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**Benefits of healthy adipose tissue in the treatment of diabetes**

Gunawardana SC. Adipose tissue related therapies for diabetes

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**Abstract**

The major malfunction in diabetes mellitus is severe perturbation of glucose homeostasis caused by deficiency of insulin. Insulin deficiency is either absolute due to destruction or failure of pancreatic β cells, or relative due to decreased sensitivity of peripheral tissues to insulin. The primary lesion being related to insulin, treatments for diabetes focus on insulin replacement and/or increasing sensitivity to insulin. These therapies have their own limitations and complications, some of which can be life-threatening. For example, exogenous insulin administration can lead to fatal hypoglycemic episodes; islet/pancreas transplantation requires life-long immunosuppressive therapy; and anti-diabetic drugs have dangerous side effects including edema, heart failure and lactic acidosis. Thus the need remains for better safer long term treatments for diabetes. The ultimate goal in treating diabetes is to re-establish glucose homeostasis, preferably through endogenously generated hormones. Recent studies increasingly show that extra-pancreatic hormones, particularly those arising from adipose tissue, can compensate for insulin, or entirely replace the function of insulin under appropriate circumstances. Adipose tissue is a versatile endocrine organ that secretes a variety of hormones with far-reaching effects on overall metabolism. While unhealthy adipose tissue can exacerbate diabetes through limiting circulation and secreting of pro-inflammatory cytokines, healthy uninflamed adipose tissue secretes beneficial adipokines with hypoglycemic and anti-inflammatory properties, which can complement and/or compensate for the function of insulin. Administration of specific adipokines is known to alleviate both type 1 and 2 diabetes, and leptin mono-therapy is reported to reverse type 1 diabetes independent of insulin. Although specific adipokines may correct diabetes, administration of individual adipokines still carries risks similar to those of insulin monotherapy. Thus a better approach is to achieve glucose homeostasis with endogenously-generated adipokines through transplantation or regeneration of healthy adipose tissue. Our recent studies on mouse models show that type 1 diabetes can be reversed without insulin through subcutaneous transplantation of embryonic brown adipose tissue, which leads to replenishment of recipients’ white adipose tissue; increase of a number of beneficial adipokines; and fast and long-lasting euglycemia. Insulin-independent glucose homeostasis is established through a combination of endogenously generated hormones arising from the transplant and/or newly-replenished white adipose tissue. Transplantation of healthy white adipose tissue is reported to alleviate type 2 diabetes in rodent models on several occasions, and increasing the content of endogenous brown adipose tissue is known to combat obesity and type 2 diabetes in both humans and animal models. While the underlying mechanisms are not fully documented, the beneficial effects of healthy adipose tissue in improving metabolism are increasingly reported, and are worthy of attention as a powerful tool in combating metabolic disease.

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**Key words:** Adipose tissue; Diabetes; Insulin-independent; Transplantation; Subcutaneous; Adipokines; Metabolic disease

**Core tip:** Diabetes mellitus is characterized by perturbation of glucose homeostasis due to insulin deficiency, either absolute or relative. Traditional treatments over the past century have focused on insulin replacement and/or enhancing insulin sensitivity. Ultimate goal in treating diabetes is to re-establish glucose regulation. Recent studies increasingly show the ability of extra-pancreatic hormones, particularly of adipose tissue origin, to compensate for insulin. Adipose tissue is a versatile endocrine organ which, under appropriate circumstances, can exert numerous metabolic benefits and may maintain glucose regulation entirely independent of endocrine pancreas. This review discusses such alternative therapies based on beneficial effects of healthy adipose tissue.

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**INTRODUCTION**

Diabetes is one of the most serious and widespread metabolic diseases today, affecting 10%-15% of the United States population and 371 million people worldwide. The major characteristics of diabetes mellitus include defects in insulin secretion at the pancreatic β cell level, and defects in insulin sensitivity at the peripheral tissue level. Depending on which of these defects is primary, diabetes is broadly classified into types 1 and 2. Type 1 diabetes (T1D) is associated with absolute deficiency of insulin due to auto-immune mediated destruction of pancreatic β cells, while type 2 diabetes (T2D) results in relative or functional insulin deficiency due to gradually progressing resistance to insulin in peripheral tissues. Such resistance leads to initial compensatory hyperinsulinemia and overexertion of β cells, which may progress into absolute insulin deficiency through eventual β cell failure. T1D accounts for 5% of cases, affecting over 2 million Americans and 11-22 million people worldwide, with 78000 new cases diagnosed each year. Characterized by absolute deficiency of insulin resulting in severe hyperglycemia, T1D is fatal if untreated. Available therapies for diabetes, directed at insulin replacement and/or improving insulin sensitivity in peripheral tissues, have various limitations, some of which could be life-threatening. Recent studies demonstrate the ability of healthy adipose tissue to complement or compensate for the function of endocrine pancreas, independent of insulin. Adipose tissue related therapies show promise in overcoming many of the limitations/complications associated with traditional treatments for diabetes.

