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Computed tomography scans of intra-abdominal fat, anthropometric measurements, and 3 nonobese metabolic risk factors

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Abstract

The present cross-sectional study of 46 adult Danish white men and women aimed to evaluate association between intra-abdominal obesity, 4 anthropometric measurements of obesity, and combinations of 3 nonobese metabolic risk factors: systolic blood pressure of 130 mm Hg or higher, serum triglyceride concentration of more than 1.7 mmol/L, and fasting capillary blood glucose concentration of 5.6 mmol/L or more. For 80% of the subjects, intra-abdominal fat on a computed tomography scan of the abdomen using a cutoff limit of more than 144 cm^2 gave a correct classification of combinations of at least 2 of the 3 metabolic risk factors. Body mass index and waist circumference were better markers of intra-abdominal obesity than waist-to-hip ratio in receiver operating characteristic analyses ($P = .0035$). Body mass index of more than 26 kg/m^2 and waist circumference of more than 0.92 m classified 76% and 74% of the subjects correctly regarding combinations of the 3 nonobese metabolic risk factors. Intra-abdominal obesity was significantly stronger associated with the combinations than a raised waist-to-hip ratio ($P = .016$). Both body mass index and waist circumference may be used as markers of intra-abdominal obesity, whereas waist-to-hip ratio was significantly inferior. Correspondingly, both body mass index and waist circumference were better than waist-to-hip ratio to indicate combinations of the 3 nonobese metabolic risk factors.

1. Introduction

The metabolic syndrome is defined as combinations of mainly 4 components: abdominal obesity, hypertension, dyslipidemia, and impaired fasting glucose. However, the definitions by the World Health Organization (1998 and 1999), the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) 2001, the European Group for the Study of Insulin Resistance 2002, the American Association for Clinical Endocrinology (AACE) 2003, and the International Diabetes Federation (IDF) 2005 differed regarding the selection of anthropometric measurements of obesity and the stress on the role of obesity for the syndrome [1-6]. The IDF 2005 defined the metabolic syndrome as central obesity measured as waist circumference combined with at least 2 nonobese metabolic risk factors.

The 6 definitions of the metabolic syndrome favored anthropometric measurements of abdominal obesity for a quantitative measurement of the abdominal fat. Nevertheless, in a Danish study, intra-abdominal fat measured using a computed tomography (CT) scan of the abdomen was more strongly associated with each of the nonobese metabolic risk factors of the metabolic syndrome than were body mass index, waist circumference, and waist-to-hip ratio [7]. Over the whole range of observed values, intra-abdominal fat had a linear relation with measurements of each of the nonobese metabolic risk factors. In addition, other studies found intra-abdominal obesity measured quantitatively using CT or MR scans was strongly associated with the nonobese metabolic

The study was performed independent of the sponsoring institutions and Foundations. Some of the authors have given talks and participated in conferences sponsored by various pharmaceutical firms.

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risk factors raised systolic blood pressure, hypertriglyceridemia, and impaired fasting glucose [8-10].

The present study aimed to evaluate several questions. Is intra-abdominal obesity associated with combinations of at least 2 of 3 nonobese metabolic risk factors? Are 4 anthropometric measurements acceptable markers of intra-abdominal fat? Can 4 anthropometric measurements work as substitutes for quantitative measurements of intra-abdominal fat in relation to combinations of 3 nonobese metabolic risk factors? May subjects with or without intra-abdominal obesity with or without combinations of 3 nonobese metabolic risk factors have similar serum fibrinogen concentrations and plasma plasminogen activator inhibitor 1 activities?

2. Subjects and methods

2.1. Study population

The study included 46 Danish subjects (40 men and 6 women) from a previously reported case-control study [7,11-13]. Twenty-two subjects were patients who had had acute myocardial infarction at the age of 41 years or younger and had survived several years after the event [11]. Twenty-four subjects were patients without coronary heart disease who had been admitted for surgery for inguinal hernia or appendicitis and had survived several years after the surgery. All subjects had been admitted to 1 of 4 hospitals in Western Jutland of Denmark. At the time of our examinations in 1999, the subjects had a median age of 46 years (range, 34-54 years). None of the patients had known diabetes mellitus.

