Metabolic Obesity: The Paradox Between Visceral and Subcutaneous Fat

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Abstract:

INTRODUCTION

Obesity, and in particular abdominal obesity, plays a major role in the pathogenesis of several metabolic and cardiovascular medical problems including type 2 diabetes, hypertension, atherosclerosis and coronary artery disease (CAD). It was also shown that obesity is associated with increased cardiovascular mortality, independent of dyslipidemia, diabetes and hypertension [1]. Over the last few years, it became quite clear that central adiposity is more strongly associated with these metabolic and cardiovascular problems than total adiposity [2-5]. Even within the normal range of body mass index (BMI), accumulation of visceral fat remains an independent cardiovascular risk factor [6]. This observation led researchers and clinicians alike to believe that clinical diagnosis of visceral adiposity may be more important than the current diagnosis of obesity using the body mass index (BMI). Interestingly, accumulating evidence also point to major differences between the intraabdominal visceral fat and the peripheral or subcutaneous fat in the pathogenesis of these medical problems, both in lean and obese individuals.

Central Abdominal Obesity

In contrast to the accumulation of fat in the gluteofemoral regions, the accumulated fat in the intraabdominal or visceral depots is strongly associated with all obesity-related complications [7]. In clinical practice, the waist circumference and waist to hip ratio (WHR) are the commonly used anthropometric measures to diagnose abdominal obesity. These measures were found to correlate with the total amount of visceral fat measured by abdominal CT scanning. They also correlate with the risk factors for coronary heart disease like hyperglycemia, hypertension and dyslipidemia. For this reason, Adult-Treatment Panel III (ATP-III) of the National Cholesterol Education Program adopted the increased waist circumference as a major component of the clinical diagnostic criteria of the metabolic syndrome, where waist circumference of equal or greater than 102 cm. ($\geq$ 40") in men or 88 cm. ($\geq$ 35") in women was used as cut off [8].

Relationship Between Abdominal Obesity and the Cardiovascular Disease

Since Vague early observation, in 1956, [9] that android fat distribution (apple-shaped body) is related to increased risk of cardiovascular disease, attention has been paid to the male-pattern of fat distribution (as determined by WHR or waist circumference) as a powerful predictor of CAD. Later, Larsson *et al* [10] and Lapidus *et al* [11] showed the importance association between WHR measure and coronary heart disease among white men and women. In 1990s, several studies also showed similar strong association between WHR or visceral fat accumulation, as determined by abdominal CT scanning, and both carotid atherosclerosis [12,13] and angiographically documented CAD [5-19]. Similarly, increased amount of visceral fat, as quantified by abdominal ultrasonography, in non-obese, normoglycemic men was found to be related to the increased carotid intimal-medial thickness (IMT) [13]. Arad *et al* [14] provided strong evidence for the independent contribution of central fat mass to the development of insulin resistance and coronary calcification, even among asymptomatic non-diabetic men and women.

The relationship between visceral fat, as quantified by abdominal CT scanning and coronary stenosis was found to be independent of age, BMI and the amount of subcutaneous fat in men with heterozygous familial hypercholesterolemia [20]. Moreover, abdominal obesity was also found to be associated with accelerated atherosclerosis independent of overall obesity and other risk factors in middle aged men with no prior atherosclerotic disease [21].

VISCERAL ADIPOSITY

Visceral obesity is defined as fat accumulation around the viscera and inside the intraabdominal solid organs. Vis-

