption, physical activity and maximal oxygen uptake (VO_2max), socioeconomic status, food consumption and nutrient intake have been described previously in detail [17,18,23 – 25].

Statistical analyses

Differences in baseline characteristics between the subjects who developed hyperinsulinemia during the follow-up and those who did not were analyzed using independent samples *t*-test. A number of possible risk factors for incident hyperinsulinemia were tested using logistic regression analysis. Statistically significant ($p < 0.05$) risk factors for hyperinsulinemia were selected as covariates for subsequent analyses of obesity, weight gain and incident hyperinsulinemia. These covariates were entered into a fixed multivariate logistic regression model jointly with dummy variables for the upper two thirds of indicators of obesity or change in weight (in separate models) using the lowest third as reference group. Linear trends for the incidence of hyperinsulinemia over the thirds of measures of obesity or change in weight were tested using logistic regression analysis. Differences in the 4-year change in weight between the thirds of baseline fasting serum insulin were analyzed using covariance analysis; linear trends across these thirds were analyzed using linear regression analysis. Statistical analyses were performed using SPSS 10.0 for Windows.

Results

Characteristics of subjects

All baseline indicators of obesity were higher among men who developed hyperinsulinemia than among those who did not (Table **1**). In addition, increases in body weight during the 4-year follow-up and increase in body weight from the age of 20 years to middle age (study baseline) were higher among incident hyperinsulinemic men than in those who remained normoinsulinemic. There was no difference in body weight at age 20 between these two groups. Furthermore, baseline fasting serum insulin, serum uric acid, diastolic blood pressure and the use of diuretics were higher and VO_2max and dietary intake of fiber were lower in men who developed hyperinsulinemia than in those who did not. There were no statistically significant differences in fasting blood glucose, serum triglycerides and HDL cholesterol, plasma fibrinogen, α-tocopherol and ascorbic acid, blood leukocyte count, systolic blood pressure, physical activity, smoking, alcohol consumption, the use of β-blockers, socioeconomic status, or family history of diabetes between men with incident hyperinsulinemia and those who remained normoinsulinemic.

Risk factors for incident hyperinsulinemia

BMI, waist circumference, WHR, body weight at baseline, change in body weight during the 4-year follow-up and change in body weight from the age of 20 years to middle age as continuous variables showed strong direct associations with the risk of developing hyperinsulinemia, adjusting for age and examination years (Table **2**). For an increment of one unit in BMI (1.0 kg/m^2), waist circumference (1.0 cm), WHR (0.01 cm/cm), body weight (1.0 kg), and weight gain in 4 years (1.0 kg), the risk of incident hyperinsulinemia increased by 40%, 11%, 8%, 8% and 30%, respectively. With an increment of 1.0 kg in body weight from the age of 20 years to middle age, the risk of hyperinsulinemia increased by 8%. In addition, increased fasting serum insulin, increased serum uric acid and the use of diuretics were associated with increased risk of developing hyperinsulinemia, and high dietary intake of fiber and high VO_2max were associated with reduced risk.

Obesity, weight gain and the risk of developing hyperinsulinemia

Men in the highest thirds of BMI (≥ 26.7 kg/m^2), waist circumference (≥ 90.0 cm), WHR (≥ 0.95), change in body weight during the 4-year follow-up (≥ 4.0 kg), and change in body weight from the age of 20 years to middle age (≥ 12.8 kg) had a higher risk of developing hyperinsulinemia during the 4-year follow-up than men in the corresponding lowest thirds adjusting for other risk factors (Table **3**). After additional adjustment for baseline insulin, the associations between BMI and weight change in middle age remained statistically significant (OR in the highest thirds 4.16, p = 0.014 and 8.70, p < 0.001, respectively). However, the associations of waist circumference, WHR and change in weight from the age of 20 years to middle age were no longer statistically significant (OR in the highest thirds 1.74, p = 0.280, 1.95, p = 0.262 and 1.95, p = 0.216, respectively).

