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Under the Surface of Subcutaneous Adipose Tissue Biology

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ABSTRACT The global obesity epidemic enhanced contemporary interest in adipose tissue biology. Two structurally and functionally distinct depots, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), are spread throughout the body. Their distribution was recognized to be a major determinant of metabolic risk. Unlike VAT, SAT showed some protective endocrine and inflammatory features that might explain the occurrence of obese but metabolically healthy persons. The unique developmental gene expression signature, angiogenesis, and adipogenic potential of SAT determines its growth ability under the positive energy balance. The overflow hypothesis suggested that when SAT is unable to expand sufficiently, fat overflows towards metabolically adverse ectopic depots. Besides white adipose tissue, recent studies found important brown adipose tissue activity responsible for thermogenesis and energy dissipation in adults as well. SAT is prone to "browning" – the appearance of particular beige adipocytes that contribute to its favorable metabolic effects. Morbid obesity, aging, hormonal status, nutrition, low physical activity, and other environmental factors impair SAT relative resistance to dysfunctional changes and promote development of metabolic disorders. The popular approach considering SAT mainly as the subject of cosmetic procedures for improving the appearance of body contours should be avoided. Complex heterogeneity of obesity revealed that a tissue of an extreme plasticity and rich interactions with vital functions of the body lies under the surface. Therapeutic manipulations to preserve and enhance healthier fat in order to correct obesity-related metabolic disorders seem to be a relevant but still unexplored opportunity.

KEY WORDS: obesity, subcutaneous adipose tissue, visceral adipose tissue, adipogenesis, inflammation, brown adipocytes

INTRODUCTION

The amount and the distribution of adipose tissue are major determinants of body weight and shape. These issues were once approached as just questions of appearance. Liposuction to remove the excess unwanted subcutaneous fat and to make body contours more attractive is still one of the most popular cosmetic surgeries. However, the burden of health risks associated with the global obesity epidemic moved the focus of the contemporary interest in adipose tissue biology towards more essential challenges. What is hiding behind the fat, one of the biggest components of the human body? What are the functions of the only tissue that is capable of such an expansion and contraction throughout life? The scientific pursuit for these answers revealed that a complex tissue of an extreme plasticity and rich interactions with many vital functions of the body lies under the skin (1,2).

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Adipose tissue distribution and metabolic risk

Adipose tissue is distributed throughout the body in distinct depots with no anatomic connections (3). Two major depots, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), were identified. The largest amount of fat, about 80% in normal weight persons, is under the skin, mainly in the gluteal, femoral, and abdominal region (4,5). VAT involves depots surrounding internal organs. Abdominal locations are the omental depot, the mesenteric depot around the intestines, and retroperitoneal fat around the kidney. Epicardial fat is in the mediastinum, perivascular fat lies along blood vessels, and VAT also infiltrates some organs like the liver, skeletal muscles, heart, and pancreas (6).

The significance of adipose tissue distribution in specific depots and their association with metabolic risk was first recognized by the French endocrinologist Jean Vague in 1947. Gynoid obesity, typical for women, was determined to be accumulation of fat in the lower body, preferentially in the gluteofemoral region. Android obesity was determined to be fat accumulation in upper body, mostly in the abdominal and truncal region, predominantly in men and carrying an increased cardiovascular risk (7). Unlike the body mass index (BMI) and the total body fat amount, fat distribution was found to have better discriminatory value in predicting metabolic disorders and to be related to mortality (6). For instance, women usually have higher total body fat proportion and lower cardiometabolic risk than men, but women with abdominal adiposity share similar metabolic complications of obesity with men (8). In the following decades, CT studies specified VAT as the cause of abdominal obesity metabolic risk (9). Statistical adjustments for VAT area abolished gender cardiovascular risk differences (10). VAT was associated with metabolic syndrome even in non-obese people (11). Large prospective population studies discovered an independent association of abdominal obesity with disorders like insulin resistance, dyslipidemia, elevated blood pressure, and cardiovascular risk (12,13).

