Trunk Fat and Leg Fat Have Independent and Opposite Associations With Fasting and Postload Glucose Levels

The Hoorn Study

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OBJECTIVE — Waist and hip circumferences have been shown to have independent and opposite associations with glucose levels. Waist circumference is positively associated with glucose levels, whereas hip circumference is negatively associated. It is unclear which tissues are involved in the pathophysiological mechanism causing these associations. The main goal was to determine which tissue in the trunk and legs, fat or lean tissue, is associated with measures of glucose metabolism.

RESEARCH DESIGN AND METHODS — In 623 participants of the third examination of the Hoorn Study, whole-body dual-energy X-ray absorptiometry was performed to determine fat and lean soft-tissue mass in the trunk and legs. Fasting and 2-h postload glucose levels after 75-g oral glucose tolerance test (OGTT) were determined. After exclusion of known diabetic patients, cross-sectional analyses were performed in 275 men aged 60–87 years (140 with normal glucose metabolism, 92 with impaired glucose metabolism; and 43 with diabetes) and in 281 women (148 with normal glucose metabolism, 90 with impaired glucose metabolism, and 43 with diabetes).

RESULTS — Greater trunk fat mass was associated with higher glucose levels after adjustment for age, trunk lean mass, leg lean mass, and leg fat mass. Standardized β (95% CI) in men were 0.44 (0.25–0.64) for fasting and 0.41 (0.22–0.60) for postload glucose. For women, these values were 0.49 (0.35 – 0.63) and 0.47 (0.33 – 0.61), respectively. In contrast, in the same regression models, a larger leg fat mass was associated with lower glucose levels. Standardized β in men were −0.24 (−0.43 to −0.05) and −0.12 (−0.31 to 0.07) and in women −0.24 (−0.37 to −0.10) and −0.27 (−0.40 to −0.13) for fasting and postload glucose, respectively. In these models, larger leg lean mass was also associated with lower glucose levels but was only statistically significant in men.

CONCLUSIONS — If trunk fat is taken into account, accumulation of fat in the legs seems to be protective against a disturbed glucose metabolism, particularly in women. Further research is needed to unravel underlying pathophysiological mechanisms.

Diabetes Care 27:372–377, 2004

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Received for publication 11 March 2003 and accepted in revised form 15 October 2003.

Abbreviations: DXA, dual-energy X-ray absorptiometry; FFA, free fatty acid; HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio; WTR, waist-to-thigh ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Obesity, particularly abdominal obesity, is associated with increased risk of insulin resistance and type 2 diabetes. The pathophysiological mechanisms involved in the development of these conditions are not completely understood. The idea that an increased release of free fatty acids (FFAs) from visceral fat into the portal vein plays a major role in the development of insulin resistance in abdominal obesity is now widely accepted (1–3). This, however, does not preclude the possibility that other tissues are involved.

In epidemiologic studies, abdominal obesity or visceral fat is often estimated by the measurement of waist circumference alone or by measurement of the waist-to-hip ratio (WHR) or waist-to-thigh ratio (WTR). Several studies, however, have shown that the association between WHR or WTR and glucose metabolism of type 2 diabetes was not only due to a larger waist circumference but also due to a smaller hip or thigh circumference (4–8). This could indicate a protective role for a larger hip circumference to high glucose levels. To determine whether this protective effect of a larger hip or thigh circumference is due to a higher lean mass or to a higher fat mass in the gluteal/femoral region, accurate assessment of body composition is necessary.

To investigate how fat and lean tissue are represented by the waist and hip circumferences, we first studied the associations of waist and hip circumferences with fat and lean tissue mass in the trunk and in the legs as measured by dual-energy X-ray absorptiometry (DXA). The main goal of the present study was to investigate the association of fat and lean tissue mass in the trunk and in the legs with glucose metabolism. The study was performed within the third follow-up examination of the Hoorn Study, a population-based cohort study of glucose tolerance.