The regional science-ethical committee had approved the study, and all subjects had given written consent to participate in the study after they had received written and oral information. The study was in accordance with the Helsinki II declaration for scientific research. The Danish Data Protection Agency had approved our analyses of data from a database.

2.2. Examinations

All subjects underwent the same clinical and paraclinical examinations [7,11-13]. We measured height and the waist and hip circumferences to the nearest centimeter, and weight to the nearest kilogram. Waist circumference was measured at the level for the midpoint between the lowest border of the rib cage and the iliac crest, with the subjects in standing position. We measured hip circumference at the widest point over the femoral great trochanters. Body mass index was calculated as the weight in kilograms divided by the square of height in meters, and the waist-to-hip ratio was calculated based on the waist and hip circumferences.

We used a Picker 2000 CT scanner (Picker International, Mentor, OH) to measure the extent of the fat areas in 2 cross-sections of the body. The abdominal subcutaneous and intra-abdominal fat areas were measured on a slice at the level of the intervertebral space between the second and third lumbar vertebrae, and the hip fat area was measured on a slice at the top of the great trochanters. Dual energy x-ray absorptiometry scanner (Lunar DPX, Pencil Beam, Lunar Radiation, Madison, WI) was used to measure the fat percentage of the whole body and of the femoral region from the hip to the knee. We also measured the systolic and diastolic blood pressure.

After the subjects had fasted for at least 12 hours, we obtained blood samples for measurements of serum concentrations of lipids and capillary blood glucose concentration. Serum triglyceride concentration was measured using a Vitros 960 apparatus (Kodak Echtachem, Eastman Kodak, Rochester, NY) according to the instructions of the manufacturer. Blood glucose concentration was measured using a hexokinase method and a Hemocue apparatus according to the instructions of the manufacturer (Roche Diagnostics, Mannheim, Germany). Serum fibrinogen concentration was measured on a Cobas Fara instrument by use of an immunoturbidimetric method (Dakocytomation Denmark, Glostrup, Denmark), and plasma plasminogen activator inhibitor 1 activity (PAI-1) was measured by use of a Berichrom assay (BCT, Dade Behring, Marburg, Germany).

2.3. Statistical analyses

In previous multiple regression analyses for our group of subjects, history with or without myocardial infarction did not have a significant, independent impact on the association between intra-abdominal fat and most nonobese metabolic risk factors [7]. Sex was not a significant independent variable as we analyzed the associations between intra-abdominal fat and metabolic risk factors [7]. Accordingly, we studied the subjects as a single group in the present study and

Table 1
Baseline characteristics of the subjects (n = 46)

Characteristic	
Height (m)	1.76 (1.51, 1.66, 1.81, 1.90)
Weight (kg)	84 (46.5, 72, 88, 122)
Body mass index (kg/m^2)	26.9 (19.3, 24.9, 29.2, 38.1)
Waist circumference (m)	0.92 (0.69, 0.82, 0.96, 1.16)
Hip circumference (m)	0.95 (80, 91, 104, 119)
Waist-to-hip circumference ratio	0.94 (0.73, 0.91, 0.98, 1.07)
Subcutaneous abdominal fat area (cm^2)	115 (18, 80, 153, 346)
Intra-abdominal fat area (cm^2)	131 (13, 36, 173, 370)
Hip fat area (cm^2)	186 (32, 147, 253, 415)
Total body fat percentage (%)	24 (8, 21, 29, 40)
Femoral fat percentage (%)	24 (8, 19, 30, 45)
Systolic blood pressure (mm Hg)	127.5 (92, 112, 140, 215)
Diastolic blood pressure (mm Hg)	80 (60, 70, 90, 138)
Serum triglyceride concentration (mmol/L)	1.54 (0.48, 0.89, 2.1, 6.77)
Serum HDL cholesterol concentration (mmol/L)	1.30 (0.85, 1.05, 1.72, 3.37)
Fasting capillary whole blood glucose concentration (mmol/L)	5.4 (4.7, 5.1, 5.7, 7.5)
Serum fibrinogen concentration (g/L)	3.65 (2.6, 3.1, 5.2, 5.1)
Plasma PAI-1 activity (kU/L)	2.95 (1.5, 2.3, 4.6, 7.6)

The table shows the median values and the 0th, 25th, 75th, and 100th percentiles in parentheses. HDL indicates high-density lipoprotein.