**AVAILABLE THERAPIES**

Both type 1 and 2 diabetes are associated with β cell failure due to different mechanisms. Insulin replacement is necessary in all cases of T1D and many cases of T2D. Treatments for T1D primarily focus on insulin replacement, either directly or through transplantation of insulin-secreting tissue such as pancreas or pancreatic islets. Whole pancreas transplantation is currently the most successful means available for achieving long-term insulin independence for T1D patients, and is also helpful in specific cases of T2D associated with significant insulin deficiency[1-3].

Traditional insulin replacement therapies, either direct or through islet/pancreas transplantation, have certain limitations. Direct insulin replacement does not cure the disease and requires repeated administration. A major concern with administration of exogenous insulin is possible overdose, requiring precise monitoring of dosage and blood glucose to avoid fatal hypoglycemic episodes. Whole pancreas transplantation, when successful, provides insulin independence for many years. However it is an invasive surgical procedure not to be undertaken lightly, and carries the risks and complications associated with any major surgery[1,4-7]. Islet transplantation, although a safer and less invasive procedure, is limited by low success rate in the long term due to apoptosis, rejection or poor vascularization of islets. Other concerns include the necessity of large numbers of donor islets and specific complications associated with portal vein cannulation such as portal vein thrombosis and portal hypertension[6-12]. The need for life-long immune-suppressive therapy is also a concern with both islet and pancreas transplantation. Thus, the need remains for better therapies aimed at establishing long-term glucose regulation with fewer complications.

Xenotransplantation of porcine and non-human primate islets has been proposed as a means to overcome the limitations in availability and preservation of human islets. A major challenge with xenotransplantation is hyperactive rejection. Methods proposed to circumvent this problem include encapsulation of islets, and local immunosuppression through genetic manipulation. While long-term graft survival and insulin independence have not yet been achieved, early studies show great potential[13-15]. Recent advances on insulin replacement include generation of insulin-producing cells from embryonic stem cells; transdifferentiation, *i.e.*, generation of endogenous β-cells from non-β-cells using transcription factors that govern pancreatic development; and engineering endogenous surrogate β-cells by tissue-specific insulin gene delivery[15-17]. Stem cell therapy is promising, except for some limitations such as the inability to generate adequate numbers of insulin-producing cells, generation of unnecessary cell types, and harmful side effects such as teratoma formation. In addition to replacing or regenerating insulin-producing cells, another intriguing potential in stem cell therapy is to prevent further destruction of beta cells by appropriately controlling the autoimmune response. Recent studies describe the potential of stem cell educator therapy for reversal of T1D[18-20]. Human cord blood-derived multipotent stem cells modulate autoimmune responses through altering regulatory T cells and human islet β-cell-specific T cell clones. While suspending the immune response results in significant improvements of glucose regulation, insulin dependence remains an ongoing concern.

Management of T2D includes various agents that improve insulin sensitivity in peripheral tissues, in combination with agents that increase insulin secretion at β cell level. With advancing β cell failure, these treatments have to be combined with insulin replacement or even pancreas transplantation[21-23]. Drugs that improve peripheral insulin resistance include thiazolidendiones and biguanides. While effective in improving insulin sensitivity at varying degrees, these drugs are limited by a number of dangerous side effects including edema, hypertension, heart failure, bone fractures, lactic acidosis and cognitive impairment[21-26]. Complementary strategies include alpha-glucosidase inhibitors which reduce blood glucose by preventing digestion and absorption at gut level. Drugs that increase insulin secretion at β cell level such as sulfonylureas and meglitinides have the same risk of hypoglycemia unawareness as insulin therapy. With progressive β cell failure in T2D the effectiveness of these drugs eventually decreases[23].

A common limitation among all aforementionedapproaches is the ongoing need for insulin, and the difficulty of maintaining physiologically appropriate levels and function of insulin after exogenous delivery or endogenous production following different treatments. Studies in the past decade point to the intriguing possibility of insulin-independent glycemic regulation. Although insulin is the major physiological regulator of glucose, numerous extra-pancreatic hormones also exert a powerful influence on glucose homeostasis. Such hormones primarily originate from the gut and adipose tissue[27,28]. While many of these hormones enhance insulin function, some have glucose-lowering actions entirely independent of insulin.