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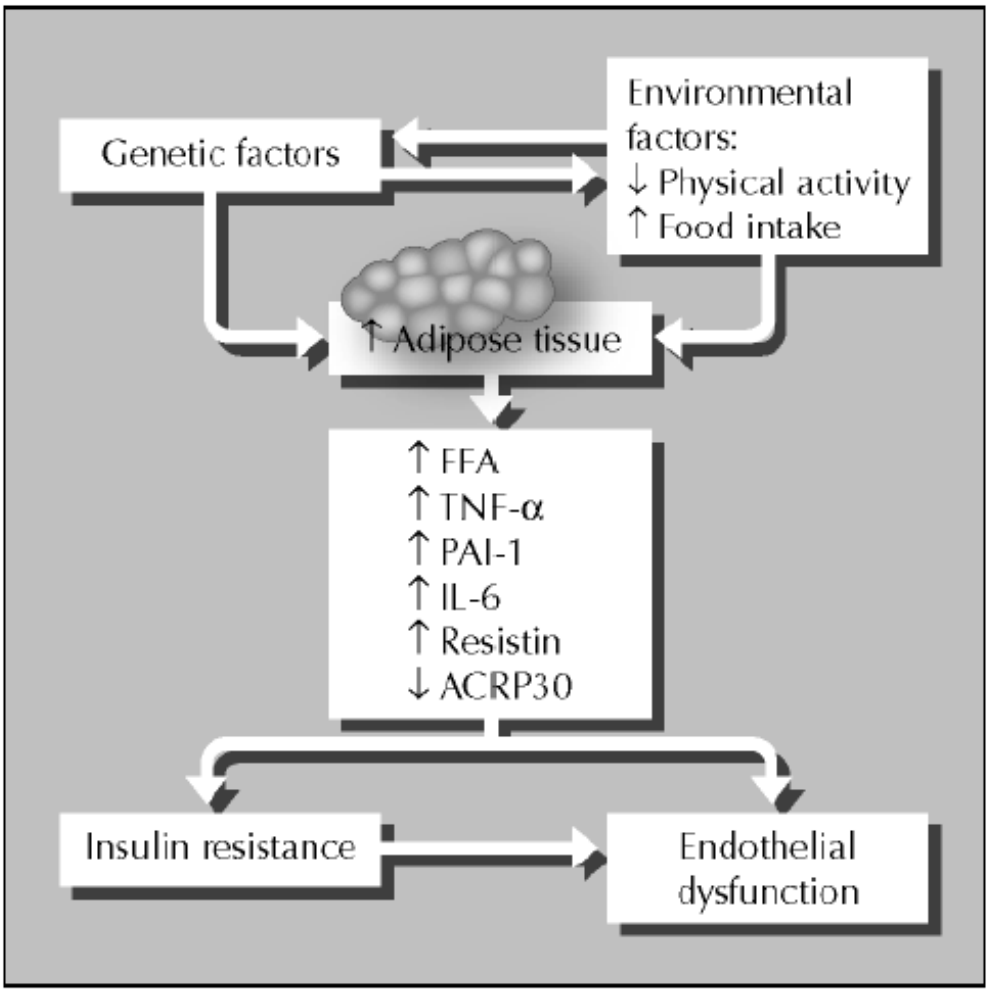

Fig. (1). The link between visceral adiposity, insulin resistance and endothelial dysfunction (Aldhahi W, and Hamdy O. Curr Diab Rep. 2003;3(4):293-8).

ceral fat has been associated with accelerated progression of atherosclerosis [22]. Progressive accumulation of intraabdominal fat increases hepatic and adipose-tissue insulin resistance and its consequent metabolic abnormalities like glucose intolerance, low HDL-cholesterol, elevated triglycerides and hypertension [23,24]. Reaven [23] described this package of metabolic abnormalities as syndrome X or the insulin resistance syndrome [25]. Many refer to this syndrome as the metabolic syndrome considering insulin resistance as its fundamental etiology. It is worth mentioning that the true definition of this syndrome and its phenotype characteristics is still in evolution.

Despite lack of clear explanation, the strong relationship between intraabdominal fat accumulation and insulin resistance was subsequently reported in several studies [25-27]. The most appealing hypothesis to explain this relationship is that intraabdominal adipocytes are more lipolytically active, which results in influx of large amount of free fatty acids into the portal circulation and to the liver. This hypothesis is called the lipotoxicity theory and has been welcomed by many researchers, until recently, as the sole explanation of the link between visceral adiposity and insulin resistance [28]. It was assumed that increased activation of the β3-adrenergic receptors, which are expressed in human visceral fat, is responsible for increased visceral fat lipolysis. The Try64Arg allele polymorphism of the β3-adrenergic receptor gene was found to be associated with increased accumulation of visceral fat and insulin resistance [29]. Interestingly, obese individuals with no polymorphism of the β3-adrenergic accumulate less visceral fat and have much lower risk factors for CAD [29]. This group may be considered healthier obese individuals. The alternative theory that recently gained a lot of acceptance and research support is that visceral adipose tissue and its resident macrophages produce more proinflamatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) and less adiponectin [30]. These cytokines changes induce insulin resistance (Fig. **1**).

There are major ethnic and gender differences in the rate of accumulation and the amount of visceral fat. For example, Asian Indians have relatively higher truncal and abdominal fat mass as compared to Caucasians and black population despite similar or less average value of waist circumference [31]. Banerji *et al* [32] showed that visceral adipose tissue mass of Asian Indians was identical to African-American men, despite lower waist circumference. In contrast, African-

American women have lower amount of abdominal visceral fat in comparison to Caucasian women [33], but much higher than African American men. Meanwhile, Japanese men and women have significant greater amount of abdominal visceral fat compared to Caucasians, after adjusting for age, sex and abdominal subcutaneous fat. However, this difference is lower than that observed between African–American women and Caucasian women [20]. Besides the genetic factors (β3-adrenergic receptor polymorphism) and ethnicity, many other factors play a role in determining the volume of visceral fat including environmental factors, imbalance of sex hormones, in particular serum free testosterone, growth hormone, IGF-1, insulin, excessive intake of sucrose and saturated fat and lack of physical activity (table **1**). Age is also a major defining factor. At any given waist circumference, older people have larger amount of visceral fat than younger individuals [34].

