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The Biochemistry and Development of Adipose Tissue and the Pathophysiology of Obesity as It Relates to Liposuction Surgery

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Liposuction surgery remains one of the most commonly performed cosmetic surgical procedures in the United States. Many questions have been raised as to the potential impact of this surgical procedure on adipose tissue metabolism as well as potential long-term effects on obesity.

The understanding of these factors is important so that the surgeon can adequately counsel patients and so that the surgeon will know what potential impact surgical intervention may have on this organ system. In addition, the surgeon must understand obesity, and in particular those differences in fat distribution that cause patients to seek surgical correction.

This article reviews fat cell metabolism and some of the mediators of the metabolic pathways involved. In addition, obesity (with particular emphasis on regional differences in fat deposition), the morphologic and metabolic differences related to the various types of obesity, and the potential health implications of these differences are discussed.

ADIPOCYTE METABOLISM

The two basic pathways in fat metabolism are lipogenesis and lipolysis. Lipogenesis involves the uptake and storage of lipids within the adipocyte; lipolysis involves the breakdown of those lipid stores for utilization by the body (Fig. 1).

Lipogenesis

Fat cells store lipids in the form of triglycerides. Triglycerides are composed of three fatty acid molecules attached to a glycerol moiety. It is interesting to note that while triglycerides are found intravascularly, the adipocyte cannot utilize them directly. Instead, the adipocyte requires, as building blocks, free fatty acids and glucose in order to form intracellular triglycerides for storage.

There are several potential acquisition sources of free fatty acids by the adipocyte. De novo synthesis and uptake of circulating free fatty acids have been described but are not considered to be important in the overall process of fatty acid acquisition. The primary means of acquiring free fatty acids is by lipoprotein lipase–mediated uptake. Lipoprotein lipase (LPL) is the rate-limiting step in fatty acid uptake and has as its substrate, circulating triglycerides. Triglycerides are available within the circulation as chylomicrons and secondarily as very low density lipoproteins (VLDL). The basic pathway for LPL-mediated fatty acid up-

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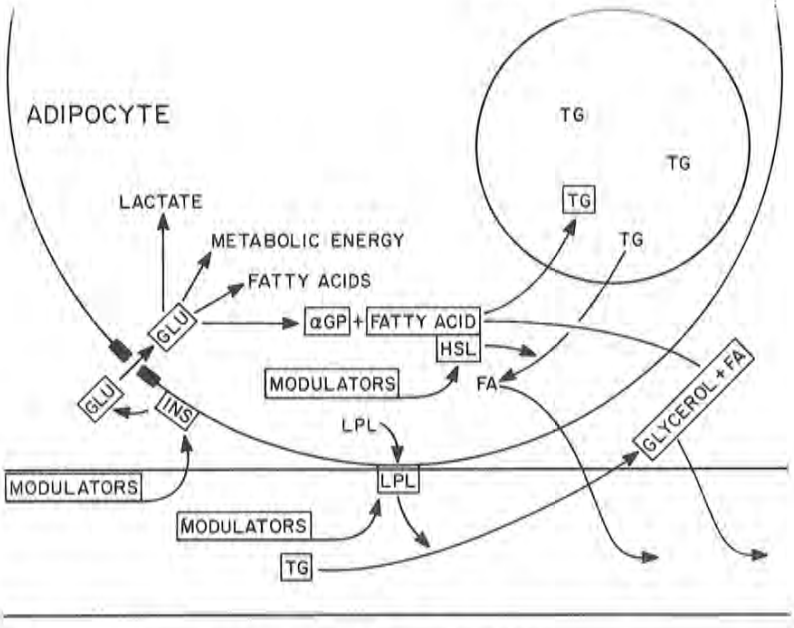

Figure 1. The pathways of adipocyte metabolism: lipogenesis and lipolysis.

take is as follows: LPL is made intracellularly and is transported into the capillary, where it attaches to the capillary wall. It then acts on triglycerides, breaking them down into glycerol and fatty acids. Glycerol is not utilized by the cell and is returned to the circulation, whereas fatty acids are carried into the cell through an as yet undefined mechanism. The free fatty acids are then combined with alpha-glycerophosphate to form triglycerides for storage.

