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REGIONAL ADIPOSE TISSUE DEPOSITION, ITS RATE OF LIPOLYSIS, AND SUBSEQUENT EFFECT ON INSULIN RESISTANCE-IN TYPE II DIABETES MELLITUS

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# REGIONAL ADIPOSE TISSUE DEPOSITION, ITS RATE OF LIPOLYSIS, AND SUBSEQUENT EFFECT ON INSULIN RESISTANCE-IN TYPE II DIABETES MELLITUS

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## Introduction

Diabetes mellitus is a disease that plagues populations world wide. More than 5 percent of U.S. citizens are afflicted with one or another form of this disease (22). This paper begins by discussing the incidence of this illness as it affects Americans. An explanation of the four forms in which diabetes mellitus manifests itself will be offered, and these will be classified according to etiology. Non-insulin dependent diabetes mellitus (NIDDM), also called type II diabetes mellitus, will be the last of these forms mentioned. Due to its prevalence, NIDDM will be the focus of this paper. The proposed pathophysiology of NIDDM will be discussed, though to researchers it still remains somewhat of a mystery. This paper will then briefly review the genetic and environmental interaction responsible for the onset of non-insulin dependent diabetes mellitus. A brief discussion of the interrelationship between decreasing physical activity and a subsequent increase in obesity will follow (38). The location of adipose tissue seems to have adverse effects on certain aspects of NIDDM, including its sensitivity to insulin. This paper proposes that either subcutaneous or visceral adipose deposits specifically reduce insulin sensitivity more than other fat stores. The connection between adipose tissue and insulin sensitivity appears to be mediated by fatty acids released from specific depots and their destination immediately following release.

## Epidemiological Data

Diabetes mellitus is a chronic disease of absolute or relative insulin deficiency. This disease is characterized by disturbances in carbohydrate, protein, and fat metabolism. A leading cause of death by disease in the United States, diabetic related syndromes are contributing factors in about 50% of myocardial infarctions and about 75% of strokes as well as renal failure and peripheral vascular disease (22). More than 80% of people with diabetes mellitus die of some form of heart or blood vessel disease (36). Diabetes is also a leading cause of blindness (22). Whereas the prevalence of hypertension and hypercholesterolemia and the incidence of and mortality from heart disease and stroke have plateaued in the US, in the 1990's the prevalence of diabetes is increasing (44). In 1995, diabetic related complications killed 59,254 Americans (36). Males comprised 26,124 of those deaths (44.1 percent of the total deaths from diabetes) (36). Females comprised 33,130 of these deaths (55.9 percent of the total deaths from diabetes) (36). More than 8,700,000 Americans have diabetes with another 8,000,000 having diabetic related symptoms (36).

## Etiologic Classification

Diabetes mellitus manifests itself in four forms, each classified by its etiology (25). Type I or insulin dependent diabetes mellitus (IDDM) occurs most commonly in childhood and adolescence; however, it can become symptomatic for the first time at any age. Usually there is an abrupt symptomatic onset secondary to severe insulin

insufficiency (polyuria, polydipsia, polyphagia, weight loss, fatigue). Type I diabetics are usually thin and develop ketosis earlier than other diabetics (25). The second form of diabetes mellitus is linked to malnutrition. Malnutrition related diabetes mellitus (MRDM) occurs in certain parts of the world far more frequently than IDDM. It is seen with particular frequency in India, certain parts of Africa, and in the West Indies and is usually found in young people (25). MRDM is characterized by severe protein malnutrition and emaciation (25). The third form of diabetes mellitus is usually associated with a secondary entity or condition (25). Pancreatic disease, acromegaly, and Cushing's syndrome are some examples (25). Type II diabetes mellitus or non-insulin dependent diabetes mellitus (NIDDM) is the last of the four forms discussed here. NIDDM usually begins gradually and occurs later in life. However, as with type I diabetes mellitus, type II may develop at any age. NIDDM is normally linked to impaired basal and stimulated insulin secretion, increased rate of endogenous hepatic glucose release, and inefficient peripheral glucose use (25).

Pathophysiology of NIDDM

The pathophysiology of NIDDM is important to understand since this form of diabetes mellitus accounts for approximately 90% of diabetics in the Western World (34,35). Type II diabetes mellitus most often develops in middle to older age groups, but as stated previously, it can develop at any age (34). The prevalence of non-insulin dependent diabetes mellitus is even greater in selected subpopulations, such as, Hispanic

Americans whose incidence is higher than in white or black populations (34). African Americans likewise have a greater prevalence than do whites (34). The highest known prevalence and incidence of NIDDM in the world is found among the Pima Indians of Arizona, where the age adjusted prevalence rate is about eight times as high as in the general U.S. population (34).