This negative metabolic impact was primarily derived from the increased ratio of VAT to SAT. However, an inverse perspective with SAT in primary focus led to some less expected outcomes. Population studies observed that the major gluteofemoral SAT depot did not contribute to an adverse metabolic profile but was even associated with protective effects (14,15). The evidence that not every accumulation of fat is harmful pointed to the existence of obese people protected from metabolic complications. Ten to almost 30% of obese persons seem to belong to this obese but metabolically healthy subgroup (16). Prospective analysis showed that this subgroup might have up to 30-50% lower risk of all-cause mortality, non-fatal, and fatal cardiovascular disease than their metabolically unhealthy obese counterparts (17). Moreover, a phenomenon of decreased morbidity and mortality with increasing BMI called the *obesity paradox* was noticed in patients with malignancies, renal failure, or already established cardiovascular diseases like heart failure, coronary artery disease, and hypertension. A debate about this survival benefit is going on, and the functional status of adipose tissue appears to play a main role in these mechanisms. The SAT depot seems to be, up to a certain point, spared from dysfunctional changes, and that might be responsible for its favorable metabolic effects (18-20).

In our attempt to review the comparative features of SAT, we will first focus on white adipose tissue (WAT), and the biologic role of brown adipose tissue (BAT) that emerged in recent years will be reviewed later (1,21).

Metabolic functions of white SAT

The maintenance of the energy storage was previously considered the main function of WAT. Layers of SAT also serve as mechanical and thermal protection like in the calcaneal region (6). Twenty five years ago, gene expression studies suggested that approximately 20% of genes in SAT and even 30% in VAT encode secretory proteins (22). This strong clue for adipose tissue secretory function was followed by the discovery of more than 600 endocrine products called adipokines. Subcutaneous adipocytes are the source for most of the leptin (23), the main signal in the homeostasis of energy, and several neuroendocrine functions. Major differences between SAT and VAT depots appeared in the secretion of inflammation-related adipokines or adipocytokines. In paired samples studies of adipose tissue gene expression, higher quantity of pro-inflammatory adipocytokines like interleukin-6 (IL-6), tumor necrosis factor *α* (TNF*α*), or monocyte chemoattractant protein-1 was typical for VAT (24,25). Adiponectin with anti-inflammatory and insulin-sensitizing properties is released predominantly from SAT (26). The amount of the largest and metabolically very important SAT depot – the gluteofemoral fat – also correlated positively with adiponectin serum levels. Non-obese subjects and subjects without metabolic disorders have higher secretion of adiponectin in SAT and the accumulation of visceral fat was associated with lowering of adiponectin and occurrence of metabolic disorders (9). Some intervention studies have shown that this

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process could be reversed. SAT adiponectin gene expression increased and the expression of inflammation-related genes was reduced by physical exercise and weight loss either by a hypocaloric diet or after bariatric surgery (27,28). The prevailing spectrum of adipocytokines in a particular depot determines its influence on the inflammatory balance and insulin resistance of the circulatory milieu. These functional differences between VAT and SAT led to the concept of their antagonistic metabolic role and introduced SAT as a possible protective endocrine organ.

The functional heterogeneity of adipose tissue depots reflects their complex structure (8). Adipocytes constitute only about one third of adipose tissue, and the rest is built from various cells of the stromovascular department: preadipocytes, endothelial cells, smooth muscle cells, fibroblasts, and inflammatory cells like macrophages and other leucocytes (6). More than 90% of adipokine release is produced by non-fat cells (29).