Since the adipocyte cannot utilize glycerol from the circulation directly, it requires as a substrate, glucose, which serves as the precursor for alpha-glycerophosphate formation. Glucose uptake, therefore, is a critical determining factor in triglyceride formation. Glucose is brought into the cell through a mechanism known as facilitated diffusion. Through the direct action of insulin on a specific insulin receptor on the cell membrane, molecules called glucose transporters are moved from the Golgi apparatus to the cell membrane. The presence of these glucose transporters within the membrane increases the rate of glucose transport across the cell membrane. Once inside the cell, there are multiple potential fates for the glucose molecule. In the process of triglyceride formation, the important step is the transformation from glucose to alpha-glycerophosphate. After triglyceride formation, the lipids are stored in a central intracellular depot.

Lipolysis

Lipolysis involves the breakdown of stored triglycerides for release from the adipocyte. The major mediator of this pathway is hormone-sensitive lipase (HSL). This enzyme breaks down triglycerides into free fatty acids and glycerol. The glycerol molecules are not reutilized by the cell and are released into the vascular system. The free fatty acids may also move into the vasculature to be used by the body, or may become a part of a pool of fatty acids that will remain intracellularly to be simply recombined with alpha-glycerophosphate to re-form triglycerides.

Mediators of Fat Metabolism

The control mechanisms for lipogenesis and lipolysis are complex and poorly understood. Whereas there are many hormones and chemicals that influence and mediate these pathways, insulin and catecholamines seem to have the most profound and acute effects on these processes.

Catecholamines have dual effects on lipolysis.[11] The beta-adrenergic receptors are stimulatory, whereas the alpha-2 receptors are inhibitory. Of the two effects, the beta effects usually predominate, thus encouraging lipolysis. Exceptions to this exist during fasting and in the

setting of diabetes mellitus and hypothyroidism, when alpha-2 inhibitory effects may dominate.[28, 42]

Insulin, aside from its function in lipogenesis, also has an inhibitory effect on lipolysis. The means by which insulin inhibits lipolysis is not well understood, except that its effect is mediated through cyclic AMP, and the inhibitory effect is strongly glucose dependent.[3]

The antilipolytic effect of the alpha-2 adrenergic receptor is better understood. Catecholamine response via the alpha-2 receptor effectively decreases the production of cyclic AMP. This inhibits protein kinase, thereby decreasing phosphorylation of hormone-sensitive lipase, the enzyme that breaks down intracellular triglycerides.[11]

There are many other mediators of these metabolic processes. For example, stimuli for lipolysis include glucagon, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone, and vasopressin.[15, 25, 60] It is theorized that the many modulators of these pathways permit a very precise and subtle control over fat metabolism in response to a wide array of both internal and external stimuli.

OBESITY

Obesity is defined as body weight that is 20% or more above the norm. It is estimated that 20% of middle-aged males and 40% of middle-aged females fulfill this criterion for the definition of obesity. Classically, obesity has been subclassified into *hyperplastic* or *hypertrophic* types, hyperplastic referring to increased fat cell number and hypertrophic referring to increased fat cell size. It is taught that childhood-onset obesity is primarily of the hyperplastic type and is poorly responsive to diet, whereas adult-onset obesity tends to be characterized by only hypertrophic changes and is potentially diet responsive. This classification system is based on the theory of adipose tissue development, which states that from the first appearance of adipocytes in the third month of fetal life, new fat cells continue to form through childhood and adolescence. At puberty, fat cell proliferation ceases and no new cells form throughout adulthood. Childhood-onset obesity is hyperplastic, new cells being stimulated to form at a time when there is a natural increase in adipocyte number. Adult-onset obesity, on the other hand, is reflected by an increase only in fat cell weight and not in number.

Recent evidence brings into question the validity of this classification system and theory of adipose tissue development. An exception is the morbidly obese adult, defined as being greater than twice normal weight, in whom hyperplastic as well as the expected hypertrophic changes are demonstrated. It is thought that in this extreme situation, adipocytes reach a maximum size, and when no further increase is possible, a message is sent to the adipoblast/preadipocyte pool for recruitment of new cells. This recruitment produces the hyperplastic changes that are noted. While the situation of the morbidly obese adult is extreme, it does demonstrate that recruitment of new adipocytes in adulthood is possible.