Visceral adiposity is associated with elevated serum levels of small-dense LDL-cholesterol particles, high apo-B [35], hypertriglyceridemia and reduced HDL-cholesterol [36,37]. Over seven years, one prospective study showed that the amount of visceral fat predicted the changes in glucose tolerance and fasting insulin, even in absence of any change in total body weight or total body fat [38]. Another study [39] showed that isolated central adiposity in women is associated with impaired insulin sensitivity and impaired fasting plasma glucose. In contrast, isolated peripheral adiposity did not have any apparent effect on glucose homeostasis. In the same study, the severest insulin resistance-dyslipidemic syndrome and aortic calcification was found in women with highest percentage central fat and lowest percentage peripheral fat. On the contrary, the most favorable metabolic profile was found in women with the lowest percentage central fat and the highest percentage peripheral fat.

VISCERAL FAT MEASUREMENTS

Since body fat is widespread and inaccessible, it has been always difficult to directly measure the total body fat. Traditionally, the gold standard technique was the hydrodensitometry (underwater weighing). This is based on the principle that fatty tissue is less dense than muscle. In fact, only few large-scale epidemiological studies evaluated body fat distribution among different body regions. This is mostly because the currently available accurate techniques are labor intensive and costly, which limit their use to only studies with smaller-sample size.

The current gold standard techniques for measuring visceral fat volume are abdominal CT (at L4-L5) and MRI techniques. These methods are not widely used because of the limitations of cost and radiation exposure. In contrast to CT, MRI technique requires additional definition of adipose tissue by changing the setting of MRI- scanner [40]. Several commercial softwares are currently available for calculation of visceral fat volume. Using these techniques confirmed the original assumption that body fat is mostly localized in the subcutaneous space and partially in the visceral area. Interestingly, they also showed that most of the fat in the central line is subcutaneous and not visceral. This may explain the difference between the value of directly measuring visceral fat volume and measuring the waist circumference. Current knowledge makes it also possible to subdivide body fat into at least three separate and measurable compartments, namely subcutaneous, intramuscular and visceral fat. [41]

OTHER MEASUREMENTS

Anthropometric Measurement

Waist circumference or WHR are used more often to indirectly estimate the intraabdominal fat volume in epidemiological studies. Although these measures showed good correlation with intraabdominal fat volume, measured by CT scanning, they are less accurate than the later [42]. This important observation is most probably related to the fact that waist circumference is mainly composed of subcutaneous fat. However these measures are cheap and can be easily used in large-scale studies. Between the two, waist circumference is a better reflection of the intraabdominal fat volume than the WHR [40,43]. However, one recent study showed that WHR is more strongly associated with type 2 diabetes, hypertension and dyslipidemia than the waist circumference and or BMI, but this difference disappeared after adjusting for age. The same study also showed that the 3 measures are equally associated with the cardiovascular risk factors [44]. For the time being, waist circumference seems to be the easiest anthropometric measurement that can be easily used by health care professionals in order to diagnose visceral adiposity or at least to get rough impression of the visceral fat volume [40]. It may be also used to monitor the changes in visceral fat volume over time [45,46].

Dual-energy X-Ray Absorptiometry (DEXA)

DEXA was developed originally to examine bone mineral density [47,48]. This technique can be also used to accurately measure total body fat and regional fat distribution. DEXA is more accurate than anthropometric measures and more practical and cost effective than CT or MRI scans. However, DEXA cannot distinguish between subcutaneous and visceral abdominal fat depots, or between subcutaneous and intramuscular peripheral fat depots. Some findings suggest that intramuscular fat within the thighs confer increased risk for type 2 diabetes and cardiovascular disease [49,50]. Meanwhile, fat mass in the trunk region, as measured by DEXA, was found to be a strong independent predictor of insulin resistance and dyslipidemia among postmenopausal women [51].

Abdominal Ultrasonography

Abdominal ultrasonography has been proposed as a suitable technique for intraabdominal fat measurement in research and clinical settings [52,53]. Several studies found good correlation between intraabdominal fat volume, measured abdominal ultrasound and abdominal CT scanning. The lack of strict protocol, for positioning the ultrasound transducer and for timing the measurement in relation to respiratory cycle, reduced reproducibility of this technique in most of these studies [43]. More recently, Stolk RP *et al*. [54] proposed a strict protocol, where all measurements were performed at the end of quiet inspiration and by compressing the transducer against the abdomen to limit distortion of the

abdominal cavity during scanning [54]. The distance between the peritoneum and the lumbar spine was used as measure of the intraabdominal fat. This distance is measured at 3 positions along the horizontal line between the highest point of iliac crest and the lower costal margin and each measure should be repeated three times. The reproducibility of this technique was excellent with coefficient of variability around 4—5% [54]. The correlation with visceral fat measurement in single CT slice at L4-L5 was excellent ($r=0.82$, $p< 0.001$). Recent studies showed that the association between intraabdominal fat, measured by ultrasound using a strict protocol, and the metabolic risk factors for CAD is more pronounced than the association between the later and the waist circumference or WHR. Meanwhile, intraabdominal fat, measured by abdominal ultrasound, was found to be associated with the metabolic risk factors similar to that measured by abdominal CT scanning [55]. Using this protocol, it may be possible to easily measure visceral fat volume in clinical practice as it yields more reliable information than simple anthropometric measurements and in accuracy closer to abdominal CT or MRI while being less costly [56].