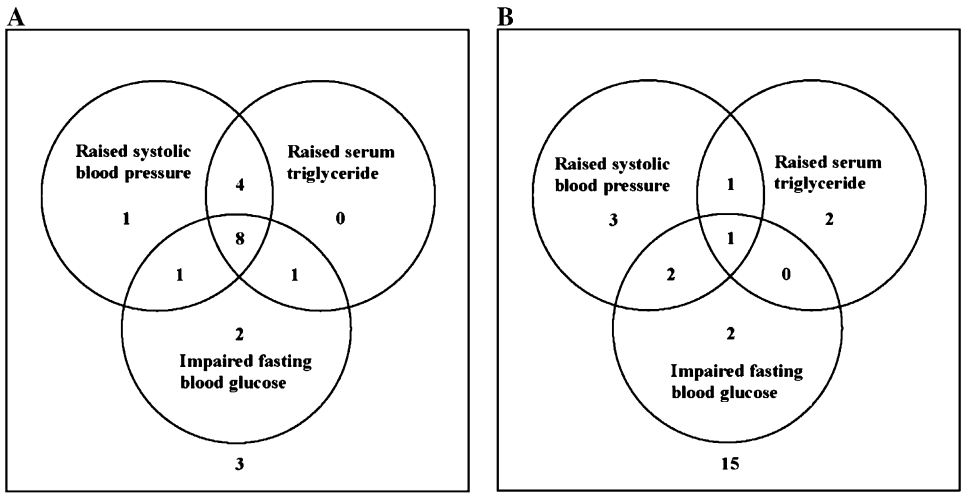

Fig. 1. Venn diagrams showing components of the metabolic syndrome for 20 subjects with intra-abdominal fat area of 135 cm^2 or more, intra-abdominal obesity (A), and for 26 subjects with intra-abdominal fat area of less than 135 cm^2 without intra-abdominal obesity (B). The circles show the subjects with 3 metabolic risk factors: systolic blood pressure 130 mm Hg or higher, serum triglyceride concentration of more than 1.7 mmol/L, and fasting capillary blood glucose concentration of 5.6 mmol/L or more. The number in the circles shows the number of subjects with the different combinations of metabolic risk factors, and the number in the rectangle outside the circles shows the number of subjects with normal values of systolic blood pressure, serum triglyceride concentration, and fasting blood glucose concentration.

evaluated the relation between 9 measurements of obesity and combinations of at least 2 of the 3 nonobese metabolic risk factors. We evaluated the 3 nonobese metabolic risk factors that were most strongly associated with intra-abdominal obesity in previous analyses of our study group and the most adequate cutoff limits such as 130 mm Hg or higher for raised systolic blood pressure [7]. We used receiver operating characteristic (ROC) analyses to evaluate how effectively 9 measurements of obesity—4 anthropometric measurements and 5 quantitative measurements—diagnosed combinations of at least 2 of the 3 nonobese metabolic risk factors. Sensitivity was defined as the proportion of subjects with raised values for measurement of obesity together with combinations of at least 2 of 3 metabolic risk factors (range, 0-1.00). Specificity was defined as the proportion of subjects with low values for measurements of obesity together with absence of combinations of at least 2 of 3 metabolic risk factors (range, 0-1.00). The best cutoff points for measurements of obesity were those that gave the highest correct classification of the subjects regarding combinations of the 3 metabolic risk factors. Subgroups of patients were compared using Fisher exact test and Mann-Whitney *U* test. A *P* value of less than .05 was denoted statistically significant. All analyses were undertaken using Stata 7.0 (Stata, College Station, TX).