RESEARCH DESIGN AND METHODS

— The Hoorn Study is a population-based cohort study of glucose metabolism and its complications that started in 1989 and has been described earlier (9). It consisted of 2,484 men and women aged 50–75 years at baseline. In 2000–2001, a third examination was performed among surviving participants who gave their permission to be recontacted. We invited all participants who had diabetes, as determined by a 75-g oral glucose tolerance test (OGTT) or by diabetes treatment ($n = 176$) at the second examination of the entire cohort in 1996–1998 (10). We also invited random samples of participants who had normal glucose tolerance ($n = 705$) or impaired glucose tolerance ($n = 193$) in 1996–1998. Of 1,074 individuals invited, 648 persons (60.3%) participated. The main reasons for not participating in the 2000–2001 follow-up examination were lack of interest (30%) or comorbidity (23%). Other reasons were advanced age (7%), unwillingness to travel (6%), participation considered too time-consuming (6%), and miscellaneous reasons (15%); 13% individuals gave no reason for refusing to participate in the follow-up examination.

For the present study, cross-sectional data of the 2000–2001 follow-up examination were analyzed. Of the 648 participants, 25 individuals were excluded because of missing DXA data. Another eight individuals were excluded because glucose tolerance data were incomplete. Participants already known to have diabetes ($n = 59$) were also excluded from the statistical analyses because treatment could potentially influence the relations under consideration. Therefore, our final study sample consisted of 556 subjects (275 men and 281 women). The study protocol was approved by the Ethical Review Committee of the VU University Medical Center, and all participants gave their written informed consent.

Body composition

Whole-body DXA was performed using the fan beam technology (QDR-2000, software version 7.20D; Hologic, Brussels, Belgium). The software provides estimates of lean tissue mass, fat mass, and bone mineral mass for the total body and for standard body regions. With the use of specific anatomic landmarks, regions of the head, trunk, arms, and legs were distinguished as shown in Fig. 1. In the analyses, we used fat and lean soft-tissue mass from the trunk and legs.

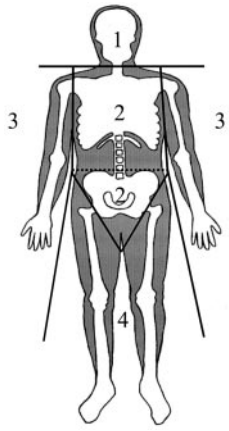

Figure 1—*Standard regions of a DXA scan: 1, head; 2, trunk; 3, arms; 4, legs.*

Anthropometry and lifestyle

Weight and height were measured in barefoot subjects wearing light clothing only. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest, and the hip circumference at the widest level over the greater trochanters. WHR was calculated as waist circumference divided by hip circumference. Self-reported information on physical activity (min/week), alcohol intake (g/day), and smoking (yes/no) was obtained by questionnaires.

Glucose metabolism

All participants underwent a single 75-g OGTT. Fasting glucose and 2-h postload glucose after OGTT were measured in plasma with the hexokinase method (Roche Diagnostics, Mannheim, Germany). Glucose tolerance status was defined according to the World Health Organization (WHO) criteria (11). Subjects were classified as having normal glucose metabolism, impaired glucose metabolism (i.e., impaired fasting glucose or impaired glucose tolerance), or diabetes. Fasting insulin was measured in plasma by a two-site immunoradiometric test (Medgenix Diagnostics, Fleurus, Belgium) and homeostasis model assessment of insulin resistance (HOMA-IR) was calculated (12).

Statistical analyses

All analyses were performed separately for men and women because of the statistically significant effect modification by sex of the relations under consideration. To test for linear trend in study sample characteristics over categories of glucose metabolism, a linear regression model was used; the glucose tolerance category was used as a linear explanatory variable. Values are expressed as means ± SD for normally distributed variables and as medians (interquartile range) in case of skewed distribution.

To study the association of the regional fat and lean mass measured by DXA (independent variables) with the waist and hip circumferences by anthropometry (dependent variables), multiple regression analyses were performed. The associations of the regional fat and lean tissue mass with the more commonly used WHR and BMI were also investigated. Effect modification by sex, glucose tolerance status, and age was evaluated by adding product terms to the model.

The contribution of regional fat and lean tissue mass to fasting glucose, postload glucose, or HOMA-IR (ln-transformed) was tested using multiple regression analyses with adjustment for age. Residual plots were examined to check for violation of the normality assumptions. Effect modification by sex and glucose metabolism status was evaluated by adding product terms to the model. To facilitate direct comparisons, results of the regression analyses are reported as standardized β. A standardized β of 0.1 indicates that when the independent variable increases by 1 SD, the dependent variable increases by 0.1 SD. We considered the stability of the regression models to be disturbed by multicolinearity if the tolerance was <0.1. The tolerance is a statistic used to determine how much the independent variables are linearly related to one another. It is calculated as $1 - R^2$ for an independent variable when it is predicted by the other independent variables already included in the model. All statistical analyses were performed using SPSS for Windows (version 10.1; SPSS, Chicago, IL).