The Paradoxical Effect of Peripheral Fat

There are limited data to address the specific role of peripheral fat mass (PFM). Interestingly, large hip circumference was found to be an independent predictor of lower cardiovascular and diabetes-related mortality. [57] Furthermore, hip circumference and leg fat showed strong negative association with atherogenic lipid and glucose metabolites. [58-60]. It was postulated that increased leg fat may reflect underlying hormonal factors (e.g. estrogen) that regulate preferential deposition of fat in the hip and thigh area. [61]. The protective effect of a large hip circumference may be due to the high lipoprotein lipase activity and low fatty acid turnover of gluteo-femoral adipose tissue [62].

Recent study showed that peripheral fat mass is negatively correlated with both atherogenic metabolic risk factors and aortic calcification [39]. In this study, peripheral fat mass showed an independent negative correlation with glucose and atherogenic lipid components. Furthermore, the lowest atherogenic lipid profile was observed in women with lowest percentage central fat and highest percentage peripheral fat. These results associate the different fat depots exhibiting different influences on lipid metabolism, with central fat mass promoting and peripheral fat mass counteracting atherogenicity. It is interesting that relative lack of peripheral fat has been also associated with poorer insulin sensitivity [51, 63]. These observations might be also explained by a possible active inhibitory influence of peripheral fat mass, which can overrule the atherogenic tendencies caused by high central fat mass.

There is also evidence suggesting that the subcutaneous fat plays an important role in modulating peripheral insulin resistance through regulating visceral fat accumulation. In a recent experimental study, bilateral removal of subcutaneous inguinal fat mass in mice resulted in increased lipid accumulation in mesenteric fat, hyperinsulinemia, decreased insulin sensitivity and increased TNF-α. These abnormalities were corrected after re-implantation of inguinal fat [64].

Biological Differences Between Visceral and Subcutaneous Body Fat

It was recently shown that the functional differences between visceral and the subcutaneous adipocytes are related to their anatomical location. For example, implantation of adipose cells into visceral area of nude mice increased serum TNF-α and insulin resistance, while it did not increase them when it was implanted in the subcutaneous regions [65]. Several studies also showed that although central fat accumulation is deleterious for cardiovascular risk in women, deposition of fat in the gluteo-femoral regions posses some degree of protection [51, 59, 66]. Meanwhile, the severity of atherosclerosis was significantly lower in generally obese women compared with those with predominant central obesity. *In vitro*, several studies demonstrated that adipocytes from visceral abdominal region are more sensitive to lipolytic stimuli and are more resistant to suppression of lipolysis by insulin than the adipocytes from gluteo-femoral subcutaneous regions [67,68]. The metabolic characteristics of the adipocytes from the subcutaneous abdominal region tend to be intermediate [69]. *In vivo* data also supports these findings [70]. Abdominal fat may directly impact hepatic free fatty acid flux due to its proximity to the portal circulation and consequently increases triglycerides synthesis and decrease hepatic insulin clearance [71,72]. Interestingly, it was noticed that there is a marked heterogeneity in handling FFA by various fat depots [73]. Other contributing mechanisms include abnormal expression and secretion of fat derived cytokines such as resistin [74], leptin, adiponectin, TNF-α and IL-6 [75].

Genetic Differences Between Visceral and Subcutaneous Body Fat

Recent evidence indicates that there are several loci determining propensity to store fat in the abdominal region [76]. Differences in several gene expressions in visceral fat in comparison to subcutaneous fat may account for the differences in the metabolic risks between the two fat depots. Many of these genes are involved in glucose homeostasis, insulin action (peroxisome proliferator activator receptor-γ [PPARγ], IGFBP-3, IGF-1, GLUT1), or in lipid metabolism (HMG CoA synthase, lysosomal acid lipase, hormone-sensitive lipase). Twenty genes, which are mostly related to lipid metabolism and glucose homeostasis, are markedly different between the 2 types of fat. For examples angiotensinogen gene is expressed five folds higher in visceral fat compared to subcutaneous fat and PPARγ is six folds higher in visceral fat in comparison to subcutaneous fat. Similarly, the expression of resistin [77] and adiponectin [78] genes is also significantly higher in visceral fat (3.8 and 12.2-fold, respectively).