Regardless of what age group, culture, or race has the greatest prevalence of NIDDM, the pathophysiology of this disease still remains somewhat of a mystery. However, as stated previously, in both the post absorptive and fed states, three important defects are thought to exist in subjects with type II diabetes mellitus. These are impaired basal and stimulated insulin secretion, an increased rate of endogenous hepatic glucose release, and inefficient peripheral glucose use (25). Briefly discussing these defects, and other physiological aspects that affect them, will help elucidate the confusing metabolic matrix that results in non-insulin dependent diabetes mellitus.

*Basal Insulin Secretion*

In type II diabetes mellitus there is a decrease in the beta cell response to the prevailing plasma glucose with resultant plasma insulin levels which will often appear normal or, if insulin resistance is present, may even be higher than in normal lean subjects (33,73). However, when adjusted for body weight and ambient glycemia, studies show that NIDDM patients have a reduced total and blunted first phase insulin secretion following an oral glucose challenge (33,73). Normal pulsatile insulin secretion has been

demonstrated in healthy subjects, with distinct pulses approximately every 10 to 15 minutes (57). These pulses occur on a background of larger oscillations approximately every 120 minutes (60). Both of these patterns are abnormal in subjects with type II diabetes and in individuals at high risk for developing the disease (57). The exact cause of these abnormalities has not been determined. Also in NIDDM subjects, up to 32% of total insulin secretion may be proinsulin compared to 15% in control subjects (76). Thus, the true insulin levels in these patients are actually lower than in normal individuals.

*Basal and Stimulated Glucagon Secretion*

An abnormality in alpha cell function also appears present in most patients with type II diabetes mellitus. At the present time, however, it is unclear whether this abnormality, results from reduced insulin regulation of the alpha cell, diminished glucose sensing, or a combination of the two (75).

*Hepatic Insulin Resistance*

Basal rates of hepatic glucose production in patients with type II diabetes mellitus have been documented as normal to increased (10,47). The increased rate of hepatic glucose production results from an impairment of the effects of insulin and glucose to normally suppress glucose release by the hepatocyte (64). Glucagon is also of major importance in the maintenance of post absorptive hepatic glucose release. Glucagon appears to be capable of maintaining more than half of the hepatic glucose production

observed in type II diabetes (8). As a result, the abnormal regulation of glucagon secretion in these subjects may help explain the observed hepatic resistance of type II diabetics to the suppressive effects of both insulin and glucose.

*Peripheral Insulin Resistance*

By using insulin and glucose clamp techniques, it has been conclusively demonstrated that a reduction of more than 55% in mean glucose disposal rate exists in subjects with type II diabetes mellitus (46). Further analysis of the *in vivo* dose response relationship suggests that this reduction in peripheral insulin responsiveness is the result of two abnormalities. First a decrease in receptor number has been reported in *in vitro* studies of monocytes, erythrocytes, and adipocytes (46,19). Despite the presence of spare or unoccupied receptors, the marked decrease in the maximal rate of glucose disposal suggests the existence of a second defect in peripheral insulin action, namely a post binding defect (46). Insulin binding studies on isolated adipocytes from individuals with type II diabetes mellitus have shown that the predominant determinant of the severity of the peripheral insulin resistance in untreated patients is this reduction in post binding insulin action (46). A general summation of the factors affecting overall insulin resistance will be made later.

NIDDM (Genetic/Environmental Interaction)

The pathophysiology of NIDDM is not the only aspect of this disease that is highly debated as its cause also remains somewhat of a mystery. Type II diabetes mellitus is thought to be the result of genetic and environmental interaction; concordance rates among monozygotic twins are between 55% and 100% (7). Similar evidence can be derived from prevalence studies on persons of mixed ethnic origin, which show prevalence rates between those expected from the parent population (45). Familial predisposition to NIDDM is possibly inherited by a single major gene in a codominant manner (72). Obesity also plays a major role in the phenotypic expression of NIDDM (55). However, it is important to note that not all obese people, even the very obese, develop NIDDM. The risk seems to be related to the duration, degree, distribution of obesity, and the maximum weight attained at age 25. In addition, the intrauterine environment during carriage may be of relevance (55). About 40% of those with impaired glucose tolerance develop NIDDM. At particular high risk are subjects who have a first degree relative with NIDDM and who have high serum insulin levels (55).