Glucagon-like peptide-1 (GLP-1) is an incretin secreted from entero-endocrine cells in response to food intake. In addition to glucose-dependent augmentation of insulin secretion, GLP-1 has a variety of beneficial effects throughout the body[28-33]. These include insulin-independent effects on glucose metabolism such as direct suppression of glucagon, decrease of hepatic glucose output, decreased absorption via delayed gastric emptying and increased glucose uptake by muscle. GLP-1 is also reported to decrease inflammation[29,33,34], decrease cardiovascular risk factors in human patients[35-37], and promote insulin-independent glucose uptake into brown adipose tissue (BAT) in mouse studies[38]. Due to their hypoglycemic effects, analogs of GLP-1 and inhibitors of DPP-4 (enzyme that metabolizes GLP-1) are now widely used as therapeutic agents for T2D[28,29,39-42]. Direct administration of GLP-1 produces acute hypoglycemia and suppression of glucagon in T1D as well[43,44], and GLP-1’s anti-inflammatory effects are believed to be potentially therapeutic in correcting insulitis and enhancing beta cell regeneration in T1D[45]. Despite these beneficial effects, incretin therapy also involves risks such as fatal pancreatitis[46,47].

**DIABETES AND ADIPOSE TISSUE**

 Adipose tissue, believed to be merely a storage organ in the past century, is now widely known for its far-reaching metabolic and endocrine functions. Adipose tissue is classified into white and brown fat based on their morphology, embryonic origin and basic function. White adipose tissue (WAT), the large energy reserve distributed all over the body, stores and accumulates fat, whereas brown adipose tissue (BAT) localized into a few small depots, metabolizes fat, generates heat and increases overall metabolism. WAT and BAT have distinct embryologic origins and appear at different stages of development. While WAT is believed to originate from mesodermal stem cells, BAT originates from dermatomyotomal precursor cells in common with skeletal muscle, and has an interchangeable developmental relationship with skeletal muscle rather than WAT[48-50]. Due to its function in energy metabolism, BAT is highly vascularized and innervated compared to WAT, giving it the characteristic “brown” appearance. Brown adipocytes contain small multilocular lipid droplets as opposed to the large unilocular droplets found in white adipocytes.

WAT is broadly classified into subcutaneous and visceral fat depots which are then further subdivided according to their specific location[51,52].Healthy WAT is a versatile endocrine organ that secretes a range of hormones which influence physiological functions at all levels, including nutrient metabolism, satiety signaling, immune/inflammatory response, and angiogenesis[27,52-55].The major adipokines of importance in metabolic homeostasis are adiponectin and leptin. Adiponectin, well known for its insulin-sensitizing effects on peripheral tissues, is secreted from WAT in micromolar quantities and acts on several receptors such as AdipoR1, AdipoR2, and T-cadherin, enhancing AMPK and the PPARα pathway in the liver and skeletal muscle. Adiponectin levels are inversely proportionate to insulin resistance, obesity and diabetes. In addition to insulin sensitization, adiponectin directly increases fatty acid oxidation; inhibits gluconeogenesis; enhances glucose uptake into adipocytes; and exerts anti-inflammatory and anti-atherosclerotic effects, which collectively enhance overall health[27,55-62]. Leptin, long known for its central effects on decreasing appetite and food intake, also increases fat oxidation in many peripheral tissues including liver, adipose tissue and skeletal muscle. Obesity is associated with increased leptin levels and resistance to leptin action, whereas enhanced sensitivity to leptin results in leanness and protection from diet-induced obesity. Non-metabolic effects of leptin include enhancing immune response, pro and anti-inflammatory effects, and angiogenesis[27,53-55,63]. Numerous other hormones of WAT origin, including but not limited to angiopoietin like proteins, apelin, insulin-like growth factor-1 (IGF-1) and visfatin, also have direct or indirect effects on glucose homeostasis through influencing functions such as insulin sensitivity, insulin secretion at beta cell level, glucose uptake in peripheral tissues, lipogenesis/lipolysis, and inflammation[27, 52-55,64-68].