Men with overall obesity (BMI ≥ 26.7 kg/m^2) but without abdominal obesity (WHR < 0.95) had an 8.1-fold risk of developing hyperinsulinemia compared with men without abdominal or over-

Table **1** Characteristics of the subjects who developed hyperinsulinemia during follow-up and of those who did not

	Incident hyperinsulinemic men (n = 38) Mean ± SD*	*Normoinsulinemic men after follow-up (n = 657) Mean ± SD*	*p-value for difference between means*	*All subjects (n = 695) Mean ± SD*	*Range*
Age (Years)	52.7 ± 6.2	51.7 ± 6.7	0.361	51.7 ± 6.7	42.0 – 61.3
Body mass index (kg/m^2)	28.4 ± 2.7	25.6 ± 2.7	< 0.001	25.7 ± 2.8	18.8 – 37.0
Waist circumference (cm)	94.2 ± 7.7	86.9 ± 8.1	< 0.001	87.3 ± 8.2	67.0 – 120.5
Waist-to-hip ratio	0.96 ± 0.05	0.92 ± 0.06	< 0.001	0.93 ± 0.06	0.75 – 1.51
Body weight (kg)	85.2 ± 10.5	77.6 ± 9.8	< 0.001	77.5 ± 10.0	47.3 – 121.8
Weight at the age of 20 (kg)†	68.1 ± 7.5	67.7 ± 7.0	0.674	67.9 ± 7.1	48 – 92
Change in weight from baseline to 4-year follow-up (kg)†	7.0 ± 5.6	2.3 ± 3.6	< 0.001	2.6 ± 3.9	– 9.6 – 24.8
Change in weight from the age of 20 to middle age (study baseline)(kg)†	15.6 ± 9.2	9.2 ± 8.7	< 0.001	9.5 ± 8.9	– 13.4 – 48.7
Fasting serum insulin (mU/l)	10.0 ± 1.4	7.8 ± 2.2	< 0.001	8.0 ± 2.2	1.0 – 12.0
Fasting blood glucose (mmol/l)	4.5 ± 0.4	4.5 ± 0.4	0.361	4.5 ± 0.4	3.2 – 6.2
Serum HDL cholesterol (mmol/l)	1.26 ± 0.24	1.35 ± 0.31	0.101	1.34 ± 0.30	0.58 – 2.78
Serum triglycerides (mmol/l)	1.43 ± 1.06	1.23 ± 0.62	0.065	1.24 ± 0.65	0.29 – 6.21
Serum uric acid (mmol/l)	351 ± 48	328 ± 52	0.006	329 ± 52	190 – 530
Systolic blood pressure (mmHg)	135.3 ± 18.0	129.7 ± 15.4	0.066	130.0 ± 15.6	88.7 – 194.0
Diastolic blood pressure (mmHg)	91.0 ± 9.8	85.9 ± 10.0	0.003	86.2 ± 10.0	58.7 – 129.0
Use of diuretics (%)	7.9	2.0	0.018	2.3	0 – 1
Dietary fiber (g/day)	21.7 ± 7.0	27.5 ± 10.5	0.001	27.2 ± 10.4	6.9 – 103.9
Maximal oxygen uptake (ml/min/kg)	28.5 ± 6.4	32.9 ± 7.3	< 0.001	32.7 ± 8.0	9.4 – 58.0
Smoking (cigarettes/day)	7.7 ± 10.4	5.3 ± 9.5	0.191	5.5 ± 9.5	0.0 – 60.0

* Incident hyperinsulinemia is defined as fasting serum insulin of ≥ 12.0 mU/l in the 4-year follow-up examination. All are baseline characteristics except those marked with †.

Table **2** Risk factors for incident hyperinsulinemia in the study cohort*

	OR	*95% CI*	*p-value*
Body mass index (kg/m^2)	1.40	1.25 – 1.57	< 0.001
Waist circumference (cm)	1.11	1.06 – 1.15	< 0.001
Waist-to-hip ratio × 100	1.08	1.03 – 1.14	0.003
Body weight (kg)	1.08	1.05 – 1.11	< 0.001
Weight at the age of 20 (kg)†	1.04	0.99 – 1.09	0.10
Change in weight from baseline to 4-year follow-up (kg)†	1.30	1.20 – 1.41	< 0.001
Change in weight from the age of 20 to middle age (study baseline) (kg)†	1.08	1.04 – 1.12	< 0.001
Serum insulin (mU/l)	1.79	1.44 – 2.21	< 0.001
Serum uric acid (mmol/l)	1.008	1.002 – 1.014	0.006
Use of diuretics	4.51	1.20 – 16.88	0.025
Dietary fiber (g/day)	0.93	0.89 – 0.98	0.001
Maximal oxygen uptake (ml/min/kg)	0.90	0.85 – 0.95	< 0.001

*From logistic regression models adjusting for age and examination years. Incident hyperinsulinemia is defined as fasting serum insulin of ≥ 12.0 mU/l in the 4-year follow-up examination. †Not baseline characteristics.