RESULTS

— The characteristics of the study sample by sex and glucose metabolism status are shown in Table 1. All anthropometric measures in both sexes, and age in women, were significantly and pos-

Table 1—*Characteristics of the study sample by sex and glucose tolerance status*

	Men				Women			
	NGM	IGM	DM	*P**	NGM	IGM	DM	*P**
n	140	92	43		148	90	43	
Age (years)	69.1 ± 6.0	69.3 ± 6.5	70.5 ± 6.4	0.26	68.3 ± 6.1	70.8 ± 6.2	73.2 ± 7.2	0.00
Fasting glucose (mmol/l)	5.46 ± 0.36	6.08 ± 0.48	7.38 ± 1.06	0.00	5.39 ± 0.37	6.08 ± 0.48	7.09 ± 1.12	0.00
Postload glucose (mmol/l)	5.45 ± 1.16	7.90 ± 0.86	10.84 ± 2.55	0.00	5.78 ± 1.12	8.13 ± 1.49	11.94 ± 2.48	0.00
Insulin (pmol/l)	47 (36–63)	61 (46–78)	79 (47–110)	0.00	45 (35–56)	75 (55–94)	82 (61–102)	0.00
HOMA-IR	1.60 (1.19–2.19)	2.30 (1.65–2.98)	3.57 (2.07–5.11)	0.00	1.51 (1.16–1.89)	2.72 (2.12–3.51)	3.17 (2.35–5.34)	0.00
Anthropometry								
BMI (m/kg^2)	26.2 ± 3.3	27.1 ± 3.1	27.9 ± 4.1	0.00	26.2 ± 3.4	28.9 ± 4.6	29.3 ± 4.7	0.00
Waist circumference (cm)	96.3 ± 9.5	99.7 ± 9.4	102.1 ± 11.1	0.00	86.0 ± 9.8	95.1 ± 11.0	96.6 ± 12.5	0.00
Hip circumference (cm)	100.0 ± 6.2	101.0 ± 6.8	102.0 ± 6.7	0.08	102.3 ± 7.3	106.8 ± 10.0	107.9 ± 11.3	0.00
WHR	0.96 ± 0.06	0.99 ± 0.06	1.00 ± 0.07	0.00	0.84 ± 0.07	0.89 ± 0.07	0.90 ± 0.08	0.00
Body composition								
Total body fat percentage (%)	26.1 ± 6.5	29.4 ± 5.7	29.9 ± 6.1	0.00	39.9 ± 6.7	43.3 ± 5.9	43.8 ± 6.6	0.00
Total body fat (g)	21,161 ± 7,346	24,780 ± 8,305	25,081 ± 7,830	0.00	27,880 ± 8117	33,511 ± 9,858	33,725 ± 9,919	0.00
Trunk fat mass (g)	11,109 ± 4,799	13,647 ± 5,580	14,103 ± 5,249	0.00	12,694 ± 4701	16,480 ± 5,217	17,322 ± 6,099	0.00
Trunk lean mass (g)	27,888 ± 3,132	27,669 ± 2,880	27,969 ± 3,270	0.95	19,881 ± 2147	20,708 ± 2,409	20,477 ± 2,429	0.03
Leg fat mass (g)	6,199 ± 2,020	6,902 ± 2,242	6,762 ± 1,991	0.03	10,421 ± 3079	11,396 ± 4,173	10,827 ± 3,283	0.19
Leg lean mass (g)	17,640 ± 2,506	17,423 ± 2,203	17,034 ± 2,711	0.16	12,258 ± 1694	12,858 ± 1,987	12,620 ± 2,122	0.07

Data are means ± SD; for insulin levels and HOMA-IR, the median (interquartile range) is reported. *P = P for trend. Abbreviations: DM, newly detected type 2 diabetes; IGM, impaired glucose metabolism; NGM, normal glucose metabolism (WHO 1999 criteria).

itively associated with a worse glucose metabolism when tested for linear trend, except for hip circumference in men. Of the DXA measurements, the fat mass in the trunk as well as in the legs in men and the fat and lean mass in the trunk in women were significantly and positively associated with worse glucose metabolism. After adjustment for age, the trunk fat mass and the leg fat mass remained positively associated with worse glucose metabolism status in men. In women, in addition to trunk fat and lean mass, leg lean mass was also positively associated with worse glucose metabolism status after adjustment for age (data not shown).