Evidence by Sjöström[54] also disputes the classic theory. He reexamined a group of women who had been studied by him 7 to 9 years earlier, looking for long-term changes in adipocyte size and number. His earlier findings in these women[53] and the studies of others[5, 7, 21, 51] in the early 1970s had supported the dogma that, in adults, changes in weight were associated with only changes in cell size. Upon reexamination, however, he found that long-term decreases, as well as increases, in weight in these subjects were associated with similar increases and decreases in *cell number*. He believed that the limitations of the previous studies related to the limited time that subjects were followed and concluded that the concept that there is a critical period of fat cell multiplication before adult age should be abandoned. He proposed a new theory to explain his observations: Short-term changes in body mass are reflected in changed fat cell weight. But if the changes exist over a long enough period, signals for a changed fat cell number are likely to be operating, resulting in changes in cell number. Of particular interest was the decrease in cell number that was noted in those subjects with prolonged weight loss. Unlike the older theory that adipocytes never decrease in number, he proposed that older lipocytes may be subject to death and phagocytic removal just as is seen in virtually all other organ systems.

REGIONAL DIFFERENCES IN FAT DISTRIBUTION

Men and women store fat in different regions of the body. The male, or *android*, distribution refers to the fact that obesity in the male is usually localized to the abdominal area, whereas the female, or *gynecoid*, distribution refers to the fact that obesity in the female tends to result in fat accumulation in peripheral stores, especially those below the waist, in the areas of the femoral and gluteal fat stores (Fig. 2). These gender differences are not universal as there are women who demonstrate central or android obesity, and more rarely there are males who express a gynecoid distribution of fat (Figs. 3 and 4).

There are significant morphologic and metabolic differences as well as health implications relative to the adipose stores in these different sites. The most exciting research in obesity in the last decade has examined these differences and has led to a much greater understanding of the role of regional differences in fat deposition and health. The following is a summary of much of this research.

In women, there are metabolic and morphologic differences in the adipocytes from the gluteal/femoral (G/F) as opposed to the abdominal areas. These differences help to account for the preferential deposition of fat in the peripheral stores in women.

The nonobese female has a greater total adipose mass than the nonobese male, and in the normal state women tend to deposit fat in a gynecoid distribution. In women, adipocytes in the G/F area are larger in size than are those in the abdomen. In addition, G/F adipocytes are more sensitive to corticosteroids and estrogen, reflecting increased lipogenic activity. In contrast, abdominal adipocytes are more sensitive to catecholamines, especially beta effects, reflecting increased lipolytic activity.[29, 35, 50]

In moderately obese women who are in a state of positive energy balance, lipogenesis, as reflected by LPL activity, is greater, and lipolytic activity is significantly less in the G/F area than in the abdomen.[24, 41] Therefore, even in the obese state, there is increased stimulus to enlarge preferentially lipid stores in the G/F areas.

It is most interesting to examine the differences in metabolic activity of adipocytes during the fasting or dieting state in women. It would be expected that in a condition of negative energy balance the body would need to utilize its lipid stores from all available adipose depots. This is, however, not the case. During the first week of fasting, abdominal lipolytic activity increases as expected. However, there is *no* increase in lipolytic activity in the G/F sites. Specifically, in the abdominal adipocytes, LPL activity is decreased while beta-cholinergic effects are increased, reflecting the fact that lipolysis is ongoing and lipogenesis has been inhibited. At the same time in the G/F stores, LPL activity is actually increased over the nonfasting state.[2, 47] Therefore, even in the fasting

Figure 2. Statues in Monte Carlo exemplifying gender differences in fat distribution.