Table **3** Odds ratios for incident hyperinsulinemia in the thirds of body mass index, waist circumference, waist-to-hip ratio, change in weight in the 4-year follow-up, and change in weight from the age of 20 years to middle age (study baseline)

	Number of incident cases (%)	*Model 1**			*Model 2**		
		OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Body mass index (kg/m^2)							
< 24.4 (reference)	4 (1.7)	1.00			1.001		
24.4 – 26.6	3 (1.3)	0.71	0.16 – 3.22	0.658	0.64	0.14 – 2.95	0.567
≥ 26.7	31 (13.4)	8.77	3.03 – 25.38	< 0.001	6.62	2.22 – 19.77	0.001
p-value for linear trend across thirds		< 0.001			< 0.001		
Waist circumference (cm)							
< 83.5 (reference)	6 (2.6)	1.00			1.00		
83.5 – 89.5	4 (1.7)	0.64	0.18 – 2.30	0.492	0.52	0.14 – 1.90	0.318
≥ 90.0	28 (12.2)	5.08	2.05 – 12.59	< 0.001	3.28	1.27 – 8.44	0.014
p-value for linear trend across thirds		< 0.001			0.002		
Waist-to-hip ratio (cm/cm)							
< 0.90 (reference)	4 (1.7)	1.00			1.00		
0.90 – 0.94	12 (5.2)	3.06	0.97 – 9.62	0.056	2.58	0.80 – 8.37	0.113
≥ 0.95	22 (9.5)	5.65	1.91 – 16.72	0.002	3.50	1.15 – 10.68	0.028
p-value for linear trend across thirds		0.001			0.027		
Change in weight in the 4-year follow-up (kg)							
< 0.9 (reference)	4 (1.7)	1.00			1.00		
0.9 – 3.9	8 (3.5)	2.52	0.71 – 8.89	0.151	0.90	0.32 – 2.59	0.852
≥ 4.0	26 (11.1)	7.97	2.57 – 24.77	< 0.001	6.53	2.89 – 14.78	< 0.001
p-value for linear trend across thirds		< 0.001			< 0.001		
Change in weight from the age of 20 to middle age (kg)							
< 5.4 (reference)	6 (2.6)	1.00			1.00		
5.4 – 12.7	6 (2.6)	1.13	0.36 – 3.62	0.832	0.94	0.28 – 3.11	0.919
≥ 12.8	26 (11.2)	5.89	2.31 – 15.05	< 0.001	4.19	1.56 – 11.25	0.007
p-value for linear trend across thirds		< 0.001			0.001		

* From logistic regression models adjusting for age and examination years and in the case of change in weight in the 4-year follow-up also for baseline weight and in the case of change in weight from the age of 20 to middle age also for weight at the age of 20 (Model 1) and additionally for serum uric acid, use of diuretics, dietary fiber and VO_2max (Model 2). Hyperinsulinemia is defined as fasting serum insulin of ≥ 12.0 mU/l in the 4-year follow-up examination.