Modulation of Body Fat Distribution

Lifestyle modifications in the form of caloric restriction and increased physical activity, metformin and PPARγ agonists, like pioglitazone and rosiglitazone, are the most common modalities used for treating insulin resistance [79-81]. Except for metformin, reduction of visceral adiposity is a common feature of these interventions. Shadid *et al.* [82] assessed the effects of pioglitazone versus diet and exercise

on body fat distribution and the relationship between fat distribution and insulin sensitivity in upper body obesity in non-diabetic men and premenopausal women. They found that diet and exercise resulted in weight loss, lowered W/H ratio and improved insulin sensitivity through reducing visceral fat and total body fat volume. In contrast, pioglitazone resulted in weight gain but also lowered W/H ratio and improved insulin sensitivity through selective increase in lower body fat without changing visceral fat. These data suggests that PPARγ agonists selectively stimulates adipocytes proliferation, mostly in peripheral adipose tissue, and consequently results in body fat redistribution. This observation also confirms a site specific responsiveness of these compounds [83] and suggests that the improvement in insulin sensitivity with PPARγ agonists may a result of such favorable fat redistribution in association with reduction in both intrahepatic and intramuscular fat.

So far, it is unclear how much reduction in visceral adipose tissue is required to induce favorable metabolic changes. One recent study showed that moderate reduction of visceral fat, as seen with short-term weight reduction programs, yields metabolic benefits on lipid profile, insulin sensitivity and blood pressure similar to that observed after major weight reduction [84]. Interestingly, most of the fat loss during the first 2 weeks of caloric restriction and exercise are from the visceral fat.

Effects of Selective Removal of Visceral or Subcutaneous Fat

Surgical removal of visceral fat in experimental animals reversed hepatic insulin resistance. It also prevented age-related deterioration in peripheral and hepatic insulin action. Meanwhile it decreased gene expression of TNF-α and leptin in subcutaneous adipose tissue [85]. Furthermore, removal of visceral fat delayed the onset of diabetes in the Zucker fatty rats, the model of obesity and diabetes [86]. In contrast, surgical removal of subcutaneous adipose tissue of similar amount did have any noticeable effect on any of the measured metabolic parameters [86]. Similarly, surgical removal of large amount of abdominal subcutaneous fat by liposuction in a group of diabetic and non-diabetic individuals did not improve insulin sensitivity in muscles, liver or adipose tissues; and did not change plasma concentrations of circulating mediators of inflammation; including C-reactive protein, IL-6, and TNF-α. It also did not change blood pressure, plasma glucose, and serum insulin or lipid profile [87]. Interestingly, the weight loss observed in this study was equal or even far more than weight loss observed in many lifestyle modification studies, while the later resulted in significant improvement in insulin sensitivity and improvement of cardiovascular risk factors. This observation could be explained by that liposuction reduces subcutaneous fat mass without changing visceral, intramuscular or hepatic fat mass. The latter is reduced mainly by weight reduction by diet and exercise.

CONCLUSION

Increasing knowledge of the pathophysiology of weight gain and the endocrinologic etiologies of obesity is leading to the development of more effective treatment tools. In order to use these new treatment tools effectively, clinicians must develop an understanding of the pathophysiology of excess weight and the metabolic role and vascular implications of visceral adiposity in at-risk individuals. The result of this new understanding is the adaptation of both weight-management and vascular-protective goals for therapy. Many interesting observations point to the possible need for a new definition of obesity based on the location of fat rather than on its volume, especially when the endocrine function and the metabolic risk are considered. The reference to increased volume of visceral fat as "metabolic obesity" may better identify more subjects at risk for cardiovascular disease than does the current definition of obesity.

REFERENCES

[1] Calle CE, Thun Mi, Petrelli JM, Rodriguez C, Heath CWJ. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097-105.

[2] Zamboni M, Armellini F, Sheiban I, De Marchi M, Todesco T, Bergamo Andreis IA. Cominacini I., Bosello o. Relation of body fat distribution in men and degree of coronary narrowings in coronary artery disease. Am J Cardiol 1992; 70: 1135-1138.

[3] Bjorntorp P. Abdominal obesity and the development of noninsulin dependent diabetes mellitus. Diabetes Metab Rev 1988;4: 615-622.

[4] Folsom A, Kaye S**,** Sellers T, Hong CP, Cerhan J, Potter J, and Proctor DN. Body fat distribution and 5-year risk of death in older women. JAMA 1993;269**:** 483-487

[5] Folsom AR, Prineas RJ, Kaye SA, and Munger RG**.** Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. Stroke 1992;21: 701- 706.

[6] NIH-NHLBI. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults. The evidence report. Bethesda: MD, 1998.

[7] Rexrode K, Carey V, Hennekens C, Walters E, Colditz G, Stampfer M, Willet W, and Manson J. Abdominal adiposity and coronary heart disease in women. JAMA 1988;280: 1843-1848.

[8] Pouliot MC, DespresJ-P, Lemieux S, Moorjani MS, Bouchard C, Tremblay A, Nadeau A, Lupien MPJ, Waist Circumference, Abdominal Sagittal Diameter. Best Simple Anthropometric Indexes of Abdominal Visceral Adipose Tissue Accumulation and Related Cardiovascular Risk in Men and Women. Am J Cardiol 1994; 73:460-8

[9] World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO Consultation. Part I: diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization; 1999.