3. Results

Table 1 shows 9 measurements of obesity, blood pressure, and 5 biochemical measurements for the 46 subjects. Twenty (44%) subjects were intra-abdominally obese. Referring to the different criteria of the 6 definitions of the metabolic syndrome, 21 (46%) subjects had a systolic blood pressure of 130 mm Hg or higher, and 1 (2%) had a systolic blood pressure of 160 mm Hg or higher. Sixteen (35%) subjects had a diastolic blood pressure of 85 mm Hg or higher, and 12 (26%) had a diastolic blood pressure of 90 mm Hg or higher. Seventeen (37%) had a serum triglyceride concentration of 1.7 mmol/L or more, and 12 (26%) had a serum triglyceride concentration of 2.0 mmol/L or higher. Intra-abdominal fat was most strongly associated with each of 3 nonobese metabolic risk factors: systolic blood pressure of $\geq$130 mm Hg, serum triglyceride concentration of >1.7 mmol/L and $\geq$2.0 mmol/L, and impaired fasting glucose with capillary whole blood glucose concentration of $\geq$5.6 mmol/L [7].

Of 20 (70%) subjects with intra-abdominal obesity, 14 had combinations of the 3 nonobese metabolic risk factors, shown in Fig. 1A, as had 4 (15%) of 26 without intra-abdominal obesity ($P < .0005$, Fisher exact test), shown in Fig. 1B. Of 18 (77%) subjects with combinations of the 3 metabolic risk factors, 14 were intra-abdominally obese. For the subjects

Table 2
Area under the ROC curves for measurements of obesity with regard to combinations of at least 2 of 3 nonobese components of the metabolic syndrome: hypertension, hypertriglyceridemia, and impaired fasting glucose (n = 46)

Measurements of obesity	Area under ROC curves
Body mass index (kg/m^2)	0.77 (0.63-0.91)
Waist circumference (m)	0.77 (0.63-0.90)
Hip circumference (m)	0.74 (0.59-0.88)
Waist-to-hip circumference ratio	0.63 (0.46-0.79)
Subcutaneous abdominal fat area (cm^2)	0.71 (0.55-0.86)
Intra-abdominal fat area (cm^2)	0.83 (0.71-0.95)
Hip fat area (cm^2)	0.74 (0.58-0.90)
Total body fat percentage (%)	0.68 (0.52-0.84)
Femoral fat percentage (%)	0.61 (0.42-0.79)

The 95% confidence intervals are shown inside parentheses.

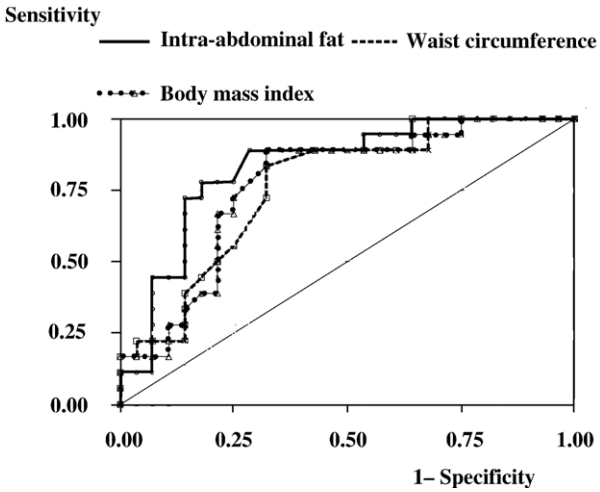

Fig. 2. Receiver operating characteristic curves for intra-abdominal fat, waist circumference, and body mass index with regard to combinations of at least 2 of 3 metabolic risk factors: systolic blood pressure of 130 mm Hg or higher, serum triglyceride concentration of more than >1.7 mmol/L, and fasting capillary blood glucose concentration of 5.6 mmol/L or more.