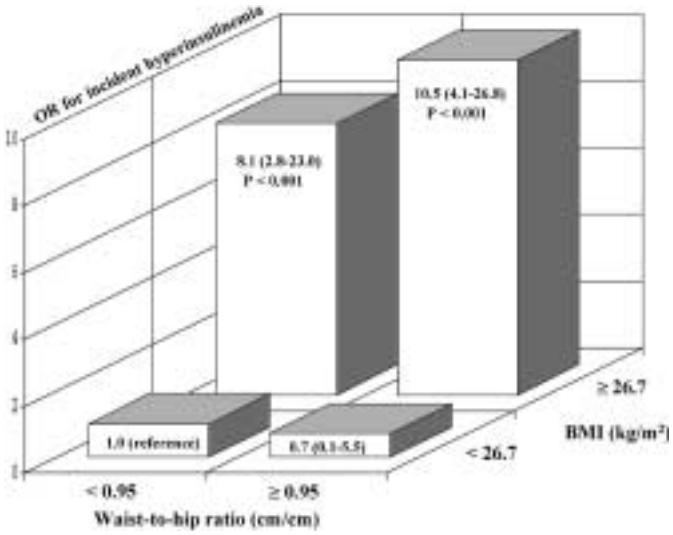

Fig. **1** The odds ratios (OR) for the incidence of hyperinsulinemia according to body mass index and waist-to-hip ratio adjusting for age, examination years, serum uric acid, use of diuretics, dietary fiber and maximal oxygen uptake.

all obesity (Fig. **1**). Overall and abdominal obesity combined was associated with a 10.5-fold risk of hyperinsulinemia.

Baseline hyperinsulinemia and weight gain during the 4-year follow-up

Baseline fasting serum insulin as a continuous variable was not statistically significantly ($p = 0.615$) associated with change in body weight during the 4-year follow-up, adjusting for age, examination years and body weight at baseline. There was no statistically significant difference in change in body weight during the 4-year follow-up between the thirds of baseline serum insulin (2.4, 2.6, and 2.7 kg, respectively, $p = 0.799$) or linear trend across these thirds ($p = 0.542$) with these adjustments, either.

Discussion

This prospective population-based study of middle-aged, non-diabetic men indicates that overall and abdominal obesity, as well as weight gain during adulthood, are associated with increased risk of developing hyperinsulinemia controlling for other risk factors. Incidence of hyperinsulinemia in men with a BMI of ≥ 26.7 kg/m^2 was over six times that of men with a BMI of < 24.4 kg/m^2. WHR provided some additional information beyond BMI in predicting future risk of hyperinsulinemia. Weight gain of ≥ 4.0 kg in 4 years at middle age was associated with six times the incidence of hyperinsulinemia compared with men with stable weight or weight loss. Moreover, weight gain of > 12.8 kg from the age of 20 years to middle age was associated with four times the incidence of hyperinsulinemia. We did not, however, find an association between fasting serum insulin at baseline and change in body weight during the follow-up.

Previous studies, most of which have had a cross-sectional study design, have shown an association between obesity and insulin resistance or hyperinsulinemia [1]. Only few prospective population-based studies have investigated whether obesity or changes in body weight predict the development of hyperinsulinemia [9–13]. In 495 non-diabetic women aged 42–50 years who were followed up for 3 years [11], the strongest predictor of fasting insulin level was baseline BMI, the second strongest being weight change after the age of 20 years. Moreover, weight gain during the 3-year follow-up was the strongest predictor of further increases in insulin levels. In the CARDIA study on 3,095 non-diabetic U.S. black and white men who were followed up for 7 years from an initial age of between 18 and 30 years, the strongest predictor for an increase in fasting insulin was the increase in body mass; BMI and waist-to-hip ratio were also associated with insulin increase [12]. In the Bogalusa Heart Study, a retrospective community-based study on children, adolescents and young adults, baseline obesity was associated with increased incidence of hyperinsulinemia in all three age groups, independent of age, gender and baseline insulin [13]. Taken together with these findings, the present study supports the role of obesity and weight gain in the development of hyperinsulinemia.

The temporal order of the association between obesity and hyperinsulinemia is, however, complex and inconclusive. Insulin resistance and hypersecretion have been proposed as a cause for the pathogenesis of obesity in populations with a high prevalence of the "thrifty genotype", such as the Pima Indians, who are very prone to obesity and type 2 diabetes [26]. An alternative hypothesis is that obesity-induced hyperinsulinemia is a physiological adaptation that limits further weight gain by increasing insulin signaling in the central nervous system in order to suppress food intake and increase energy expenditure [14]. Indeed, there is prospective evidence from studies on adult Pima Indians [2,3] and Hispanic and Caucasian subjects [4–8] that insulin resistance and hyperinsulinemia are associated with lower rates of weight gain in non-diabetic individuals. On the contrary, higher levels of insulin predicted a gain in body weight and obesity in Pima Indian children [9] and in U.S. black and white young adults [12]. It has been suggested that hyperinsulinemia promotes weight gain in children and young adults, and that subsequent increase in insulin resistance and compensatory hyperinsulinemia then limits further weight gain in adults [9,27]. However, the evidence for both temporal directions in the changes in insulin and obesity in middle-aged and older men in the Normative Aging Study [28] and in young adults in the CARDIA study [8,12] blurs the picture. It is difficult to draw a conclusion on the temporal order between obesity and hyperinsulinemia due to their complex and dynamic relationship. In addition, a number of other factors affect the results of different studies. These include age, race, genetic factors, gender, hormonal changes during puberty and menopause, follow-up time and the measurements of insulin and obesity.