[10] Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J 1984; 288:1401-1404.

[11] Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. Br Med J 1984; 289:1257- 1261.

[12] Bonora E, Tessari R, Micciolo R, *et al.* Intimal-medial thickness of the carotid artery in nondiabetic and NIDDM patients: relationship with insulin resistance. Diabetes Care 1997;20:627-31.

[13] Yamamoto M, Egusa G, Hara H, Yamakido M. Association of intra-abdominal fat and carotid atherosclerosis in non-obese middle-aged men with normal glucose tolerance. Int J Obes Relat Metab Disord I 997;21 :948-51.

[14] Arad Y, Newstein D, Cadet F, *et al.* Association of multiple risk factors and insulin resistance with increased prevalence of asymptomatic coronary artery disease by an electron-beam computed tomographic study. Arterioscler Thromb Vasc Biol. 2001; 2l: 2051-2058.

[15] Hartz A, Grubb B, Wild R, Van Nort JJ, Kuhn E, Freedman D, Rimm A. The association of waist hip ratio and angiographically determined coronary artery disease. Int J Obes 1990; 14:65 7-665.

[16] Hauner H, Stangl K, Schmatz C, Burger K, Blomer H, Pfeiffer EF. Body fat distribution in men with angiographically confirmed coronary artery disease. Atherosclerosis 1990; 85: 203-210.

[17] Nakamura I, Tokunaga K, Shimomura I, Nishida M, Yoshida S,Kotani K, Islam AH, Keno Y, Kobatake T, Nagai Y, Fujioka 5, Tarui S, Matsuzawa Y. Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. Atherosclerosis 1994; 107: 239-246.

[18] Thompson CJ, Ryu jE, Craven TE, Kahl FR, Crouse JR III. Central adipose distribution is related to coronary atherosclerosis. Arterioscler Thromb 1991; 11: 327-333.

[19] Flynn MA, Codd MB, Gibney MJ, Keelan El, Sugrue DD. Indices of obesity and body fat distribution in arteriographically defined coronary artery disease in men. Ir I Med Sci 1993; 162: 503-509.

[20] Nakamura T, Kobayashi H, Yanagi K, *et al*. Importance of intra-abdominal visceral fat accumulation to coronary atherosclerosis in heterozygous familial hypercholesterolaemia. Int J Obes Relat Metab Disord 1997; 2l: 580-6.

[21] Lakka TA, Lakka HM, Salonen R and *et al.* Abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men. Atherosclerosis 2001;154:497-504

[22] Lakka TA, Lakka HM, Salonen R and *et al.* Abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men. Atherosclerosis 2001;154:497-504

[23] Reaven GM. Bunting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37: 1595-607.

[24] Pascot A, Despres JP, Letnieux I. *et al*. Contribution of visceral obesity to the deterioration of the metabolic risk profile in men with impaired glucose tolerance. Diabetologia 2000;43: 1126-35.

[25] Després JP. Abdominal obesity as important component of insulin-resistance syndrome. Nutrition l993;9:452-9.

[26] Walton C, Lees B, Crook D, Godsland IF, Stevenson IC. Relationships between insulin metabolism, serum lipid profile, body fat distribution and blood pressure in healthy men**.** Atherosclerosis 1995;118:35-43.

[27] Kahn BB, Flier IS. Obesity arid insulin resistance. J Clin Invest 2000;106:473-81.

[28] Bergman RN, Mittleman SD. Central role of the adipocyte in insulin resistance. J Basic Clin Physiol Pharmacol 1998, **9:**205–221

[29] Widen E, Lehto M, Kanninen T, *et al*. Association of polymorphism in the β3-adrenergic receptor gene with features of the insulin resistance syndrome in Finns. N Engl J Med 2004;333:348-51

[30] Yokota T, Oritani K, Takahashi I, *et al.* Adiponectin, a new member of the family of soluble defense collagens, negatively regulated the growth of myelomonocytic progenitors and the functions of macrophages. *Blood* 2000, 96:1723–1732

[31] Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. Nutrition 2004; 20: 482–491

[32] Banerji MA, Lebowitz J, Chaiken RL, Gordon D, Kral JG, Lebovitz HE. Relationship of visceral adipose tissue and glucose disposal is independent of sex in black NIDDM subjects. Am J Physiol 1997; 273: E425–E432.

[33] Conway JM, Yanovski SZ, Avila NA, Hubbard VS. Visceral adipose tissue differences in black and white women. Am J Clin Nutr 1995;61:765-771

[34] Conway JM, Yanovski SZ, Avila NA, Hubbard VS. Visceral adipose tissue differences in black and white women. Am J Clin Nutr 1995;61:765-771

[35] Despres JP. The jnsulin-resistance-dyslipidemic syndrome of visceral obesity: effect on patients' risk. Obes Res. 1998;6:8S-17S.