Inflammation and adipose tissue

Upregulation of proinflammatory genes typical for macrophages in obesity revealed that they are the most abundant and functionally dominant type of immune cells accumulated during adipose tissue expansion. Several possible inflammatory triggers involved in this process were proposed. Growth of adipose tissue might not be followed by adequate angiogenesis, and local hypoxia might cause adipocyte apoptosis and necrosis. Obese adipocytes release higher amounts of free fatty acids and proinflammatory adipocytokines but less adiponectin (30-33). In response to these signals, a basic inflammatory mechanism is initiated with the activation of monocytes, their migration, and recruitment of macrophages. Macrophages further support inflammation with release of pro-inflammatory adipocytokines. This state of chronic low grade inflammation and impaired insulin sensitivity leads to a *vicious circle* of adipose tissue dysfunction (34).

Only about 5% of macrophages are dispersed among adipose tissue cells of thin persons. In persons with obesity, macrophages form crown-like structures that surround apoptotic or necrotic adipocytes and their proportion rises up to 50% (35). The quantity of macrophages varies according to the adipose tissue depot. It is higher in VAT than SAT, and this difference exists in both lean and obese persons (33). SAT is infiltrated by macrophages at a lower rate than VAT in obese persons (36). The heterogeneity of macrophages in adipose tissue depots is a further point of differentiation. Obesity induces a switch in macrophage polarization (37). Alternatively activated M2 macrophages release anti-inflammatory cytokines like IL-10 and contribute to tissue homeostasis and repair (38). Classic pro-inflammatory M1 macrophages are recruited and differentiated from CCR2+ blood monocytes. They release inflammatory cytokines such as interleukin-1β, IL-6, and TNFα, sustain the state of chronic low-grade inflammation, and impair insulin signaling. M1 macrophages rise with obesity, especially in VAT, and decrease after bariatric surgery. M2 macrophages are found predominantly in the fat of lean individuals. They are more abundant in SAT and rise after weight loss (33). This balance of M1/M2 macrophages has a major role in the metabolic impact of different adipose tissue depots. M2 macrophages counter adverse metabolic actions of M1 cells (39). They are also involved with preadipocyte differentiation, adipogenesis, and angiogenesis necessary for the expansion of SAT, preventing ectopic fat tissue accumulation and contributing to the protective role of SAT (40,41). Adiponectin from healthy adipocytes and activation of peroxisome proliferator-activated receptors (PPAR) were shown to promote macrophage polarization toward this phenotype (38).

Besides the innate immunity, adaptive immune mechanisms are also involved in adipose tissue (42). CD8+ T-cell infiltration of VAT in obesity happens at the early stages of inflammation in obesity. CD4+ helper lymphocytes in persons with obesity are also induced towards the pro-inflammatory Th1 phenotype. These events are considered to precede and mediate macrophage infiltration and macrophage M1 polarization (43). In obese metabolically abnormal subjects, inflammatory changes were also involved in the skewing of naive subcutaneous adipose CD4+ T-cells toward a Th17 phenotype that produce IL-17 and IL-22 and interefere with insulin sensitivity (44). Anti-inflammatory phenotype lymphocytes CD4+ T reg and CD4+ Th2 are simultaneously decreased in obesity and were found to be predominant in adipose tissue of lean subjects. Their signals such as IL-10 inhibit macrophage migration, induce M2 macrophages polarization, and are inversely associated with insulin resistance (45,46). The flow-cytometry comparison of T-cell subsets in different fat depots showed that pro-inflammatory phenotypes of lymphocytes were less frequent, and anti-inflammatory lymphocytes were more frequent in SAT than in VAT. T-cell profiles also correlated between SAT and VAT with systemic markers of inflammation and insulin resistance, which indicated their potential role as a mediator between obesity and its complications (46).

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The expansion of adipose tissue

Unlike other non-tumor tissues, the particular feature of adipose tissue is its ability of expansion throughout adult life. Some adipose tissue depots expand more than others. The predominant expansion of SAT or VAT depends on their particular angiogenic and adipogenic potential (1).