A number of plausible physiological mechanisms through which increased mass of adipose tissue could cause insulin resistance and compensatory hyperinsulinemia have been proposed, as reviewed in detail previously [16,29–34]. The increased lipolytic activity of visceral fat produces free fatty acid flux through the portal vein to the liver; consequently, the high concentration of free fatty acids directly affects hepatic metabolism, leading to hyperinsulinemia in the systemic circulation. Visceral fat is also resistant to the antilipolytic effects of insulin. Visceral fat contributes also to the overall flux of free fatty acids in the systemic cir-

culation and induces peripheral insulin resistance. The increased mobilization and lipolytic activity of abdominal fat are present also in the non-portal draining areas, such as retroperitoneal and subcutaneous abdominal fat [35]. These properties, as well as the total mass of adipose tissue, have been suggested as major determinants of those pathophysiological processes related to increased adipose tissue, rather than the site itself [35, 36]. In fact, insulin resistance was related to total body fat and, interestingly, more closely to truncal subcutaneous fat than to intraperitoneal fat in a study involving non-diabetic middle-aged men [37]. In addition, the role of changes in insulin-signaling pathways, as well as the contribution of cytokines, such as TNF-α, and hormones, such as leptin, as mechanisms for the association between obesity and insulin resistance remain to be evaluated [16]. On the whole, the independent contribution of fat located at different sites of the body to the development of a variety of diseases is inconclusive [38].

BMI is a useful, albeit crude, population-level measure of overweight and overall obesity [39, 40]. Body weight and height are simple to measure, and have been widely included in clinical and population health surveys. In our study, both BMI and weight gain were strong predictors of incident hyperinsulinemia. BMI does not distinguish between the weight of fat and muscles or body frame. Moreover, abdominal fat mass can vary considerably within a narrow range of total body fat or BMI, and WHR and waist circumference provide additional information on the nature of obesity. These anthropometric measures are cheap and easily available; they have been associated with abdominal fat mass as measured by computed tomography or magnetic resonance imaging [41]. Thus, WHR and waist circumference have been recommended for the assessment of abdominal obesity in population-based studies [41]. In many population studies, however, abdominal obesity has not been assessed or has been measured by the participants themselves. In our study, WHR provided some additional information beyond BMI in predicting the risk of hyperinsulinemia.

We used elevated concentrations of fasting serum insulin as a proxy measure of insulin resistance. Fasting serum insulin levels correlate with indices of insulin resistance determined with the euglycemic hyperinsulinemic clamp technique in subjects with normal glucose tolerance, glucose intolerance or type 2 diabetes [42]. Therefore, fasting serum insulin has been suggested and often used as a measure of insulin resistance in population studies, in which invasive and complex measurements are not feasible. A disadvantage in our study is that different insulin RIA kits were used at baseline and in the 4-year follow-up. However, we excluded those who had diabetes at baseline or 4 years later and used the same insulin cut-off to exclude hyperinsulinemic men at baseline and to define incident hyperinsulinemia in the follow-up. We had a unique opportunity to analyze whether weight gain from early adulthood to middle age is associated with the incidence of hyperinsulinemia. During this period, lasting approximately 30 years, the subjects experienced a wide variety of weight change, and weight gain was a significant predictor of incident hyperinsulinemia during middle age. This confirms our previous finding, from the same study population, that weight gain from early adulthood to middle age is associated with an increased risk of developing insulin resistance syndrome [19].