Physical Inactivity/Obesity

Considerable evidence supports a relationship between physical inactivity and NIDDM (50). Helmrich, Ragland, Leung, and Paffenbarger used questionnaires to examine patterns of physical activity and other personal characteristics in relation to the subsequent development of NIDDM in 5,990 male alumni of the University of

Pennsylvania (38). NIDDM developed in a total of 202 men during 98.524 years of follow up from 1962 to 1976. Leisure time physical activity, expressed in kilocalories expended per week, was inversely related to the development of NIDDM (38). The incidence rates declined as energy expenditure increased from less than 500 kcal to 3,500 kcal. For each 500 kcal increment in energy expenditure, the age adjusted of incidence NIDDM was reduced by 6 percent (38). A decrease in activity also tends to lead to an increase in weight gain (38).

**TABLE 1**


adapted from data from the American Heart Association

Roughly 85% of patients with NIDDM in the United States are overweight or obese (59). The National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases have recently redefined overweight as having a body mass index (BMI) of 25 to 30. They also defined obesity as anyone having a BMI over 30. (BMI is determined by a person's weight in Kg divided by that individual's height, in meters, squared.) 65,700,000 American adults are thought to have a BMI of over 25 (36). (Please see **Table 1** for additional information on obesity.) Obesity is virtually always associated with insulin resistance which is arguably the

earliest detectable and dominant metabolic defect in patients with this disease (24,51). Moreover, there is evidence to suggest that the association between obesity and insulin resistance may be a cause and effect relationship. For instance, it has been shown in humans and in animals that weight gain decreased insulin sensitivity, while weight loss increased insulin sensitivity and glucose tolerance (29,58,69). In the small percentage of NIDDM patients who are not overweight, even small increases in body weight (including normal growth in childhood and adolescence) can exacerbate glucose tolerance and precipitate fasting hyperglycemia. Once again, tying weight to the possible development of NIDDM (67).

Free Fatty Acids

As stated above, insulin resistance is frequently found in obese subjects and is an early hallmark in subjects likely to develop non-insulin dependent diabetes mellitus (9,58,69,18). Insulin travels from its secretory cell, the pancreatic beta cell, through the circulation to its target tissue. Therefore, events at any of these loci can affect or influence the ultimate action of this hormone. It is helpful to categorize insulin resistance according to known etiologic mechanisms. Olefsky states that insulin resistance can be due to three general categories of causes: an abnormal beta cell secretory product, circulating insulin antagonists, or a target tissue defect in insulin action (18). Sub classifications exist within each of these categories. For example, an abnormal beta cell secretory product could be due to an abnormal insulin molecule or, the incomplete

conversion of proinsulin to insulin (18). Circulating insulin antagonists; could be present as elevated levels of counter regulatory hormones such as growth hormone, cortisol, glucagon, and catecholamines (18). Circulating insulin antagonists can also take the form of free fatty acids (FFAs), anti-insulin antibodies, anti-insulin receptor antibodies or as tumor necrosis factor alpha (18). Finally, as discussed in the pathophysiology of NIDDM, target tissue defects could be present in the form of insulin receptor or post receptor abnormalities (18). (Please see **Table 2.**)

**TABLE 2**

Causes Of Insulin Resistance

Abnormal beta-cell secretory product
- Abnormal insulin molecule
- Incomplete conversion of proinsulin to insulin

Circulating insulin antagonists
- Elevated levels of counter regulatory hormones
  - Growth Hormone, Cortisol, Glucagon, or Catecholamines
- Free fatty acids
- Anti-insulin antibodies
- Anti-insulin receptor antibodies
- TNF alpha

Target tissue defects
- Insulin receptor defects
- Postreceptor defects

adapted from Olefsky

Though there are many mechanisms hypothesized to be responsible for insulin resistance, FFAs were the first of these to be identified. In 1963, Randle et al.