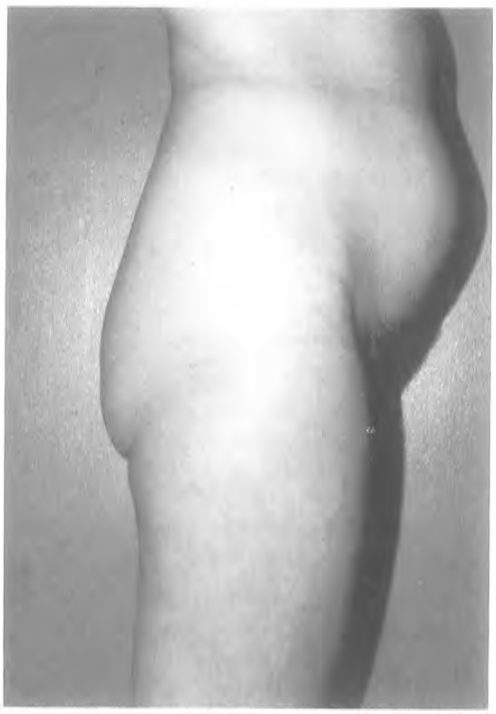

Figure 3. Android fat deposition in a female.

state the female body shows a strong tendency to retain and even increase lipid stores in the G/F areas.

In summary, in the normal and obese female and in the fasting state, the stimuli to increase lipid stores in the gynecoid fat deposits are always greater than lipolytic effects.[49] In the female who repeatedly diets unsuccessfully, experiencing small losses and gains of weight, there may be little change in the abdominal stores. On the other hand, there may be excessive deposits in the G/F areas.[49] Over time, this may result in a disharmonious distribution of fat, producing what has been called a "half-and-half" person, in whom one half of the body does not seem to belong to the other (Fig. 5). One exception to the constant lipogenic stimulus in the G/F adipose stores is during lactation.[50] During this time, the G/F adipocytes demonstrate identical lipolytic activity as abdominal cells. Teleologically, this suggests that the abdominal and peripheral fat stores serve very different functions. It suggests that abdominal stores are dedicated to the storage and rapid mobilization of energy reserves, whereas the

G/F sites serve as a storage depot for pregnancy and lactation.[42] The continued increased level

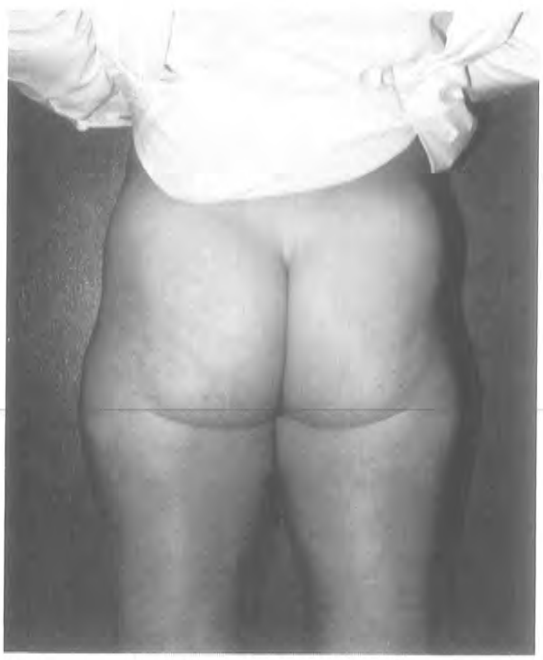

Figure 4. Rare gynecoid male.

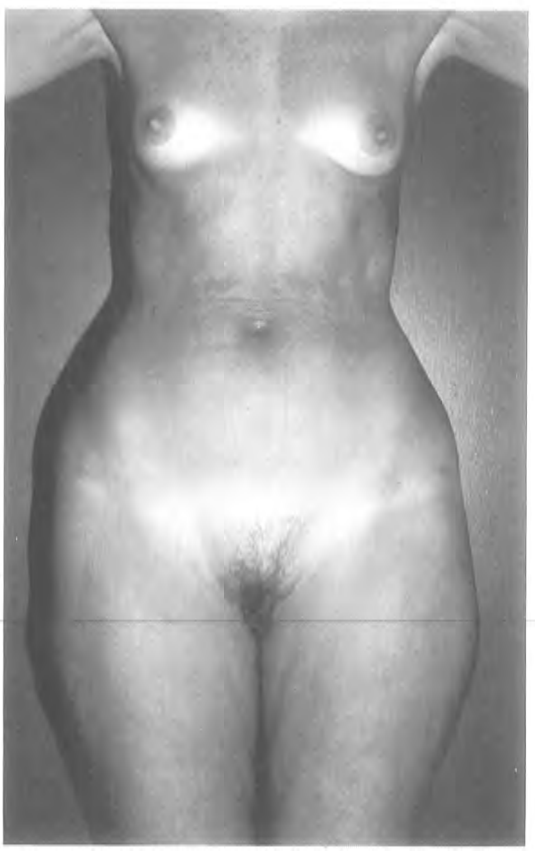

Figure 5. Dysharmonious fat distribution, the "half-and-half" person.

ipogenesis during fasting seen in the G/F
s means that even in a time of food depri-
on, there will remain sufficient adipose
es for lactation.