Under normal healthy conditions, these extra-pancreatic hormones actively complement endocrine pancreas in overall glucose regulation. However, WAT can exert a beneficial influence only as long as it remains healthy and un-inflamed. Inflammation results in conversion of WAT from a beneficial to harmful organ, which then secrets increasing amounts of hyperglycemic adipokines such as resistin and retinol binding protein 4 (RPB4), and pro-inflammatory cytokines such as tumor necrosis factor apha (TNFα) and interleukeins 1 and 6[54,55, 69-73]. Such compounds increase inflammation and exacerbate hyperglycemia, leading to a vicious cycle of insulin resistance and T2D. While obesity is generally associated with adipose tissue deregulation, recent studies show that it is the metabolic dysfunction of adipose tissue which primarily leads to insulin resistance, regardless of the presence of obesity[70]. Such metabolic dysfunction is also associated with decreased sensitivity to leptin and resultant hyperleptinemia. Although leptin generally improves metabolism and leanness, pro-inflammaotopry properties of leptin would lead to further perturbation of adipose tissue function. One of the primary functions of insulin is lipogenesis and maintenance of adipose tissue. Absence of adequate amounts of insulin results in lipolysis and necrosis of adipocytes. In T1D absolute insulin deficiency results in extensive loss of adipose tissue. Even though T2D tends to be associated with obesity, the adipose tissue in T2D patients is unhealthy, and inflamed with extensive cell death and macrophage infiltration[69-73]. T1D is also characterized by generalized inflammation particularly affecting adipose tissue[74,75]. Thus diabetes is associated with progressive dysfunction of adipose tissue.

Considering the strong correlation between adipose tissue inflammation and metabolic disease, maintaining adipose tissue in a healthy state is critical in preventing metabolic disease, and decreasing inflammation is a promising approach to improve and correct such disorders. A major mechanism of insulin-sensitizing agents such as thazolidenediones is to reduce inflammation in adipose tissue[76-78]. When human T1D patients are treated with insulin replacement, either directly or through transplantation of insulin secreting tissue, there is recovery of adipose tissue[79,80]. While it is generally believed that insulin is necessary for the maintenance of adipose tissue, our recent research shows that it is feasible to generate and maintain healthy adipose tissue in the absence of insulin, and that healthy adipose tissue can compensate for the function of endocrine pancreas[81-83]. Transplantation of embryonic brown adipose tissue (BAT) in the subcutaneous space of diabetic mice results in remarkable regeneration of WAT, decrease of WAT inflammation, and reversal of diabetes.

**ADIPOSE TISSUE RELATED THERAPIES FOR T1D**

The ultimate cure for T1D is to establish permanent and long-term physiological glucose homeostasis. Considering the limitations associated with insulin replacement, and the remarkable influence of non-pancreatic hormones on glucose regulation, establishing glucose control without insulin is an intriguing and increasingly plausible solution.

Insulin-independent amelioration of T1D includes mono-therapy with specific hypoglycemic adipokines, first reported in the past decade. There is a strong negative correlation between diabetes and plasma adiponectin levels[53-58]. Adiponectin gene expression and plasma levels are increasingly used as predictors of metabolic disease in human patients[84-88]. Administration of adiponectin *via* gene therapy has been long known to improve metabolism in T2D in swine and rodent studies, and a few reports indicate similar results with T1D as well[89-95]. Adiponectin gene therapy with hydrodynamic injection into streptozotocin-diabetic mice resulted in improved glucose homeostasis[90], while long-term central infusion of recombinant adiponectin in normal and pancreatectomized rats resulted in improved metabolic homeostasis through several mechanisms including increase in insulin sensitivity and fat oxidation, and decreases in visceral adiposity, hepatic glucose output and beta cell death[91]. The ability of leptin to correct T1D independent of insulin is now well-documented. As first demonstrated in 2008 by Yu *et al*[96], hyperleptinemia produced by adenoviral transfer results in long-term reversal of T1D in mice. Leptin is now well known to correct T1D independent of insulin in rodent models, primarily through suppression of the hyperglycemic effects of glucagon[96-99]. In both chemically and genetically induced T1D models, leptin administration can produce long-lasting normoglycemia within days of initiation of therapy.

Mono-therapy with other adipokines is also reported to alleviate T1D. Apelin can alleviate complications of T1D in mice, and prevent loss of beta cell mass and alleviate ER stress, major pathogenic mechanisms of T1D[100,101]. ln human T1D patients IGF-1 is shown to significantly decrease insulin requirement as well as plasma glucose and HbA1c when used as an adjunct to insulin therapy[102]. Incretin therapy, primarily used in T2D, is shown to have significant benefits in T1D as well. Direct administration of GLP-1 produces acute hypoglycemia and suppression of glucagon in human T1D patients[43,45], and the anti-inflammatory effects of GLP-1 and DPP-4 inhibitors are potentially therapeutic in correcting insulitis and enhancing β cell regeneration in T1D in both rodents and humans[103-106].