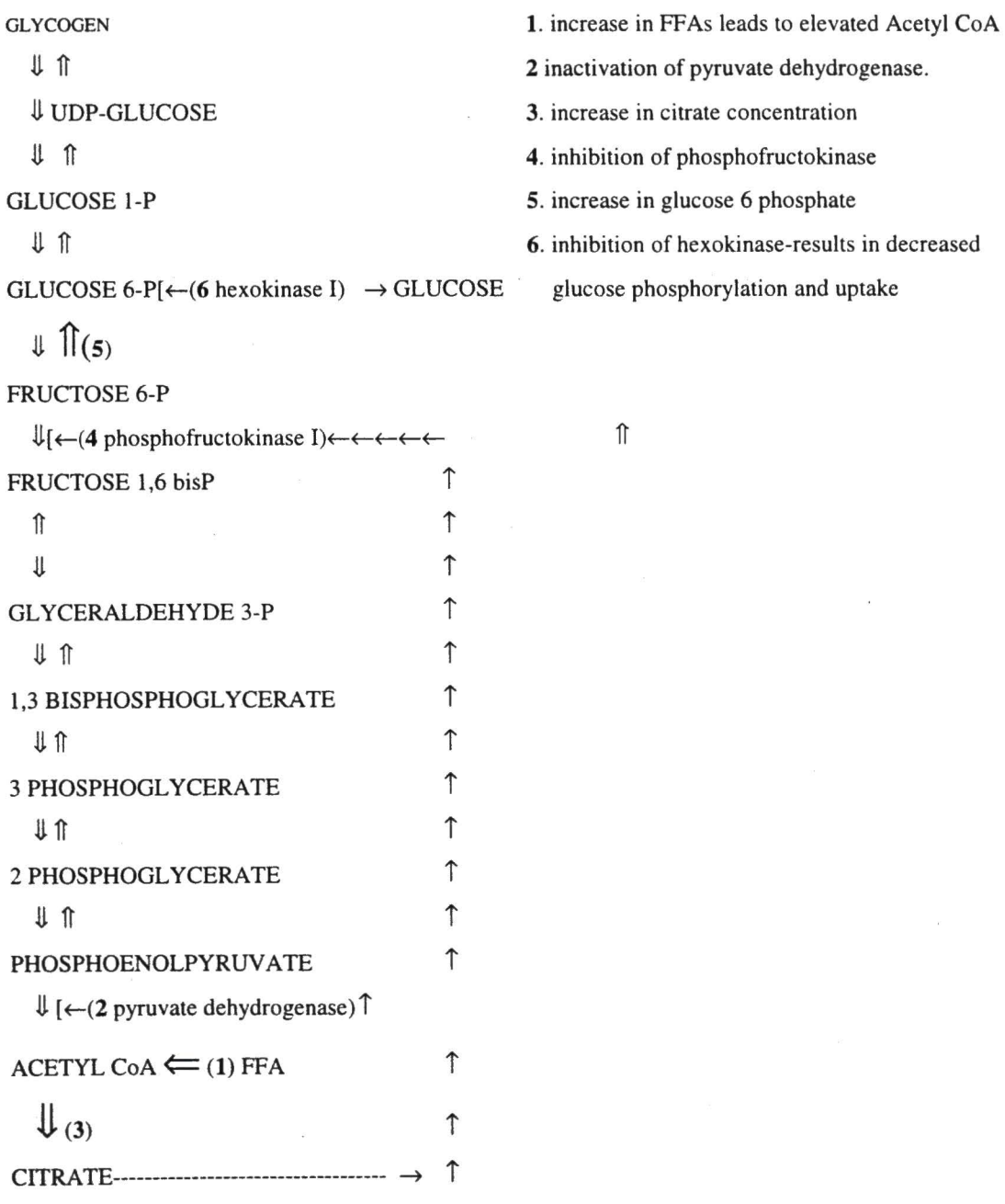
hypothesized that FFAs interfered with insulin mediated glucose metabolism in skeletal muscle by way of the glycolytic pathway (61). Randle and his colleagues proposed that increased FFA availability and oxidation results in elevated intramitochondrial acetyl-coenzyme A and NADH/NAD+ ratios with a subsequent inactivation of the pyruvate dehydrogenase complex (61). This, in turn, causes citrate concentrations to increase which lead to inhibition of phosphofructokinase and accumulation of glucose-6-phosphate (G6P) (61). Increased concentrations of G6P would inhibit hexokinase I resulting in decreased glucose phosphorylation and uptake (61). (Please see **Figure 1**.)

Randle's hypothesis was the result of experiments performed with isolated rat heart and diaphragms. However, *in vivo* studies in humans did confirm that FFA infusion impairs whole body glucose uptake (41). In these experiments, during FFA infusion, most of the glucose was disposed non-oxidatively as glycogen into skeletal muscle (41).

Newer data have shown that during systemic elevation of FFAs, a reduction in carbohydrate oxidation is responsible for roughly one third of the decreased glucose uptake (14). Impairment of the non-oxidative glucose metabolism, which mostly reflects glycogen synthesis, accounts for the other two thirds of the fatty acid dependent decrease in glucose uptake (14). Boden et al. suggest that two different mechanisms that are concentration dependent are the cause for FFA inhibition of glycogen synthesis (14). At higher concentrations, FFA increased intramuscular G6P is found, suggesting a FFA induced inhibition of glycogen synthase (14). However, at lower concentrations of FFAs,

## FIGURE 1

Randle's Hypothesis




adaptation of Randle's hypothesis

a decrease in G6P was detectable, suggesting impaired glucose uptake or phosphorylation upon insulin stimulation (14).