[36] Després J-P, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990;10:497-511.

[37] Pouliot MC, Després J-P, Nadeau A, *et al.* Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes. 1992;41 :826-834.

[38] Pouliot MC, Després J-P, Nadeau A, *et al.* Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes. 1992;41 :826-834.

[39] Tanko LB, Bagger YZ, Alexandersen P, *et al.* Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. Circulation 2003;107:1626-1631

[40] Bosello O.and Zamboni M. Visceral obesity and metabolic syndrome. Obes rev 2000;1:47-56

[41] Chowdhury B, Sjöström L, Alpsten M, Kostanty J, Kvist H, Lofgren RA. multicompartment body composition technique based on computerized tomography. Intern J Obes 1994; 18: 219-234.

[42] Van der Kooy K, Leenen R, Deurenberg P. Seidell JC. Westerterp KR, Hautvast JG. Changes in fat-free mass in obese subjects after weight loss: a comparison of body composition measures. Int I Obes Relat Metab Disord 1992;16:675—83.

[43] Van der Kooy K, Seidell JC. Techniques for the measurement of visceral fat: a practical guide. Int J Obes l993;l7: 187—96.

[44] Cameron A, Shaw J, Welborn T and Zimmet Paul. Comparison of associations between three measures of obesity and cardiovascular risk factors in Australian Adults. Diabetes 2003;52(Suppl.1);pA216

[45] Lemieux S. Prud'homme D, Trenmblay A, Bouchard C, Despres JP Anthropometric correlates to changes in visceral adipose tissue over 7 years in women. Int J Obes Relat Metab Disord 1996;20:618-24.

[46] Lemieux S, Prud'homme D. Nadeau A. Tremblay A, Bouchard C, Despres JP Seven-year changes in body fat and visceral adipose tissue in women. Association with indexes of plasma glucose-insulin homeostasis.

[47] Pierson RN Jr., Wang I, Heymsfield SB and *et al.* Measuring body fat: Calibrating the rulers. lntermethod comparisons in 389 normal Caucasian subjects. Am J Physiol 1991;261:E103-El08, 9.

[48] Svendsen OL, Hassager C, Christiansen C. Accuracy of measurements of body composition by dual-energy x-ray ahsorptiometry *in vivo*. Am J Clin Nutr 1993;57:605-608.

[49] Krssak M, Falk Peterson. K, Dresner A, DiPietro L, Vogel SM, Rothman DL, Roden M, and Shulman GI. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia 1999;42:113-116.

[50] Phillips DI, Caddy 5, Ilic V, Fielding BA, Frayn KN, Borth-wick AC, and Taylor R. Intramuscular triglyceride and muscle insulin sensitivity: evidence for a relationship in nondiabetic subjects. Metabolism 1996;45: 947-950.

[51] Van Pelt RE, Evans EM, Schechtman KB, *et al.* Contributions of total and regional fat mass to risk for cardiovascular disease in older women. Am J Physiol Endocrinol Metab.2002; 282:E1023-E1228.

[52] Armellini F, Zamboni M, Robbi R, *et al*. Total and intra-abdominal fat measurements by ultrasound and computerized tomography. Int J Obes Relat Metab Disord 1993;17:209-14

[53] Tornaghi C, Raiteri R, Pozzato C. *et al.* Anthropometric or ultrasonic measurements in assessment of visceral fat? A comparative study. Int J Obes Relat Metab Disord 1994; 18:771-5.

[54] Stolk RP, Wink 0, Zelissen PM, Meijer R, van Gils AP, Grobbee DE. Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. Int J Obes Relat Metab Disord 2001;25:1346-51

[55] Armellini F, Zamboni M, Castelli S, *et al.* Measured and predicted total and visceral adipose tissue in women. Correlations with metabolic parameters. Int J Obes Relat Metab Disord 1994; 18:641-7.

[56] Stolk RP, Meijer R, Mali WP, *et al.* Ultrasound measurements of intraabdominal fat estimate the metabolic syndrome better than do measurements of waist circumference. Am J Clin Nutr 2003;77:857-60

[57] Lissner L, Bjbrkelund C, Heitmann BL, *et al.* Larger hip circumference independently predicts health and longevity in a Swedish female cohort. Obes Res. 2001;9:644-646.

[58] Seidell IC, Perusse L, Despres JP *et al.* Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. Ant J Gun Nutr. 200l;74:315-321.

[59] Williams MJ, Hunter GR, Kekes-Szabo T, *et al.* Regional fat distribution in women and risk of cardiovascular disease. Am J Clin nutr. l997;65:855-860.