While these reports demonstrate the remarkable ability of alternate hormones to complement and/or compensate for insulin, mono-therapy with individual hormones still carries the same complications associated with insulin mono-therapy. Another major barrier in its applicability to human patients is administration. Gene therapy and adenoviral transfer, as has been used in rodent studies of successful adiponectin and leptin monotherapy, are not viable options due to adverse effects. In addition, adverse effects associated with large supraphysiological doses of these hormones should be kept in mind, including carcinogenesis as has been reported with leptin[107,108]. In addition to the pro-inflammatory and immunogenic properties of leptin, other potential adverse effects include hypertension and thrombosis, and hypoglycemic risk due to excessive suppression of glucagon[63].

Considering the anti-diabetic properties of the aforementioned adipokines when administered alone, it is predictable that a combination of beneficial adipokines at physiological levels would perform better through additive and/or complementary effects, with fewer adverse reactions caused by supraphysiological doses. The feasibility of such an approach is demonstrated in our recent study, where replenishment of healthy WAT following subcutaneous BAT transplants led to reversal of T1D without insulin[81-83]. Transplantation of embryonic BAT into T1D mouse models, chemically or autoimmune induced, results in fast and long-lasting euglycemia accompanied by weight gain, proliferation of subcutaneous WAT, and remarkable decrease of WAT inflammation. These effects are independent of insulin, as indicated by consistently subnormal levels of plasma insulin and drastically low pancreatic insulin content post-mortem. Reversal of diabetes is associated with significant increases of adipokines including adiponectin, leptin and IGF-1, as well as suppression of glucagon. Thus it appears that glucose homeostasis is achieved through a chronic equilibrium of alternate hormones originating from newly replenished healthy WAT[81-83]. Both the severe loss of WAT and inflammation of WAT associated with T1D are corrected by BAT transplants, presumably due to adipogenic and anti-inflammatory factors arising from the transplant. BAT is long known to protect against inflammation as well as improve metabolism[109,110].

Use of BAT transplants to reverse T1D without insulin is a promising step towards simpler and safer therapies for this serious disease. This approach bypasses the serious limitations associated with traditional insulin replacment therapy, such as hypoglycemia unawareness and the need for invasive surgery and/or immunosuppresive therapy. The subcutanous site is superficial and easily accessible, and can be used for repeated transplants if necessary. Since glycemic regulation is achieved by a physiological combination of endogenously-generated hormones, this approach avoids all limitations in mono-therapy with other hormones as well. In addition to the underlying mechanisms being as yet unknown, the major limitation in this technique is the need for embryonic tissue which is currently not applicable in clinical situations. Work in progress include attempts to reproduce the results with adult adipose tissue transplants with appropriate modifications.

**ADIPOSE TISSUE RELATED THERAPIES FOR T2D**

Metabolic diseases such as insulin resistance, obesity and T2D are characterized by unhealthy adipose tissue, deficient in beneficial adipokines such as adiponectin, and with excess of harmful or inflammatory factors[53-55,69-73]. Recovery from such metabolic disease, through drug therapy, lifestyle changes or surgical intervention, is associated with decrease of inflammation and improved functionality of adipose tissue, including increased secretion of beneficial adipokines[111-118].

Many studies report alleviation of T2D through administration of individual adopokines. Adiponectin gene therapy or hydrodynamic delivery have normalized the metabolic perturbation associated with diet-induced obesity, insulin resistance and T2D in several different animal models including rats, mice and swine[89-95]. In diet-induced diabetic swine, a single injection of purified recombinant human adiponectin resulted in acute decrease of basal blood glucose levels associated with an increase of insulin sensitivity but independent of insulin secretion[89]. Long-term central infusion of recombinant adiponectin in normal rats and pancreatectomized high fat fed rats, a type 2 diabetes (T2D) model, resulted in improved metabolic homeostasis through several different mechanisms, including increase in insulin sensitivity and fat oxidation, and decreases in visceral adiposity, hepatic glucose output and beta cell death[91]. Adiponectin gene therapy is also known to ameliorate hypertension associated with obesity in mouse models[92-94]. While there is promise in adiponectin mono-therapy, so far the glycemic regulation has been either transient or not followed for an adequately long period, and administration remains a problem with clinical applications. Mouse studies show that Angiopoietin like proteins improve glucose and lipid homeostasis and alleviate metabolic disease such as T2D obesity and cardiovascular disease[64,65, 119]. IGF-1 administration resulted in remarkable improvement of glucose regulation and insulin sensitivity in human patients with T2D or T1D, even though this therapy is limited by a number of undesirable side effects[102,120]. Leptin is demonstrated to reverse T1D independent of insulin in rodent models[96-99], and recent reports show promising effects on T2D as well[121-123]. However on short term human trials have not yielded positive results so far[121].