In conclusion, even moderate overall and abdominal obesity and weight gain during adulthood were independently associated with increased risk of developing hyperinsulinemia in non-diabetic middle-aged men. These prospective population-based data emphasize the importance of avoiding obesity and weight gain during adulthood to prevent hyperinsulinemia and, eventually, type 2 diabetes.

Acknowledgements

We thank Kristiina Nyyssönen, Ph. D., and Kari Seppänen, M.Sc., for supervising the laboratory measurements. This study was supported by grants from the Academy of Finland (grants for projects 41471, 1041086, 2041022 researcher and 46558 researcher), the Ministry of Education of Finland, and the National Heart, Lung, and Blood Institute of the U.S.A. (grant HL44199 researcher). Hanna-Maaria Lakka, M.D., Ph. D., was supported by grants from the University of Kuopio Foundation and the Finnish Medical Foundation. Timo Lakka, M.D., Ph. D., was a postdoctoral fellow of the Academy of Finland.

References

[1] Després J-P, Marette A. Obesity and insulin resistance. Epidemiologic, metabolic, and molecular aspects. In: Reaven GM, Laws A (eds). Insulin resistance. The metabolic syndrome X. Humana Press, Totowa, New Jersey: 1999: 51 – 81

[2] Swinburn BA, Nyomba BL, Saad MF, Zurlo F, Raz I, Knowler WC, Lillioja S, Bogardus C, Ravussin E. Insulin resistance associated with lower rates of weight gain in Pima Indians. J Clin Invest 1991; 88: 168–173

[3] Schwartz MW, Boyko EJ, Kahn SE, Ravussin E, Bogardus C. Reduced insulin secretion: an independent predictor of body weight gain. J Clin Endocrinol Metab 1995; 80: 1571–1576

[4] Valdez R, Mitchell BD, Haffner SM, Hazuda HP, Morales PA, Monterrosa A, Stern MP. Predictors of weight change in a bi–ethnic population. The San Antonio Heart Study. Int J Obes Relat Metab Disord 1994; 18: 85–91

[5] Hoag S, Marshall JA, Jones RH, Hamman RF. High fasting insulin levels associated with lower rates of weight gain in persons with glucose tolerance: the San Luis Valley Diabetes Study. Int J Obes Relat Metab Disord 1995; 19: 175–180

[6] Yost TJ, Jensen DR, Eckel RH. Weight regain following sustained weight reduction is predicted by relative insulin sensitivity. Obes Res 1995; 3: 583 – 587

[7] Hodge AM, Dowse GK, Alberti KG, Tuomilehto J, Gareeboo H, Zimmet PZ. Relationship of insulin resistance to weight gain in non-diabetic Asian Indian, Creole, and Chinese Mauritians. Mauritius Non-communicable Disease Study Group. Metabolism 1996; 45: 627 – 633

[8] Folsom AR, Vitelli LL, Lewis CE, Schreiner PJ, Watson RL, Wagenknecht LE. Is fasting insulin concentration inversely associated with rate of weight gain? Contrasting findings from the CARDIA and ARIC study cohorts. Int J Obes Relat Metab Disord 1998; 22: 48–54

[9] Odeleye OE, de Courten M, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. Diabetes 1997; 46: 1341–1345

[10] Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. Lancet 1989; 1: 1356–1359

[11] Wing RR, Matthews KA, Kuller LH, Smith D, Becker D, Plantinga PL, Meilahn EN. Environmental and familial contributions to insulin levels and change in insulin levels in middle-aged women. JAMA 1992; 268: 1890–1895

[12] Folsom AR, Jacobs DR Jr, Wagenknecht LE, Winkhart SP, Yunis C, Hilner JE, Savage PJ, Smith DE, Flack JM. Increase in fasting insulin and glucose over seven years with increasing weight and inactivity of young adults. The CARDIA Study. Am J Epidemiol 1996; 144: 235–246