It is important to note that some studies do not agree that there is a significant deleterious association between an increase in FFAs and glucose uptake (11,77). However, it has been recently demonstrated in healthy volunteers that the fatty acid mediated inhibition of insulin stimulated carbohydrate oxidation occurred early (within 1-2 h) whereas the inhibition of glucose uptake developed only after ~ 4h of fat infusion (15). Therefore, insufficient time of fat plus insulin infusion (2h in most studies) is the most likely reason why the inhibitory effect of fatty acids on glucose uptake was not found in many studies (11,77).

It is reasonable to assume, therefore, that chronically elevated plasma FFAs, perhaps together with FFAs released from intramuscular fat depots, contribute to the insulin resistance commonly seen in obesity (52). It should also be pointed out that FFA induced insulin resistance serves an important physiological role in the normal individual, preserving glucose for oxidation in the central nervous system when glucose is scarce, for instance, during fasting, prolonged exercise, or late pregnancy. In obesity, these same mechanisms can become counterproductive, inhibiting glucose utilization when there is no need to spare glucose.

Adipose Tissue/Regional Deposition/Lipolysis

The density of adipose tissue and the subsequent release of FFAs from these depots are now believed to be regionally dependent. An increase in FFA release is thought to mediate the observed decrease in insulin sensitivity. The net balance between fatty acid uptake and FFA release determines whether a body fat depot will accumulate or dissipate triglyceride stores. Increased regional fat accumulations could result either from greater triglyceride uptake or from lower FFA release (43). Taking a closer look at adipose tissue itself, at its site of deposition, and specifically at the differences in regional lipolysis is the next step in understanding the pathophysiology and treatment of obesity and NIDDM.

*Adipose Tissue*

The body is composed of white and brown adipose tissue. Brown adipose tissue is the less common form and is primarily involved in heat production (40). Brown fat is found in newborn mammals, but if they are non-hibernators the brown fat declines greatly during the course of maturation (40). There are negligible brown adipose stores in the human adult, so this section will focus on white adipose tissue referred to here, simply as adipose tissue. White adipose tissue in the human adult provides a surplus of energy storage (40). There is a continuous subcutaneous layer of adipose tissue, which is distributed differently in men and women (40). The abdominal and gluteal fat stores are more well developed in the female than in the male (40). The smaller amount of subcutaneous fat found in males accounts, in large measure, for the difference in total

body fat seen between the two sexes (40). In males about 15% of their body weight is adipose tissue, compared to about 20% in females (40).

Innervation of adipose tissue is primarily vasoconstrictive in nature, since neural stimulation causes reduction in the volume of the tissue (40). This neural stimulation causes increased lipolysis, breakdown of triglycerides and release of free fatty acids and glycerol. Since there is no direct innervation to the adipocyte, adrenergically stimulated lipolysis is presumed to result from norepinephrine released from the perivascular plexus and its subsequent transport through the interstitium or plasma to adipocyte membrane receptors (40). In addition to catecholamines, glucagon, ACTH, thyroxin, TSH, and somatotrophin are also lipolytic. In contrast, insulin inhibits lipolysis and promotes lipogenesis.

*Regional Deposition of Adipose Tissue/Lipolysis*

There seems to be an agreement among the majority of scientists that upper body adipose tissue influences insulin sensitivity more than lower body adipose tissue (9,20,48). For example, in 1956 Vague observed that upper body fat distribution has particularly adverse metabolic consequences (74). In 1998, Markovic and her colleagues stated that abdominal fat loss improves the lipid profile in obese subjects (53). However, the debate continues as to whether subcutaneous or visceral fat depots affect insulin sensitivity to a greater degree.

*Subcutaneous Adipose Tissue*

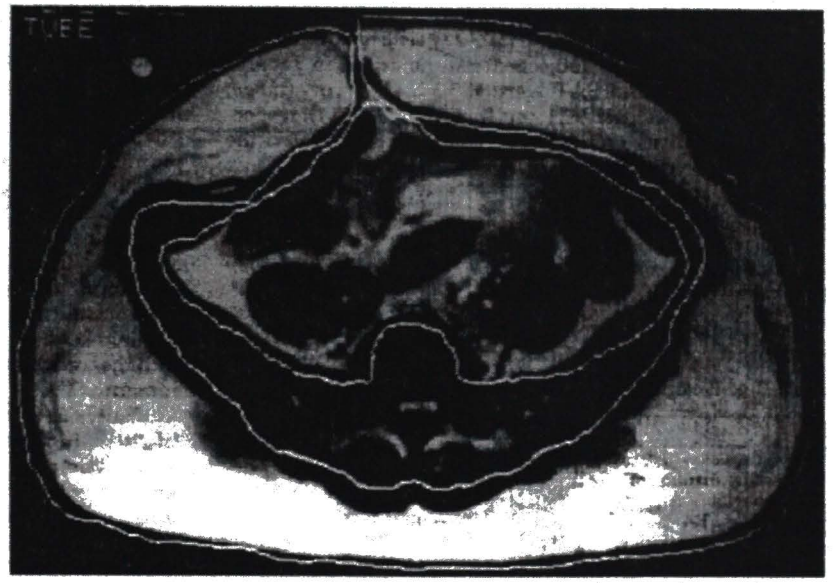
Many researchers believe that subcutaneous adipose depots are responsible for a decrease in insulin sensitivity (42,65,70). In 1979, Kral et al. investigated the possible differences in metabolism between abdominal and femoral subcutaneous fat depots, in an effort to elucidate mechanisms of weight loss (70). These investigators determined that the subcutaneous abdominal adipocytes had a greater lipolytic rate than did the femoral adipocytes (70). Kral et al. stated that this increased rate of lipolysis would promote FFA release, thereby decreasing insulin sensitivity (61,70).