This expansion occurs through close interaction of adipocyte precursors and stromovascular cells. Adipose tissue is highly vascularized, and angiogenesis was determined to be fundamental for adipogenesis. *In vitro* models showed that capillary network growth precedes adipose tissue development and endothelial cells contribute to stimulation of preadipocyte differentiation (47,48). SAT has a higher capillary density and higher capacity to expand its capillary network than VAT. Gene array analyses also revealed significant differences in the expression of angiogenic genes between depots, especially an increased subcutaneous expression of angiopoietin-like protein 4 that corresponds to its higher proangiogenic potential (1).

Preadipocyte capacities for proliferation are a further contributor to different adipose depot expansion. The proportion of preadipocytes varies in different fat depots from 10 to almost 50%. The proportions of preadipocyte subtypes with different proliferative capacities are also different (4,49,50). In direct comparison, abdominal subcutaneous preadipocytes had the highest capacity to replicate and differentiate, while mesenteric preadipocytes had an intermediate capacity, and omental cells had the lowest (34). Replication and differentiation of preadipocytes leads to hyperplastic adipose tissue expansion: the number of adipocytes increases and they remain smaller. When expansion occurs through enlargement of adipocytes, adipogenesis is hypertrophic and adipose tissue is built of a smaller number of large cells (51). The predominant type of adipogenesis determines the size and the number of fat cells in different depots and contributes to individual predisposition to obesity-related metabolic disorders. Femoral fat as the major SAT depot is expanded largely by hyperplastic adipogenesis. Subjects with greater leg fat mass also had smaller abdominal subcutaneous adipocytes and a more favorable metabolic profile. Smaller size and increased number of subcutaneous adipocytes is associated with a favorable metabolic profile, and the presence of hypertrophic adipocytes is strongly related to metabolic disorders even independently of obesity (51,52). The reduction in subcutaneous adipocyte volume following bariatric surgery improved insulin sensitivity more than reductions in fat mass. Adipocytes are the only cells whose size may carry such a physiological change (53,54). Larger adipocytes shift towards dysfunctional metabolic activity, and smaller adipocytes have a lower lipolytic rate and produce less adverse proinflammatory adipocytokines but larger amounts of adiponectin (55). The role of adiponectin in this context may be viewed as a kind of cell hunger signal, and from the moment that adipocyte is satiated and overfilled, it switches to an opposite pro-inflammatory program. Adiponectin is crucial for adipose tissue expansion and its dominant subcutaneous secretion corresponds with the adipogenic potential of this depot (56,57).

The overflow hypothesis

A paradigm of the dysfunctional, overfilled adipocyte could be transferred to the expansion of the whole adipose tissue as well. That was proposed by the overflow or the expandability hypothesis. It presumes that the inability of SAT to expand sufficiently under the positive energy balance results in the overflowing of fat towards ectopic locations like the abdomen, liver, skeletal muscles, around the heart, and blood vessels. The expansion of ectopic adipose tissue depots is not only a passive storage of energy surplus but an active process of leaving metabolically favorable SAT depots, and results in adverse metabolic consequences (57).

Implications of the overflow hypothesis are visible in several practical examples. Gluteofemoral adipose tissue in women has been shown to provide both safe fat storage and systemic metabolic regulation (8). The favorable impact of these SAT depots was recognized in gynoid obesity, PPARγ agonist use, and in multiple symmetric lipomatosis. Conversely, extreme SAT deficit in lipodystrophies was associated with ectopic fat accumulation and severe insulin resistance (58). Two different surgical treatments of obesity have opposite effects on body fat redistribution and metabolic risk. After suction lipectomy in the tight region in non-obese women, fat re-accumulated preferentially in the ectopic abdominal region (59). Following bariatric surgery, a preferential mobilization of visceral fat occurred, as compared with total and SAT (60,61). These examples show why inhibiting adipogenesis is not the solution for metabolic complications of obesity. In the context of preventing re-gaining lost weight, the clue for avoiding metabolic disorders might be found in the options for retaining adipose tissue accumulation in favorable subcutaneous reservoirs and not ectopic depots (57).