[13] Srinivasan SR, Myers L, Berenson GS. Temporal association between obesity and hyperinsulinemia in children, adolescents, and young adults: the Bogalusa Heart Study. Metabolism 1999; 48: 928 – 934
[14] Eckel RH. Insulin resistance: an adaptation for weight maintenance. Lancet 1992; 340: 1452 – 1453
[15] Porte D Jr, Seeley RJ, Woods SC, Baskin DG, Figlewicz DP, Schwartz MW. Obesity, diabetes and the central nervous system. Diabetologia 1998; 41: 863 – 881
[16] Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000; 106: 473 – 481
[17] Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. Ann Clin Res 1988; 20: 46 – 50
[18] Salonen JT, Lakka TA, Lakka H-M, Valkonen V-P, Everson SA, Kaplan GA. Hyperinsulinemia is associated with the incidence of hypertension and dyslipidaemia in middle-aged men. Diabetes 1998; 47: 270 – 275
[19] Everson SA, Goldberg DE, Helmrich SP, Lakka TA, Lynch JW, Kaplan GA, Salonen JT. Weight gain and the risk of developing insulin resistance syndrome. Diabetes Care 1998; 21: 1637 – 1643
[20] Lakka H-M, Lakka TA, Tuomilehto J, Sivenius J, Salonen JT. Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men. Arch Intern Med 2000; 160: 1160 – 1168
[21] Salonen JT, Salonen R, Seppänen K, Rauramaa R, Tuomi–lehto J. High density lipoprotein, HDL2 and HDL3 subfractions and the risk of acute myocardial infarction: a prospective population study in Eastern Finnish men. Circulation 1991; 84: 129 – 139
[22] Salonen JT, Nyyssönen K, Tuomainen T-P, Mäenpää PH, Korpela H, Kaplan GA, Lynch J, Helmrich S, Salonen R. Increased risk of non-insulin-dependent diabetes mellitus at low plasma vitamin E concentrations: a four year follow up study in men. BMJ 1995; 311: 1124 – 1127
[23] Salonen JT, Nyyssönen K, Korpela H, Tuomilehto J, Seppänen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. Circulation 1992; 86: 803 – 811
[24] Lakka TA, Venäläinen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity to the risk of acute myocardial infarction in men. N Engl J Med 1994; 330: 1549 – 1554
[25] Lynch JL, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, Salonen JT. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med 1996; 156: 1307 – 1314
[26] Neel JV. Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962; 14: 353 – 362
[27] Ravussin E, Gautier JF. Metabolic predictors of weight gain. Int J Obes Relat Metab Disord 1999; 23 (Suppl. 1): 37 – 41
[28] Lazarus R, Sparrow D, Weiss S. Temporal relations between obesity and insulin: longitudinal data from the Normative Aging Study. Am J Epidemiol 1998; 147: 173 – 179
[29] Björntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis 1990; 10: 493 – 496
[30] Bonadonna RC, Bonora E. Glucose and free fatty acid metabolism in human obesity. Relationships to insulin resistance. Diabetes Rev 1997; 5: 21 – 51
[31] Carey DGP. Abdominal obesity. Curr Opin Lipidol 1998; 9: 35 – 40
[32] Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes 2000; 49: 883 – 888
[33] Lawrence VJ, Coppack SW. The endocrine function of the fat cell-regulation by the sympathetic nervous system. Horm Metab Res 2000; 32: 453 – 467
[34] Engeli S, Sharma AM. Role of adipose tissue for cardiovascular-renal regulation in health and disease. Horm Metab Res 2000; 32: 485 – 499
[35] Garg A. The role of body fat distribution in insulin resistance. In: Reaven GM, Laws A (eds). Insulin resistance. The metabolic syndrome X. Humana Press, Totowa, New Jersey: 1999: 83 – 96
[36] Campbell LV, Carey DG, Chisholm DJ. Measurement of central adiposity. A bet each way? Diabetes Care 1996; 19: 1033 – 1034
[37] Abate N, Garg A, Peshock RM, Stray–Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest 1995; 96: 88–98
[38] Seidell JC, Bouchard C. Visceral fat in relation to health: is it a major culprit or simply an innocent bystander? Int J Obes Relat Metab Disord 1997; 21: 626 – 631
[39] World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. WHO Technical Report Series, 894. World Health Organization, Geneva, Switzerland: 2000
[40] Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch Intern Med 1998; 158: 1855 – 1867
[41] Williams SRP, Jones E, Bell W, Davies B, Bourne MW. Body habitus and coronary heart disease in men. A review with reference to methods of body habitus assessment. Eur Heart J 1997; 18: 376 – 393
[42] Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol 1993; 137: 959 – 965