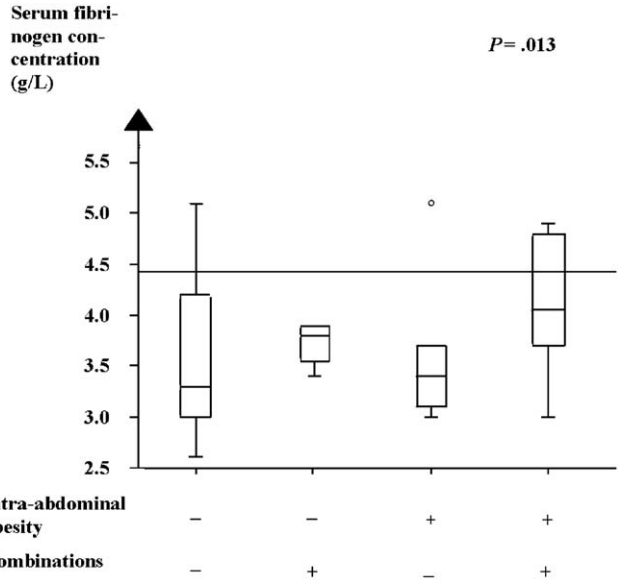

Fig. 3. Box diagram showing serum fibrinogen concentration for 4 subgroups of the 46 subjects according to presence of intra-abdominal obesity and combinations of at least 2 of 3 nonobese metabolic risk factors. The boxes show the 25th, 50th, and 75th percentiles; the whiskers show the 0th and 100th percentiles; and the circle shows an outlier. A thin horizontal line shows the upper limit of reference values. The *P* value reflects the comparison of subjects with intra-abdominal obesity and combinations of metabolic risk factors and the subjects without.

without intra-abdominal obesity, those with combinations of the 3 nonobese metabolic risk factors and those without did not differ significantly regarding the extent of intra-abdominal fat (median area, 99 cm^2 [range, 3-131 cm^2] vs 38 cm^2 [range, 13-132 cm^2]; $P = .18$, Fisher exact test). Similarly for the subjects with intra-abdominal obesity, those with or without combinations of the 3 nonobese metabolic risk factors did not differ significantly regarding the extent of intra-abdominal fat (median, 209 cm^2 [range, 144-370 cm^2] vs 180 cm^2 [range, 136-287 cm^2]) ($P = .68$, Fisher exact test).

Body mass index and waist circumference were significantly associated with intra-abdominal fat in multiple linear regression analyses. The regression model had the formula: intra-abdominal fat (cm^2) = 504 + 6.9 × body mass index (kg/m^2) + 491 × waist circumference (m) ($R^2 = 0.78$, $P < .00005$).

Sex, status regarding coronary heart disease, waist-to-hip ratio, and total body fat percentage did not have statistical significance in the multiple linear regression analyses.

Body mass index and waist circumference were markers of intra-abdominal fat and significantly better than waist-to-hip ratio in ROC analyses ($P = .0035$).

The ROC curve analyses for the measurements of obesity corresponding to the presence or absence of combinations of at least 2 of the 3 nonobese metabolic risk factors are shown in Table 2 and Fig. 2. As indicated by the areas under ROC curves, intra-abdominal fat, body mass index, and waist circumference performed better to indicate combinations of the 3 metabolic risk factors than other measurements of obesity. Intra-abdominal fat gave a correct classification of 80% of the subjects and did so significantly better than waist-to-hip ratio ($P = .016$). Intra-abdominal fat, body mass index, and waist circum-

Table 3
Sensitivity and specificity of measurements of obesity regarding combinations of at least 2 of 3 nonobese components of the metabolic syndrome: raised systolic blood pressure, hypertriglyceridemia, and impaired fasting glucose (n = 46)

Measurements of obesity	Cutoff point	Sensitivity (%)	Specificity (%)	Correct classification (%)	Positive likelihood ratio	Negative likelihood ratio
Body mass index (kg/m^2)	26.0	89	68	76	2.8	0.16
Waist circumference (m)	0.92	83	68	74	2.6	0.24
Hip circumference (m)	1.01	56	79	70	2.6	0.57
Waist-to-hip circumference ratio	0.95	61	68	65	1.9	0.57
Subcutaneous abdominal fat (cm^2)	155	44	89	72	4.1	0.62
Intra-abdominal fat area (cm^2)	144	78	82	80	4.4	0.27
Hip fat area (cm^2)	230	64	83	76	3.9	0.42
Total body fat percentage (%)	26	61	75	70	2.4	0.51
Femoral fat percentage (%)	28	43	76	64	1.8	0.75

The cutoff points gave the best correct classifications according to ROC analyses.