ALTH IMPLICATIONS OF REGIONAL OBESITY

eneralized obesity has long been associated
an increased health risk.[1, 10, 16–19, 22, 26, 44, 61]
ue in 1956[57] was the first to report an
ciation between an android distribution of
nd various metabolic disturbances. In the
decade, studies of obesity have provided
ng evidence that abdominal obesity, inde-
dent of both generalized obesity and gyne-
obesity, is a strong risk factor for the
elopment of diabetes mellitus,[28, 42, 43, 46] car-
ascular disease,[9, 37, 40] hypertension,[4, 36, 38]
ke,[37, 40] and possibly some female can-
.[36, 37, 48]

measure of the relationship between cen-
and peripheral obesity was developed that
pares the circumference of the abdomen to
of the hips. This ratio, the waist-hip ratio
IR), has repeatedly been shown to be a
ble predictor for those health risk factors
ted to central obesity.[37, 40] Whereas a waist
umference measurement reflects both intra-
ominal and subcutaneous adipose depots,
puted tomographic studies have shown that
abdominal subcutaneous stores are reflec-
of intra-abdominal stores, and the WHR
efore fairly accurately predicts intra-abdom-
adipose collections.[6, 8, 56] It is probable that
ntra-abdominal, rather than the abdominal,
utaneous fat stores are the determining
r for those health risks associated with
ral obesity. The visceral fat cells are prob-
of particular importance because of their
ionship to the portal circulation. The break-
n products of lipolysis from these adipocytes
directly into the portal circulation and can
se the liver to high concentrations of free
acids.[4] Exposure of the liver to excessive
fatty acids can cause hypertriglyceride-
.[27]

Diabetes Mellitus

besity has long been associated with an
eased risk of noninsulin-dependent diabetes mellitus (NIDDM).[23, 43, 46, 62] There is now evidence that much of the risk of diabetes is related to regional differences in fat deposition, especially to central obesity.[12, 20, 30, 39] Kissebah placed the risk of diabetes and general obesity at 3.17 but noted that in patients with a typical android distribution of fat, the risk increased to 10.34.[29] Obese men have a higher risk of developing diabetes than do obese women,[63] and women with central obesity have a similarly increased risk for developing diabetes as do men, with both groups carrying an increased risk over women with a more typical gynecoid obesity.[20, 33] It has been estimated that a woman with typical peripheral obesity can support 20 to 30 kilograms of additional weight before reaching the same relative risk as a patient with central obesity.[33] Central obesity, independent of general obesity, is associated with hyperinsulinemia[45] and glucose intolerance[34] and has also been linked to decreased hepatic insulin extraction,[13] decreased peripheral sensitivity to insulin, and decreased peripheral responsiveness to insulin.[34]

Cardiovascular Disease

Cardiovascular disease (CVD), its risk factors, and cardiovascular mortality are strongly linked to obesity.[19, 22] There is now significant evidence suggesting that the link is more strongly related to an android deposition of fat rather than to adiposity in general.[9, 37, 40] There appears to be a strong association between central obesity and angina, myocardial infarction, and death.[36] Risk factors for CVD, including abnormalities of serum lipids and serum insulin, elevated fasting glucose, and hypertension are more common in obese men than in obese women.[33] Furthermore, women with abdominal obesity demonstrate a male-risk profile for these cardiovascular risk factors as compared to women with gynecoid obesity.[29, 36] In addition, hypertension, serum cholesterol, and smoking are independently and positively associated with central obesity.[4, 14, 36, 38] Larsson[38] states that as a risk factor central obesity is of the same order of magnitude as other risk factors for CVD, although the risk appears to decrease with advancing age. As a predictor of premature death among middle-aged men, those at highest risk

were men of low body weight but with an elevated WHR.[38] A recent interesting report links increased WHR to abnormalities of specific clotting factors[55] that have been associated with an increased risk of CVD.