Various other *in vitro* studies have also demonstrated a decrease in insulin sensitivity caused by increased subcutaneous abdominal fat (65,42). These studies have shown that adipose tissue isolated from the subcutaneous abdominal regions has a higher lipolytic activity than that from visceral (mesentery or omentum), and subcutaneous femoral regions (65,42).

Recently new imaging techniques have been used to further investigate the relationship between subcutaneous adipose tissue and insulin sensitivity. Computerized tomography (CT) and magnetic resonance imaging (MRI) allow direct visualization of internal adipose tissue compartments (66). (Please see **Figure 2**, for an example of an MRI.) Abate et al. used MRI and CT techniques to measure fat mass in combination with the various glucose and insulin clamps, which were used to measure insulin sensitivity (2). They found that intraperitoneal adipose tissue (considered visceral) does not play a major role in the variability of both peripheral and hepatic insulin sensitivity observed

with changes in generalized adiposity (2). Subcutaneous abdominal adipose tissue was found to have the strongest relationship with peripheral and hepatic insulin sensitivity (2).

**FIGURE 2**




Light shaded area = subcutaneous adipose tissue
Dark shaded area = visceral adipose tissue

adapted from Gautier et al.

In 1996, Goodpaster et al. not only used CT, MRI, and the various clamp techniques in measuring fat mass and insulin sensitivity, but also used dual energy x-ray absorptiometry (DEXA) (31). They were thus able to look at cross sectional data on abdominal and mid thigh adipose tissue. DEXA aided in the determination of regional fat mass and fat free mass (31). Once fat mass had been quantified, glycemic insulin

infusions were conducted to determine insulin sensitivity. Goodpaster et al. concluded that subcutaneous abdominal fat correlated very closely with insulin resistance (31). Therefore, their current findings support the concept that a strong link exists between insulin resistance and subcutaneous abdominal obesity and that this association is not largely contingent upon the content of visceral fat (31).

*Visceral Adipose Tissue*

In 1979, Kral et al., as indicated above, conducted a study that showed that subcutaneous adipose tissue had a greater effect on insulin sensitivity than did subcutaneous fat tissue from femoral regions (70). Kral and his colleagues did, however, state that it may be important to consider the influence of visceral (omental) adipose tissue (70). These researchers suggested that since visceral adipose tissue released its FFAs directly into the portal vein, the opportunity to influence hepatic insulin sensitivity might be significant (70). Many researchers seem to agree with Kral et al. as they state that an abundance of visceral fat is a stronger predictor of insulin insensitivity and subsequent NIDDM, than overall fatness (13,21). To further examine this idea, various studies have investigated the effects of weight loss on fat distribution and lipid metabolism (3,26,48). These studies have usually assessed regional fat deposition by anthropometric measurements such as waist-hip ratio and waist circumference. However, the results offered by these studies are contradictory (5,16). Kooy et al. believe that waist-hip ratio and waist circumference determinations are unreliable measures of

visceral adiposity (48). These researchers compared the results of studies done using the waist-hip ratio and waist circumference techniques to those determined by the relatively new MRI technology (48). After comparing the results, Kooy et al. determined that changes in waist-hip ratio and even in waist circumference are not good indicators of variance in visceral adiposity (48).

Recently, studies using MRI and CT have estimated different fat depot in obese women before and after weight loss (3,26). The results of these imaging studies showed that abdominal fat depots, especially the visceral depot, were reduced with weight loss. These observations are in agreement with findings from *in vitro* experiments that showed that visceral abdominal adipocytes are more lipolytically active than gluteal and femoral adipocytes. Therefore, due to their higher rate of FFA release, visceral fat will have a greater affect on insulin sensitivity (4,63).