Anthropometry

The associations of the fat and lean mass in the trunk and legs with anthropometric measures are shown in Table 2. Waist circumference was strongly positively associated with trunk fat, whereas hip circumference was positively associated with both leg fat and leg lean mass. WHR was most strongly and positively associated with trunk fat mass and was negatively associated with both lean and fat mass in the legs. In contrast to the WHR, BMI was mainly associated with fat mass, especially trunk fat. When age was added to these models, the associations did not change substantially (data not shown). There was no significant effect modification by glucose tolerance status or age.

Glucose metabolism

Table 3 shows the results of multiple linear regression analyses involving fat and lean tissue mass in the trunk and legs in relation to fasting and postload glucose levels and HOMA-IR. After adjustment for age, leg lean and leg fat mass, and each other, larger trunk fat mass as well as larger trunk lean mass were associated with higher fasting glucose (model 1). However, in the same regression model, larger leg fat and leg lean mass were associated with lower fasting glucose. In both sexes, only larger trunk fat mass, and not trunk lean mass, was significantly associated with higher postload glucose levels (model 2). In contrast, larger leg fat mass was associated with lower postload glucose, but was only statistically significant in women. Similar results were found for ln-transformed HOMA-IR (model 3). Trunk fat mass was the strongest independent predictor of glucose levels and

Table 2—*Independent associations of trunk fat and lean mass with the waist circumference, of leg fat and lean mass with the hip circumference, and of fat and lean mass in the trunk and legs with WHR and BMI*

	Men		Women	
	β*	95% CI	β*	95% CI
Waist circumference				
Trunk fat	0.81‡	10.76–0.87	0.82‡	0.77–0.87
Trunk lean	0.23‡	0.18–0.29	0.19‡	0.14–0.25
Hip circumference				
Leg fat	0.68‡	0.62–0.74	0.67‡	0.59–0.74
Leg lean	0.41‡	0.35–0.53	0.24‡	0.17–0.32
WHR				
Trunk fat	0.78‡	0.63–0.93	0.69‡	0.60–0.81
Trunk lean	0.31‡	0.14–0.48	0.21†	0.05–0.37
Leg fat	−0.22†	−0.27 to −0.07	−0.42‡	−0.54 to −0.29
Leg lean	−0.40‡	−0.56 to −0.23	−0.06	−0.23 to 0.10
BMI				
Trunk fat	0.57‡	0.48–0.66	0.67‡	0.61–0.73
Trunk lean	0.19‡	0.09–0.29	0.02	−0.06 to 0.10
Leg fat	0.24‡	0.14–0.33	0.28‡	0.22–0.34
Leg lean	0.09	−0.01–0.19	0.08†	0.00–0.16

*β, standardized β, †$P < 0.05$, ‡$P < 0.001$.

HOMA-IR. Adjustment for height did not change the associations (data not shown). In addition, adjustment for physical activity, alcohol intake, and smoking did not change the results (data not shown). There was no statistically significant effect modification by glucose tolerance status, except that the associations of trunk fat and trunk lean mass with fasting glucose was stronger in diabetic subjects (data not shown). Among the four independent variables used in the linear regression models, the highest correlation (Pearson) was between lean mass in the trunk and lean mass in the legs (0.825 in men and 0.815 in women). The stability of the regression models, however, was not disturbed by multicolinearity. Residual plots were not disturbed, and similar results were found when glucose levels were ln-transformed and included as study outcome (data not shown).

CONCLUSIONS — In this study, we show that waist or hip circumference does not simply represent the amount of fat at that region. Although the waist circumference is mainly associated with fat mass in the trunk, the hip circumference is strongly associated with both fat mass and lean mass in the legs, particularly in men. Furthermore, our study shows that, as expected, larger trunk fat mass is associated with higher glucose levels. In contrast, accumulation of fat in the legs was associated with lower glucose levels. In men, large lean mass in the legs seems to have an additional independent protective effect.