Female Cancers

Female cancers, specifically endometrial and ovarian cancer, have been associated with obesity, and central obesity may be a strong predictor for these cancers.[36, 55] Evidence for this is related to the irregular menses and abnormal ovulatory cycles that are found in women with central obesity and in women with these cancers.

Other Health Risks

There is some evidence in support of the increased incidence of stroke in relation to central obesity.[4] Whereas central obesity is a strong predictor of a variety of health risks and is also a predictor for general absenteeism and loss of work, it is not a predictor for a sense of health well being.[38]

Pathogenesis of Health Risks

The exact pathogenesis of the relationship between android obesity and increased health risk remains unclear. The increase in risk seems to relate not to increases in subcutaneous adipose stores, but to intra-abdominal and especially omental fat stores.[28, 52] These visceral fat cells may have their effect because of their intimate relationship to the portal circulation. As mentioned, the liver is directly exposed to the glycerol and free fatty acid breakdown products of visceral adipocytes; therefore, increased intra-abdominal fat stores, with their increased metabolic rate, result in increased exposure of the liver to these breakdown products. It is theorized that the exposure of the liver to excessive free fatty acids may result in hepatic dysfunction. Patients with central obesity have demonstrated decreased insulin extraction by the liver,[13, 28] which can result in an increased insulin load in the posthepatic circulation and in the peripheral circulation. This decreased hepatic sensitivity to insulin is also seen as decreased receptor sensitivity by peripheral adipocytes. This results in hyperinsulinemia and hyperglycemia.[28, 34] These changes are seen not only in the basal state, but also after glucose tolerance tests. These abnormalities reflect the increased risk of diabetes but may also be related to the increased risk of CVD, stroke, and hypertension through increased risk factors for those conditions. There is some recent evidence to suggest that patients with central obesity have reduced fibrinolytic activity, possibly due to increased levels of plasminogen activator inhibitor.

There is growing evidence that these differences in body fat distribution and the various accompanying health risks may be governed by sex hormone balance.[28, 39, 58, 59] Kissebah[28] presents evidence in support of the importance of sex hormones as the primary determinant. He notes that the administration of exogenous testosterone to hypogonadal males and the increases in androgens that accompany the onset of puberty in the male are accompanied by central deposition of fat. He notes that the administration of testosterone to females increases central adipose stores, whereas the administration of estrogen to males increases the number of fat cells in the thighs. He also cites the association of polycystic ovary syndrome in females as associated with an upper body distribution of fat. Females with android obesity respond to ACTH stimulation with the expected increase in cortisol levels but also demonstrate increases in androstenedione and testosterone. Elevated free testosterone levels have been reported to be elevated in women with an increased WHR. The tendency toward deposition of fat in the abdominal stores increases in postmenopausal women, which may reflect changes in androgen/estrogen concentrations associated with menopause.

Surgical Intervention

There are no long-term studies documenting the positive or negative impact of liposuction surgery on patient health. Liposuction surgery removes, at most, 10 to 15% of the adipocyte pool and, in most cases, probably significantly

less than that number. This probably has a negligible impact on overall adipose tissue metabolism.[31, 32] With recent evidence suggesting that new adipocyte formation is possible in adulthood, adipocytes may simply regenerate to replace those that are lost or may redistribute. There has been concern expressed that abdominal liposuction removing subcutaneous adipocytes may result in an increased deposition of intra-abdominal fat cells,[31] thereby potentially increasing the health risks. These are hypothetical considerations only, and further study is clearly necessary to support or refute these theories.

SUMMARY

It is clear that central obesity is a strong predictor of multiple health risks. It appears likely that much of the influence for the preferential deposition of fat in these various stores is related to sex hormones, although other factors clearly play a role, including genetic, environmental, nutritional, and other factors. Whereas a great deal has been discovered about these relationships in the past 10 years, further study is necessary to clarify them and determine what role dietary and surgical interventions may play in the prevention and reversal of those risk factors.

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