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Genetic factors

Adipose tissue distribution has a strong genetic component. Recent genome-wide association studies revealed evidence of many genes and SNP that are significantly associated with waist-hip ratio or other measurements of visceral or subcutaneous fat amounts (62). Waist-hip ratio as a parameter that differentiates gluteofemoral from a central distribution pattern was estimated to have up to 61% heritable variation independent of BMI (63). When changes in the amount of adipose tissue occur, its accumulation also follows a specific individual pattern with preferential subcutaneous or visceral depot expansion which is also largely determined by their heritable potential (1). Genetic background of adipose tissue distribution is recognized in some extreme examples of fat disorders like familial multiple lipomatosis or steatopygia. Several gene mutations were also found to be the cause of different congenital lipodystrophies.

When genome-wide transcriptional analysis was applied in comparisons of SAT and VAT, hundreds of genes were found to be differently expressed. Particularly distinguished is a family of the developmental genes like Shox2, Tbx15, and several genes from the homeobox group: HoxA5, HoxC8, HoxC9 (62,64). Further analysis also extended differences between abdominal and gluteal depots of SAT, and HoxC13 is an example of the HOX gene exclusively expressed in the gluteal depot (65). Studies have shown that the unique gene expression signature in adipocytes from different depots remains after numerous *in vitro* replication cycles, suggesting that their distinct metabolic phenotype seems to be developmentally programmed. This might also sustain the relative resistance of SAT to inflammatory and other dysfunctional impairments (62,66). The involvement of developmental genes might also reflect the origin of adipose tissue depots from different mesodermal regions (62). Recent ontogenic studies suggested that VAT depots derive from mesothelial Wt1-expressing cells and differ from SAT and BAT that have no Wt1-positive source in their origin (67). However, developmental biology is still an area with lot of unanswered questions, such as whether the embrionic origin of abdominal and gluteofemoral SAT depots also differs (68).

Brown and beige adipose tissue

Brown adipose tissue is a second type of adipose tissue, different from white tissue and also present in all mammals. They differ in their color and morphology but especially in their physiological role. WAT is used for energy storage, and BAT is responsible for the opposite – the expenditure of energy. It uses stored lipids in the process of thermogenesis and dissipates energy in the form of heat. Significant amounts of BAT are found in human neonates, especially in the deep cervical, supraclavicular, interscapular, and paravertebral regions, along big vessels, and near the pancreas, adrenals, and kidneys (69). The color of mature brown adipocytes derives from the large number of big mitochondria with high expression of the uncoupling protein-1 (UCP-1). UCP-1 is a distinctive marker because other histological features such as multilocular lipid droplets and the smaller size of brown adipocytes may be attenuated when BAT is not stimulated or when WAT is subjected to fasting. A dense network of capillaries and noradrenergic sympathetic nerves is also present (3). BAT pads almost disappear until adulthood, and it was therefore assumed that BAT loses its physiologic relevance at that age. However, in 2009 several study groups reported that scanning by 18F-FDG PET/CT captures the presence of BAT functional activity in adult humans. These depots were confirmed in the anterior neck and supraclavicular region, extending sometimes to the thorax (70). Samples of neck adipose tissue taken during thyroid surgery revealed distinct islands of UCP1 positive cells accounting for up to one third of all adipocytes in subjects that were younger and leaner (71). Outdoor temperature was one of the predictive factors for detection of BAT and it was found in almost 96% of young and healthy men exposed to cold (72). Higher BAT activity was observed in women, and it inversely correlated with BMI or percentage of adipose tissue (70).

Studies of adipocyte differentiation shed a new light on the discovery of BAT in adult humans. Adipocytes share mesenchymal stem cells as common precursors with myocytes, chondrocytes, and osteocytes, but a further process of differentiation into white or brown adipocytes splits into different cell lineages. Brown adipocytes derive from the myogenic factor 5 (myf5) expressing lineage, just as skeletal muscle cells and white adipocytes differentiate predominantly from myf5-negative progenitors (73). However, the newly rediscovered brown adipocytes do not share the same precursor with the classic brown adipocytes but seem to derive from the same cell lineage as white adipocytes. They are considered a new intermediary type, different from white and classic brown cells but capable of expressing UCP1 and called beige or brite adipocytes. Although the expression of UCP-1 in unstimulated beige adipocytes is close to that of white, beige adipocytes have the same capacity for thermogenesis as classic brown cells when activated.