The recognition of the importance of upper body versus lower body obesity in diabetes and cardiovascular disease by Vague in 1956 led to the development of the WHR and WTR measurements (13). Because it was found in the 1980s that the WHR was more closely associated with intra-abdominal fat than with subcutaneous fat, associations of WHR with disease have generally been interpreted as caused by the increased accumulation of visceral fat (14,15). Whether WHR also represents other body tissues was unclear. Data on direct comparison between anthropometrically measured circumferences, particularly hip circumference and WHR, and regional body composition, includ-

Table 3—*Independent associations of trunk fat, trunk lean mass, leg fat, and leg lean mass (adjusted for each other) with fasting glucose levels (model 1), with postload glucose levels (model 2), and with HOMA-IR (model 3), additionally adjusted for age*

	Men			Women		
	β*	95% CI	*P*	β*	95% CI	*P*
Model 1: fasting glucose						
Trunk fat mass	0.44	0.25–0.64	0.00	0.49	0.35–0.63	0.00
Trunk lean mass	0.26	0.05–0.46	0.02	0.27	0.09–0.45	0.00
Leg fat mass	−0.24	−0.43 to −0.05	0.01	−0.24	−0.37 to −0.10	0.00
Leg lean mass	−0.27	−0.48 to −0.06	0.01	−0.15	−0.34 to 0.03	0.11
Model 2: postload glucose						
Trunk fat mass	0.41	0.22–0.60	0.00	0.47	0.33–0.61	0.00
Trunk lean mass	−0.02	−0.22 to 0.19	0.89	0.08	−0.10 to 0.25	0.38
Leg fat mass	−0.12	−0.31 to 0.07	0.23	−0.27	−0.40 to −0.13	0.00
Leg lean mass	−0.12	−0.33 to 0.10	0.28	−0.04	−0.22 to 0.14	0.69
Model 3: ln-HOMA-IR						
Trunk fat mass	0.59	0.41–0.76	0.00	0.65	0.52–0.77	0.00
Trunk lean mass	0.16	−0.03 to 0.36	0.10	0.19	0.03–0.34	0.02
Leg fat mass	−0.18	−0.35 to 0.00	0.05	−0.19	−0.30 to −0.06	0.00
Leg lean mass	−0.18	−0.38 to 0.01	0.07	0.00	−0.16 to 0.16	0.98

*β, standardized β.

ing both fat and lean tissue, are limited, and little is known about the influence of sex and age on this relationship. Only one previous study of 24 men showed a negative association between WHR and the thigh muscle area by computed tomography, suggesting that high WHR may also result from low muscle mass in the legs (16). In our study, we show that the waist and hip circumferences are not only associated with fat mass at the respective body regions. The hip circumference, a surrogate marker of lower body obesity, was also strongly associated with leg lean mass, particularly in men. WHR was positively associated with trunk fat mass but also negatively associated with both lean and fat mass at the legs.

Because our study showed that the anthropometric measures seemed to represent different tissues, we examined which tissue would be responsible for the earlier observed associations between anthropometric measures and glucose tolerance. Larger waist circumference but smaller hip circumference has been associated with worse glucose tolerance status or diabetes in several studies (4–8). From the present study, we can conclude that, particularly in the trunk, fat tissue is associated with unfavorable glucose metabolism. This could be consistent with the established role of visceral fat, which releases FFA directly into the portal vein, causing disturbances in glucose metabolism (1–3). Some studies, however, found that subcutaneous abdominal fat is more closely related to insulin resistance than visceral fat (17,18).

In contrast to fat mass in the trunk, fat mass in the legs was negatively associated with glucose levels and HOMA-IR. These data are consistent with recently published data on the contributions of regional fat mass by DXA to several cardiovascular risk factors in women, such as insulin resistance and dyslipidemia (19,20). It has been suggested that fat tissue in the gluteal or femoral region plays a protective role, because adipocytes in these regions are less sensitive to lipolytic stimuli (21,22). Therefore, these regions are more likely to take up FFA from the circulation and are less likely to release them readily (so called "FFA trapping") (23). Hereby increased peripheral fat stores may protect other organs, such as the liver and the pancreas, as well as skeletal muscle tissue from high FFA exposure. Accumulation of fat in the liver has been found to be positively associated with insulin resistance (24,25), and infiltrating muscle fat in the thigh, which only accounted for ~3% of total thigh fat, was also positively associated with insulin resistance (26). Recent work also points to a possible role of lipids in β-cell deterioration ("lipotoxicity") associated with type 2 diabetes (27). The ectopic fat storage hypothesis is also supported by the observation that adipose tissue deficiency is accompanied by ectopic fat storage and related to insulin resistance and diabetes (28,29). Furthermore, transplantation of adipose tissue back in lipoatrophic animals reverses elevated glucose levels, and leptin-replacement therapy in women with lipodystrophy improved glycemic control (30,31).