Physical training is well known to increase insulin sensitivity and reduce cardiovascular risk factors such as hypertension, dyslipidemia, and fat mass accumulation (39). Consequently, physical training should theoretically be a part of the overall management of NIDDM. Agnes Mourier et al. conducted a study on 24 patients, 20 men and 4 women, who had NIDDM (56). Their average BMI was 30 kg/m2 and they had a mean age of 45 years (56). These subjects exercised 3 times a week for about one hour and trained at 75% of their VO2 max for 2 months (56). The physical training decreased their visceral adipose tissue by about 48% as measured by MRI (56). Preferential loss of visceral adipose tissue induced by exercise training can be explained by previous studies

showing that omental and mesenteric adipocytes are more sensitive to the lipolytic effect of catecholamines released during exercise (6,1). Mourier et al. also observed improved insulin sensitivity by 46% and tied that improvement to the loss of visceral adipose tissue (56). These researchers also state that the improvement in insulin sensitivity was not entirely linked to visceral adipose tissue (56). They say that though reduced visceral adipose tissue had the greatest influence in improving insulin sensitivity, there are many other factors that influence the body's sensitivity to insulin (56).

Other studies using computerized tomography have indicated that several abnormalities which often precedes NIDDM, such as insulin resistance, increased blood pressure, and dyslipidemia, were more pronounced in subjects with abdominal visceral fat (71,28). A prospective study conducted in Japanese-American men showed that in individuals who develop NIDDM, increased deep abdominal fat is present before the onset of NIDDM (9,68). Furthermore, studies undertaken using both MRI and CT technologies stated that in Caucasians, type II diabetes mellitus was associated with a greater accumulation of deep abdominal fat than in nondiabetic subjects with similar weight (68,32).

Gautier et al. (1997) evaluated abdominal fat distribution in patients with NIDDM (30). These researchers sought to examine further the relationship between the amount of visceral adipose tissue and insulin resistance (30). The average age of their patients was 45 and the duration of their diabetes was less than 10 years (30). All of the patients were Caucasian, however, no information was given on the gender make-up of the subjects

(30). Lastly, the majority of the patients were obese (30). Gautier and his colleagues once again found that insulin sensitivity is inversely associated with the amount of visceral adipose tissue found in NIDDM patients (30). A greater amount of visceral adipose tissue resulted in a lower sensitivity to insulin (30). These researchers suggested that the high lipolytic response of the visceral adipose tissue to catecholamines exposes the liver to high FFA concentrations via the portal circulation, thereby leading to insulin resistance (30). Gautier et al. also stated that FFAs inhibit insulin stimulated whole body glucose uptake and utilization in patients with NIDDM (30).

Problems in weighing the importance of Subcutaneous versus Visceral Adipose Tissue

The original aim in writing this paper was to evaluate how exercise and diet affected those with NIDDM. As I progressed, it became apparent that fat reduction *per se* was important regardless of the route used to achieve it. Different theories then emerged suggesting that fat loss in certain areas affected type II diabetics, and their sensitivity to insulin, more than other areas. That information led to the debate between scientists attempting to determine whether a reduction of visceral or subcutaneous adipose tissue had the greater effect on insulin sensitivity. Once again the question and answer are far from simple. Though the use of MRI and CT technology have provided both sides of the argument with better data, the debate has not been resolved. There are many variables which skew or limit the results of experiments performed by parties on both sides of this debate. None of the studies have taken all of these factors in account, and in reality it

may be impossible to do so. However, it is important to point out these factors as they have affected past experiments and may affect the results of those yet to be conducted. Subjects chosen for evaluation of regional adipose tissue distribution and lipolysis, need to be selected carefully. This alone negates the randomness that underlies a valid study. However, due to the fact that individuals' race, gender, age, and duration of NIDDM all seem to affect the metabolism of regionally differentiated adipose tissue, different populations may provide different results.

For instance, several studies suggest that the association between central adiposity and insulin resistance differ with respect to ethnicity, with some investigators indicating less influence in African-Americans, while other studies indicate a strong effect in Japanese-Americans (62,23). Though there have not been many studies that have tested this hypothesis, its point has been made. Bergstrom's study on Japanese-American men and Gautier's evaluation of Caucasians may only present data relevant to Japanese and Caucasian populations (63,30). Many researchers, such as Mourier et al. do not provide the ethnic make up of their subject group (56). Therefore, although their experimental procedures seem to be excellent, to which ethnic population is their results meaningful?