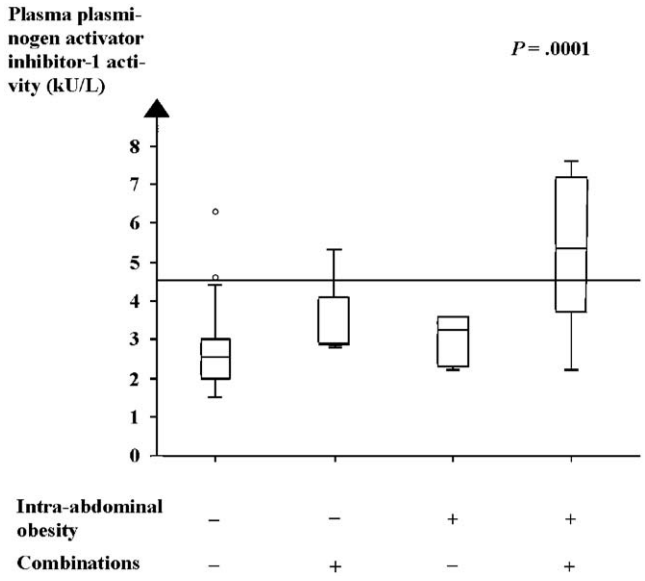

Fig. 4. Box diagram showing plasma PAI-1 activity for 4 subgroups of the 46 subjects according to presence of intra-abdominal obesity and combinations of at least 2 of 3 nonobese metabolic risk factors. The boxes show the 25th, 50th, and 75th percentiles, the whiskers show the 0th and 100th percentiles, and the circles show outliers. A thin horizontal line shows the upper limit of reference values. The *P* value reflects the comparison of subjects with intra-abdominal obesity and combinations of metabolic risk factors and the subjects without.

ference gave a better correct classification of combinations of the 3 nonobese metabolic risk factors than the other 6 measurements of obesity (Table 3).

Eighteen subjects with a body mass index of more than 26.0 kg/m^2 had combinations of the 3 metabolic risk factors, and 13 (72%) of these subjects were intra-abdominally obese. Excluding the 20 subjects with intra-abdominal obesity from analyses of the overall association between measurements of obesity and combinations of the 3 metabolic risk factors, 3 of 7 subjects with a high body mass index and 0 of 19 subjects with a low body mass index had the combinations (P = .012, Fisher exact test).

Subjects with combinations of the 3 metabolic risk factors had a significantly higher serum fibrinogen concentration than those without (P = .0095, Mann-Whitney U test), whereas the fibrinogen concentration did not rise significantly for subjects with intra-abdominal obesity (P = .05, Mann-Whitney U test) (Fig. 3). Subjects with intra-abdominal obesity had significantly higher plasma PAI-1 activity than those without (P = .0005, Mann-Whitney U test) and rose also for subjects with combinations of the 3 metabolic risk factors (P = .0002, Mann-Whitney U test) (Fig. 4).

4. Discussion

Intra-abdominal obesity had a strong linkage to combinations of at least 2 of 3 nonobese metabolic risk factors. Body mass index and waist circumference were similarly good markers of intra-abdominal fat and similarly good substitutes for intra-abdominal fat regarding the association with combinations of at least 2 of 3 nonobese metabolic risk factors. Waist-to-hip ratio was an inferior anthropometric marker of intra-abdominal obesity compared with the 2 other anthropometric markers. Furthermore, subjects with both intra-abdominal obesity and combinations of the 3 nonobese metabolic risk factors had higher serum fibrinogen concentration and plasma PAI-1 activity than those without.

As support for the external validity of our study, the subjects with or without a history of coronary heart disease had similar clinical characteristics with regard to major coronary risk factors as those of another Danish case-control study [14]. Despite we analyzed 9 measurement of obesity for men and women as one group, intra-abdominal fat had the strongest association with combinations of at least 2 of 3 nonobese metabolic risk factors.

Many studies supported the linkage between intra-abdominal obesity and individual nonobese metabolic risk factors [15-21]. Our present study expanded the findings of a previous Danish study that showed that intra-abdominal fat had a significant association with each of several nonobese metabolic risk factors [7]. Here we reported that intra-abdominal obesity also was strongly associated with combinations of 3 nonobese metabolic risk factors.