Adipose tissue is an endocrine gland that secretes many proteins. Examples include adiponectin, leptin, resistin, angiotensinogen, interleukin-6, tumor necrosis factor-α, adipsin, plasminogen activator inhibitor-1, and probably many other yet unknown factors. Regional differences in secretion of these factors could also be an alternative or additional explanation for the observed relationships between adipose tissue and glucose levels. There are some known differences in secretion between abdominal subcutaneous and visceral fat (32–34), but less is known about differences between gluteal and abdominal subcutaneous fat.

In men, a significant negative association was found between glucose and HOMA-IR levels and lean mass in the legs, probably because lean mass in the legs measured by DXA reflects mainly skeletal muscle tissue and muscle tissue is one of the sites of insulin resistance and the main target of insulin. In women, this negative association with lean tissue was also found but was not statistically significant. The lean mass in the trunk was not negatively associated with glucose levels; it was even positively associated with fasting glucose levels. However, these results should be interpreted with caution, because lean mass in the trunk as measured by DXA reflects not only muscle mass but also visceral organ mass (e.g., liver and intestinal organs).

The main limitation of our study is that DXA does not allow separate quantification of intermuscular and subcutaneous fat in the legs and visceral fat and subcutaneous fat in the trunk. The contribution of subcutaneous fat to the total amount of fat in the legs, however, is relatively large (± 90%) (26). Therefore, the associations found in our study with fat mass in the legs are probably mainly due to the subcutaneous fat depot. As subcutaneous fat accounts for the largest fat component in the trunk, an important role of subcutaneous trunk fat apart from the visceral fat cannot be excluded. Another possible limitation of DXA is that, particularly in women, gluteal fat and abdominal fat cannot be perfectly distinguished. Possibly, part of the gluteal fat was included in the trunk region and part of the abdominal fat was included in the leg region. Therefore, we may have underestimated the true associations. Finally, because of the selection of the study population, subjects with impaired glucose metabolism and diabetes were relatively overrepresented. Adjustment for glucose tolerance status, however, did not change the conclusions.

In summary, caution is needed when interpreting waist and hip circumferences. Whereas larger waist circumference mainly reflects higher fat mass in the trunk, the hip circumference and WHR are influenced by both fat and lean mass from the legs. We also conclude that although higher fat mass in the trunk was the strongest determinant of disturbed glucose metabolism, larger fat mass in the legs and larger lean mass in men only have a considerable and opposite association with glucose metabolism. These findings provide a relevant new insight in the association between obesity, body composition, and type 2 diabetes. Further investigation of the underlying pathophysiological mechanism is needed to explain the negative association of leg fat with glucose metabolism.

Acknowledgments— The third examination of the Hoorn Study was kindly supported by the VU University Medical Center and by Dutch Diabetes Research Foundation (DFN) Grant no. 98.901, Dutch Organization for Scientific Research (NWO) Grant no. 940-35-034, the Netherlands' Heart Foundation (NHS) Grant no. 98-154, and the Health Research and Development Council of the Netherlands (ZON) Grant no. 22000040.