Men and women seem to store adipose tissue differently. Kooy et al. states that women have more subcutaneous fat at the abdominal and hip level than do men (48). Also, as stated previously, intra-abdominal depots seem to drain their FFAs into the portal vein (63). An enlarged intra-abdominal fat depot leads to an increase in lipolysis and therefore, an increase in portal disposition of FFAs is hypothesized to cause

metabolic aberrations such as insulin insensitivity (63). Men and women are thought to show gender specific lipolytic patterns with respect to portal versus non-portal disposition of FFAs (62). Rebuffe-Scrive et al. found that visceral fat depots, which drained their FFAs into portal circulation, had an increased rate of lipolysis in men, while subcutaneous fat depots, that drained their FFAs into non-portal circulation, had a greater rate of lipolysis in women than in men (63). These researchers believe that the increased rate of lipolysis viscerally for men is due to the fact that their visceral adipocytes are larger than those in women (63). Larger adipocytes are thought to have a greater lipolytic rate than smaller ones in the same region (63). In a similar fashion, Rebuffe-Scrive et al. believe that women's subcutaneous adipocytes are larger than men's, thereby causing them to have a greater lipolytic rate (63). Various researchers also believe that visceral adipocytes in men are more sensitive to catecholamine stimulated lipolysis than they are in age matched women (63,37).

Therefore, it seems apparent that research subjects, due to their gender may skew the results of experiments weighing the importance of subcutaneous versus visceral fat and its affect on insulin sensitivity. This paper relied heavily on a study by Abate et al., whose subject group incorporated only men (2). The results from this research should, therefore, not be generalized to include women. Goodpaster et al. used an equal number of men and women in his study; how is this data to be evaluated (31)? Mourier's study included 24 individuals, 20 of who were male and only 4 of whom were female (56). Mourier's results seem more indicative of adipose tissue lipolysis and the resulting

insulin sensitivity in men. Though the differences in lipolytic rates between men and women remain unsettled, their potential differences need to be considered when designing studies that may be affected by those differences.

Age is yet another factor that needs to be considered when conducting studies of insulin sensitivity. Aging is associated with an increased prevalence of impaired glucose tolerance (IGT) and a decrease in insulin sensitivity (17). Approximately 40% of the population over the age of 60 years have IGT (17). The pathophysiology of IGT in the elderly is multi factorial, involving insulin resistance, hyperinsulinemia, impaired beta-cell function, and increased hepatic glucose production (17). Although primary post receptor defects have been identified in older individuals with IGT, the deterioration in glucose tolerance and insulin sensitivity often associated with aging may be related to an increase in total and abdominal adiposity as well as a decrease in physical activity and muscle mass (17). Therefore, if a study population is 60 years of age or older, the results from that study should not be generalized.

The last important variable that should be taken into consideration when choosing a test group, is that group's status in relation to NIDDM. Since type II diabetes mellitus often involves a decrease in insulin sensitivity, these diabetics are frequently chosen for related studies (56,30). Various researchers feel that insulin sensitivity in NIDDM may be altered or affected depending on the duration of the disease (38,50). Scientists believe that if the onset of NIDDM has been less than 10 years, then a reduction in specific regional fat mass may improve insulin sensitivity (38,50). However, many also feel that

if a patient has had the disease for over 10 years, regional reduction in adipose tissue may no longer improve insulin sensitivity (38,50). It is, therefore, important to take this factor into account when selecting and evaluating a specific subject group.

## Conclusion

Sixteen million Americans are affected by diabetes mellitus, most commonly by non-insulin dependent diabetes mellitus (36). Roughly 85% of type II diabetics are overweight or obese (59). This extra adipose tissue decreases insulin sensitivity due to an increase in plasma free fatty acid release (18,61,41). Both visceral and subcutaneous adipose tissues have been specifically evaluated for their influence on insulin sensitivity. After comparing current research on each depot and after evaluating various problems associated with that research, a clear conclusion cannot be made. Scientists on both sides of the subcutaneous versus visceral debate seem to be deadlocked as to which area has a greater influence on insulin sensitivity. In addition, since race, gender, age, and duration of NIDDM all seem to affect adipose tissue mass and rate of lipolysis, a firm conclusion may prove to be quite elusive. Despite this confusion, upper body adiposity still seems to be the dominant feature determining relative insulin insensitivity (9,20,48). Though research may soon prove which upper body region determines insulin insensitivity, that determination cannot currently be made. For an individual who is insensitive to insulin, losing weight is key regardless of the route, diet or exercise.

Future research on adipose tissue deposition, and its importance in relation to insulin sensitivity might progress at a more rapid rate if clinicians with access to specific populations become involved in that research. Physicians who perform lipo-surgery are surrounded by subjects/patients who may help answer this metabolic question. If interested physicians would collect relevant data from their patients, before and after the mechanical adipose removal, a large database of location specific information could be compiled. This information would not be difficult to reduce and conclusions on area specific adipose tissue and its effects on insulin sensitivity might be determined.

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