The IDF 2005 definition of the metabolic syndrome reflected a frequently stated opinion that waist circumference and/or waist-to-hip ratio were better markers of intra-abdominal fat than body mass index [5]. Valsamakis et al [22] found that waist circumference was the best anthropometric measurement to predict intra-abdominal fat and one of the best measurements to predict the metabolic syndrome as defined by ATP-III 2001. The best cutoff point for waist circumference was 0.94 m. Conversely, AACE 2003 argued for body mass index as the only useful measurement of obesity [23]. The AACE found that 27% of the subjects with body mass index of 27 kg/m^2 or more had combinations of at least 2 of 4 metabolic risk factors (hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, and impaired fasting glucose), whereas only 13% of the subjects with a lower body mass index had such combinations. In contrast in our study, both body mass index and waist circumference were significant markers of intra-abdominal obesity and acceptable surrogate markers of intra-abdominal obesity concerning the association with combinations of 3 nonobese metabolic risk factors.

A high body mass index was mainly linked to the 3 nonobese metabolic risk factors due to the association between the high body mass index and intra-abdominal obesity. Excluding subjects with intra-abdominal obesity, a high body mass index had only a weak direct relation to the nonobese metabolic risk factors.

Complementary to intra-abdominal fat, combinations of the 3 nonobese metabolic risk factors were associated with raised levels of fibrinogen and PAI-1. Thus, combinations of the 3 metabolic risk factors may be important even in

subjects without obesity. Intra-abdominal obesity had a stronger linkage with PAI-1 than with fibrinogen. Our study accords with the findings of previous studies [13,24].

Twenty-three percent of the subjects with combinations of the 3 nonobese metabolic risk factors were not intra-abdominally obese. Thus, although most of our subjects with combinations of the metabolic risk factors accords with the IDF 2005 definition of the metabolic syndrome with its stress on the importance of abdominal obesity, our study also indicated that the IDF definition may not include all subjects with combinations of metabolic risk factors. The ATP-III definition for the metabolic syndrome can diagnose the syndrome in absence of abdominal obesity and would include all subjects in our study with combinations of metabolic risk factors. However, the ATP-III definition did not stress the possible pathogenetic role of abdominal obesity for most subjects with combinations of the nonobese metabolic risk factors.

In a recent study, subjects with predominantly abdominal obesity had high levels of cytokines such as interleukin 6 and tumor necrosis factor α, insulin resistance, aortic arteriosclerosis, and low-grade inflammation, whereas subjects with predominantly gluteofemoral obesity did not have similar rises of cytokines, insulin resistance, and aortic arteriosclerosis [25]. Nevertheless in our study, measurements of intra-abdominal fat and waist circumference vs measurements of intra-abdominal gluteal fat area and hip circumference did not have opposing associations with combinations of nonobese metabolic risk factors.

Two pathologic processes may contribute to combinations of the 3 nonobese metabolic risk factors. Obese subjects with combinations of metabolic risk factors may be insulin-resistant mainly due to mechanism related to abdominal obesity. Intra-abdominal obesity may contribute to the 3 nonobese metabolic risk factors through insulin resistance and/or hyperinsulinemia. Insulin resistance may contribute to hypertension, hypertriglyceridemia, and impaired fasting glucose. Abdominal obesity may also produce angiotensinogen, free fatty acids, and hypoadiponectinemia, and these factors may also contribute to the metabolic risk factors. Nonobese subjects may be insulin-resistant due to mechanisms other than abdominal obesity.

Interplay between obesity and nonobese metabolic risk factors warrants further studies. An ongoing prospective study evaluates the long-term mortality from obesity and nonobese metabolic risk factors [26].

Our cross-sectional study had several limitations. It analyzed data from a small group of Danish white and middle-aged subjects, predominantly men. We did not include women selected according to the fat distribution, undertook only one examination of the subjects, and did not carry out an oral glucose tolerance test or other measurements of insulin resistance.

Of 9 measurements of obesity, intra-abdominal obesity had the strongest association with combinations of at least 2 of 3 nonobese metabolic risk factors. Both body mass index and waist circumference may be used as markers of intra-abdominal obesity in relation to the combinations of the 3 nonobese metabolic risk factors, whereas waist-to-hip ratio was an inferior marker.

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