References

1. Bjorntorp P: Metabolic implications of body fat distribution. *Diabetes Care* 14: 1132–1143, 1991

2. Despres JP, Lemieux S, Lamarche B, Prud'homme D, Moorjani S, Brun LD, Gagne C, Lupien PJ: The insulin resistance-dyslipidemic syndrome: contribution of visceral obesity and therapeutic implications. *Int J Obes Relat Metab Disord* 19 (Suppl 1):S76–S86, 1995
3. Arner P: Insulin resistance in type 2 diabetes: role of fatty acids. *Diabetes Metab Res Rev* 18 (Suppl 2):S5–S9, 2002
4. Seidell JC, Han TS, Feskens EJ, Lean ME: Narrow hips and broad waist circumferences independently contribute to increased risk of non-insulin-dependent diabetes mellitus. *J Intern Med* 242:401–406, 1997
5. Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Kostense PJ, Yudkin JS, Heine RJ, Nijpels G, Seidell JC: Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. *Am J Clin Nutr* 77:1192–1197, 2003
6. Seidell JC, Perusse L, Despres JP, Bouchard C: Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr* 74: 315–321, 2001
7. Lissner L, Bjorkelund C, Heitmann BL, Seidell JC, Bengtsson C: Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res* 9:644–646, 2001
8. Snijder MB, Dekker JM, Visser M, Yudkin JS, Stehouwer CD, Bouter LM, Heine RJ, Nijpels G, Seidell JC: Larger thigh and hip circumferences are associated with better glucose tolerance: the Hoorn Study. *Obes Res* 11:104–111, 2003
9. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, Heine RJ: Prevalence and determinants of glucose intolerance in a Dutch caucasian population: the Hoorn Study: *Diabetes Care* 18:1270–1273, 1995
10. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. *JAMA* 285:2109–2113, 2001
11. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation*. Geneva, World Health Org., 1999
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
13. Ashwell M, Chinn S, Stalley S, Garrow JS: Female fat distribution: a photographic and cellularity study. *Int J Obes* 2:289–302, 1978
14. Seidell JC, Bouchard C: Visceral fat in relation to health: is it a major culprit or simply an innocent bystander? *Int J Obes* 21:626–631, 1997
15. Molarius A, Seidell JC: Selection of anthropometric indicators for classification of abdominal fatness: a critical review. *Int J Obes Relat Metab Disord* 22:719–727, 1998
16. Seidell JC, Bjorntorp P, Sjostrom L, Sannerstedt R, Krotkiewski M, Kvist H: Regional distribution of muscle and fat mass in men: new insight into the risk of abdominal obesity using computed tomography. *Int J Obes* 13:289–303, 1989
17. 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* 96: 88–98, 1995
18. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE: Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 46:1579–1585, 1997
19. Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM: Contributions of total and regional fat mass to risk for cardiovascular disease in older women. *Am J Physiol Endocrinol Metab* 282:E1023–E1028, 2002
20. Tanko LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C: Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. *Circulation* 107:1626–1631, 2003
21. Arner P: Differences in lipolysis between human subcutaneous and omental adipose tissues. *Ann Med* 27:435–438, 1995
22. Rebuffe-Scrive M, Enk L, Crona N, Lonnroth P, Abrahamsson L, Smith U, Bjorntorp P: Fat cell metabolism in different regions in women: effect of menstrual cycle, pregnancy, and lactation. *J Clin Invest* 75:1973–1976, 1985
23. Frayn KN: Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 45:1201–1210, 2002
24. Tiikkainen M, Tamminen M, Hakkinen AM, Bergholm R, Vehkavaara S, Halavaara J, Teramo K, Rissanen A, Yki-Jarvinen H: Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. *Obes Res* 10:859–867, 2002
25. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, Goto T, Westerbacka J, Sovijarvi A, Halavaara J, Yki-Jarvinen H: Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Endocrinol Metab* 87:3023–3028, 2002
26. Goodpaster BH, Thaete FL, Kelley DE: Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. *Am J Clin Nutr* 71:885–892, 2000
27. McGarry JD: Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes* 51:7–18, 2002
28. Ravussin E, Smith SR: Increased fat intake, impaired fat oxidation, and failure of fat cell proliferation result in ectopic fat storage, insulin resistance, and type 2 diabetes mellitus. *Ann N Y Acad Sci* 967: 363–378, 2002
29. Robbins DC, Horton ES, Tulp O, Sims EA: Familial partial lipodystrophy: complications of obesity in the non-obese? *Metabolism* 31:445–452, 1982
30. Gavrilova O, Marcus-Samuels B, Graham D, Kim JK, Shulman GI, Castle AL, Vinson C, Eckhaus M, Reitman ML: Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest* 105:271–278, 2000
31. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, Garg A: Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 346:570–578, 2002
32. Eriksson P, Van Harmelen V, Hoffstedt J, Lundquist P, Vidal H, Stemme V, Hamsten A, Arner P, Reynisdottir S: Regional variation in plasminogen activator inhibitor-1 expression in adipose tissue from obese individuals. *Thromb Haemost* 83: 545–548, 2000
33. Van Harmelen V, Dicker A, Ryden M, Hauner H, Lonnqvist F, Naslund E, Arner P: Increased lipolysis and decreased leptin production by human omental as compared with subcutaneous preadipocytes. *Diabetes* 51:2029–2036, 2002
34. Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, Rosato FE, Goldstein BJ: Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosaglitazone. *J Endocrinol Metab* 87:5662–5667, 2002