They are dispersed in WAT depots and represent the majority of brown activity in human adults (74,75).

The process of beige adipocyte appearance or the so-called "browning of WAT" demonstrate the high plasticity of adipose tissue. Two options for the origin of beige adipocytes were proposed: the development by transdifferentiation from pre-existing white adipocytes or stemming from adipocyte precursors (76,77). Nearly 40% of preadipocytes in SAT were shown to be able to differentiate in UCP1-expressing beige adipocytes upon stimulation. Their amount and differentiation stage affects the browning of different adipose tissue depots and it seems that this process preferentially occurs in SAT over VAT (74). In VAT, brown adipogenic differentiation was determined only in extreme conditions of chronic adrenergic stimulation caused by pheocromocytoma and paraganglioma but it was unsuccessful in overcoming detrimental metabolic effects (78). VAT accumulation during prolonged glucocorticoid use was associated with the suppression of the browning process through transcriptional regulation of microRNA-27b expression that targets the coregulatory protein Prdm16 (79). Adipocyte-specific deletion of Prdm16 in animals induced a loss of beige adipocyte function and their SAT acquired properties of VAT, and severe insulin resistance developed. Prdm16 and the presence of beige adipocytes might be an important distinction between SAT and VAT and the browning process crucial for benign metabolic impact of SAT (80).

Functional dynamics and heterogeneity of SAT

While SAT often stays on the bright side of metabolic homeostasis, it is also subject to changes that contribute to the development of metabolic disorders. In morbid obesity, SAT angiogenesis decreased and this impairment correlated with insulin resistance (1). In an experimental overfeeding study, the smaller and not the larger adipocytes promoted ectopic fat accumulation and were associated with a worsened metabolic response to weight gain (81). The adipogenic capacity of preadipocytes was lower in subcutaneous than in omental adipose tissue with aging which explained the preferential expansion of omental fat in older persons (34,82). The lack of estrogens after menopause inhibits the expandability of the subcutaneous depot and enhances the same process of the visceral depot (83). Developmental gene expression signatures specific for different adipose tissue depots were also exposed to changes through epigenetic DNA methylation (84).

This evidence supports the claim that severe obesity, ageing, changes in hormonal status, nutrition, low physical activity, and other environmental factors affect the local microenvironment and subsequently attenuate functional differences between SAT and VAT (6,85). The most indicative is the example of upper-body fat accumulation where SAT and VAT are anatomically the closest. The measurement of waist circumference revealed abdominal and particularly VAT as a major cardiometabolic risk factors. More recent studies also found that neck circumference is associated with the same risks even after adjustment for VAT and BMI. Taking into account that neck circumference is determined primarily by neck SAT, it is supposed to be representative of upper-body SAT. As a large pathogenic depot, upper body SAT might explain the missing residual cardiometabolic risk that remains beyond that brought by VAT (86). The pathophysiologic background of this presumption was supported by the specific upper-body SAT secretory profile. It is a major source of systemic FFA, larger than the VAT depot and the lower-body SAT (87). Although interstitial concentration of adiponectin did not differ between abdominal and femoral SAT, abdominal SAT rather than VAT was inversely associated with serum adiponectin levels in a population study while tight SAT remained positively associated with it (68,88).

An even broader perspective emerged when SAT was subdivided into the superficial and deep layer. This separation by superficial fascia in some regions seems to be not only anatomic but also functional (50). Superficial and deep abdominal SAT amounts show variation by sex: 65% of abdominal fat in men and about 50% in women are located in the deep layer (89). Differential gene expression analysis suggested important heterogeneity among layers: just like VAT, deep abdominal SAT was shown to have overexpression of inflammatory genes and a higher number of macrophages than superficial SAT (90). Deep abdominal SAT is also strongly related to insulin resistance. Superficial abdominal SAT had a weak association with insulin sensitivity but a firm association with plasma leptin and followed the pattern observed for thigh SAT (91).