[60] Tatsukawa M, Kurokawa M, Tamari Y, *et al.* Regional fat deposition in the legs is useful as a presumptive marker of antiatherogenesity in Japanese. Proc Soc Exp Biol Med. 2000;223:156-162

[61] Lindberg UB, Crona N, Silferstolpe C, Bjdrntorp P, Rebuffe-Scrive M. Regional adipose tissue metabolism in postmenopausal women after treatment with exogenous sex steroids. Horm Metab Res 1990;22:345-51

[62] Rebuffe-Scrive M, Enk L, Crona N, *et al*. Fat cell metabolism in different regions in women. Effect of menstrual cycle, pregnancy, and lactation. J Clin Invest l985;75:1973—6.

[63] Raynaud F, Perez-Martin A, Bran IF, *et al*. Insulin sensitivity measured with the minimal model is higher in moderately overweight women with predominantly lower body fat. Horm Metab Res. I999;31:415-4I7.

[64] Ishikawa K, Takahashi K, Bujo H, et al. Regulating subcutaneous fat accumulation alters insulin sensitivity. Diabetes 2004;53(suppl2):A408

[65] Shibasaki M, Takahashi K, Itou T, *et al*. Alterations of insulin sensitivity by the implantation of 3T3-L1 cells in nude mice. A role of TNF-α. Diabetologia 2002;45:518-526

[66] Terry RB, Stefanick ML, Haskell WL, and Wood PD. Contribution of regional adipose tissue depots to plasma lipoprotein concentrations in overweight men and women: possible protective effects of thigh fat. Metabolism 1991;40: 733—740.

[67] Calle CE, Thun Mi, Petrelli JM, Rodriguez C, Heath CWJ. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097—105.

[68] Wahrenberg H, Lonnqvist F, and Arner P. Mechanisms underlying regional differences in lipolysis in human adipose tissue. J Clin Invest 1989;84: 458-467.

[69] Amer P. Differences in lipolysis between human subcutaneous and omental adipose tissues. Ann Med 1995;27: 435-438.

[70] Jensen MD. Lipolysis: contribution from regional fat. Annu Rev Nutr 1997;17: 127-139.

[71] Jensen MD. Health consequences of fat distribution. Horm Res 1997;48: 88-92.

[72] Montague CT, O'Rahillv S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes 2000;49:883-8.

[73] Caserta F, Tchkonia T, Civelek VN, Prentki M, Brown NF,McGarry JD, Forse BA, Corkey BE, Hamilton JA, and Kirkland ,JL. Fat depot origin affects fatty acid handling in cultured rat and human preadipocytes. Am J Physiol Endocrinol Metab 2001;280: E238-E247.

[74] Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima KS, Lazar MA: The hormone resistin links obesity to diabetes. Nature 2001;409:307-312.

[75] Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM:IRS.1-mediated inhibition of Insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996;271:665-668.

[76] Perusse L, Rice T, Chagnon YC, Despres J-P, Lemieux 5,Roy S, Lacaille M, Ho.Kim MA, Province MA, Rao DC, and Bouchard C. A genome-wide scan for abdominal fat assessed by computed tomography in the Quebec Family Study. Diabetes 2001;50:614-621.

[77] Gabriely I and Barzilai N. Surgical removal of Visceral Adipose tissue: Effects on insulin action. Curr Diab Rep 2003;3:201-6

[78] Hofmann C, Lorenz K, Braithwaite SS, *et al*. Altered gene expression for tumor necrosis factor-alpha and its receptors during drug and dietary modulation of insulin resistance. Endocrinology 1994;134:264—270.

[79] Lamarche B, Despres JP, Pouliot MC, Moorjani S, Lupien PJ, Theriault G, Tremblay A, Nadeau A, Bouchard C. Is body fat loss a determinant factor in the improvement of carbohydrate and lipid metabolism following aerobic exercise training in obese women? Metabolism. 1992 ;41(11):1249-56.

[80] Hu FB, MansonJE, Stampfer MJ, Colditz G, Liu 8, Solomon CC, Willett WC:Diet, lifestyle, and the risk of type 2 diabetes meilutus In women. N End J Med 2001;345:790-797.

[81] Tuomilehto J, Lindstrom J, Eriksson JG, Vaile TI', Hamalainefl H, IlanneParikka P, Keinanen-KiukaannielrLi S, Laakso M, Louheranta A, Rastas M, Salndnen V Uusltupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl JMed 2001;344:1343—1350.

[82] Shadid S and Jensen MD. Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. Diabetes Care 2003;26:3148-52

[83] Miyazaki Y, Mahankali A, Matsuda M, *et al*. Effect of Pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002; 87:2784-91

[84] Brochu M, Tchernof A, Turner AN, *et al*. Is there a threshold of visceral fat loss that improves the metabolic profile in obese postmenopausal women? Metabolism 2003;52:599-604

[85] Barzilai N, She L, Liu BQ, *et al*. Surgical removal of visceral fat reverses hepatic insulin resistance. Diabetes. 1999; 48:94-98.

[86] Gabriely I, Ma XH, Yang XM, *et al*. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process. Diabetes 2002;51:2951-2958.

[87] Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, Mohammed BS. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med. 2004;350(25):2549-57.

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