Inconsistencies that remain in the characterization of SAT might be avoided by independent investigations of its depots that should be subdivided both vertically (upper and lower) and longitudinally (superficial and deep). More data would be needed to decipher the complex heterogeneity of adipose tissue and examine the hypothesis that some compartments might have their own even more specific developmental, structural, and functional features such as distinct mini-organs (92).

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Future landscape of adipose tissue derived treatments

Autologue fat grafts have been used with variable success in reconstructive and aesthetic surgery, and these procedures are expected to advance with growing knowledge about adipose tissue (93). Recent research in regenerative medicine acknowledged adipose tissue as a rich source of multipotent adipose stem cells that is easily available through liposuction. Adipose stem cells are able to differentiate in at least myogenic, osteogenic, chondrogenic, adipogenic, and neurogenic lineages and have a great perspective for use in tissue engineering (94).

The opportunities perceived in adipose tissue complexity and its unique plasticity suggested the use of adipose tissue manipulations for correcting obesity related metabolic disorders (95,96). Thiazolidinediones such as pioglitazone are the drugs with beneficial antidiabetic action that has been determined to take effect while increasing the amount of SAT. Several novel concepts were considered. The most basic would be activation of BAT in order to increase thermogenesis, reverse the energy balance towards dissipation, and attenuate insulin resistance and inflammation. Further options envisaged taking advantage of adipose tissue plasticity by induction of white adipose tissue browning. This process has a favorable metabolic impact from direct BAT effects but also from functionally complementing white SAT. White adipose tissue browning was induced by cold exposure, exercise, sympathetic stimulation, triiodthyronine, thiazolidinediones, cardiac natriuretic peptides, bone morphogenetic protein 8b, and fibroblast growth factor 21 and might have therapeutic potential (97,98). Another option for cell-based therapy would also be the transplantation of healthy adipose tissue or adipocyte progenitors that were programmed for overexpression of beneficial adpokines or brown activity (96). Metabolically beneficial adipose tissue enhancement is a common idea shared by all those possible therapeutic approaches.

CONCLUSION

Recognizing a particular subgroup of severely obese but metabolically normal persons was a critical shift towards awareness of the complex heterogeneity of obesity (36). Although it is a minority of less than 30%, the distinction of these obese persons gains significance when considered in the context of the worldwide obesity epidemic (16). The possible existence of this *fat and fit phenotype* might be a risky message when it is still undetermined whether it is only a transient or a truly healthy state. However, our awareness about it is important because they do not seem to actually benefit from standard interventions like diet, drugs, or surgery (99).

Under the surface of heterogeneous obesity, there appeared structural and functional variances of SAT and VAT depots. They differ in adipogenesis, angiogenesis, endocrine and inflammatory features, and lipid and energy metabolism. Besides the evident genetic and developmental specificities, they are also subject to various dysfunctional changes caused by aging and environment (84). Avoiding fat overflowing to adverse ectopic depots and efficient energy storage in a metabolically favorable SAT depot as in the gluteofemoral region seems to be a crucial approach for the preservation of metabolic health.

Taking into account intrinsic and environmental predispositions to obesity, the actual success rate of obesity treatments is relatively modest. Current perspectives shift between elusive behavioral interventions, insufficient drug efficacy and safety, and surgical interventions such as plastic or bariatric procedures (95,96). However, achievable solutions are certainly possible. Since recent population data suggested that inactivity is more risky than obesity itself (100), we might recall the beneficial role and the possible browning effect of exercise on SAT. The therapeutic strategy based on SAT plasticity and enhancing the healthier fat still remains an unexplored opportunity.

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