As with T1D, transplantation/regeneration of healthy adipose tissue is a potential approach for correction of T2D, insulin resistance and obesity. Several studies on rodent models show improvement of glucose tolerance following transplantation of healthy WAT, in both normal and diabetic subjects[124-130]. Lipoatrophic diabetes, characterized by hyperglycemia and hyperinsulinemia combined with severe loss of adipose tissue, is corrected by transplantation of WAT from healthy donors in a dose-dependent manner[125]. Subcutaneous transplantation of gonadal fat pads from healthy donors into leptin-deficient obese ob/ob mice resulted in decrease of obesity, normalization non-fasting insulin levels and insulin tolerance, and restoration of fertility in females. The results were long-lasting, and dependent on the age and length of leptin deficiency of recipients, and the dose of WAT transplanted[126]. Transplantation of human WAT into leptin-deficient mice resulted in significant improvements in body weight and hepatic steatosis in a dose-dependent manner, associated with increased plasma levels of donor-origin leptin[127]. The importance of the source of WAT is demonstrated in several studies where the removal of visceral fat and replacement with subcutaneous fat, or transplantation of subcutaneous fat from healthy donors, is shown to alleviate or prevent metabolic dysregulation[128-130]. Intra-abdominal and peritoneal transplantation of epididymal WAT prevented the development of age-induced insulin resistance in rats, while transplantation of visceral adipose tissue from normal healthy donors prevented the spontaneous development of T1D and severe fat loss in BB/OK rats in a sex-dependent manner[129,130].

WAT transplantation, while promising, has not yet been successful in complete reversal of metabolic disease. Possible reasons include the inability of WAT transplants to transform inflamed WAT of recipients to a healthy state, as BAT transplants can. In addition there are ongoing problems with transplant rejection and immune response, and maintenance of adipose tissue grafts may be problematic in T1D where adequate insulin is not available to prevent lipolysis. Considering BAT transplants lead to replenishment of WAT without insulin, it is possible that specific factors arising from BAT and/or embryonic tissue may help maintain WAT grafts. Once identified, BAT-derived messengers may prove useful in maintaining WAT transplants. While complete reversal of T1D without insulin has been achieved only with embryonic BAT so far, recent studies show promise in adult BAT transplants in alleviating T2D and obesity. Glucose tolerance in diet induced obese mice is significantly improved through transplantation of inguinal fat pads from healthy donors into the subcutaneous space of recipient mice[131]. High fat diet induced obesity and insulin resistance in mice were reversed by visceral or subcutaneous transplantation of healthy adult BAT, in addition to improvements in glucose tolerance, insulin sensitivity and fat mass[132,133]. Mechanisms include increased glucose uptake into peripheral tissues, increased sympathetic activity and elevated levels of BAT-derived signaling molecules such as FGF21 and IL-6.

Another technique to improve the health of adipose tissue is to increase the content of endogenous BAT. There is a well-documented relationship between BAT content and nutritional homeostasis[109,110,134]. Recent studies show that human adults have BAT depots, and that the content of BAT is inversely proportionate to obesity and metabolic disease[135-139]. BAT deficiency in mice results in progressive obesity without hyperphagia, and selective stimulation of β-3 adrenergic receptors, abundantly expressd in BAT, leads to increased energy expendtiture and weight loss without affecting food intake[109]. Induction of brown fat lipoatrophy in mice results in increased visceral adiposity associated with excessive secretion of pro-inflammatory cytokines such as TNFα, followed by vascular insulin resistance and vascular dysfunction[139]. Methods such as stimulation of β-3 adrenergic receptors, administration of compounds such as thyroid hormone or atrial natriuretic peptide, and specific BAT-derived messenger molecules, are known to increase endogenous BAT content[140-146]. Thyroxine (TH) therapy on a patient with extreme insulin resistance was reported to produce full remission from T2D preceded by proliferation of BAT[140]. Specific transcriptional factors arising from BAT such as PRDM16 are now known to impart BAT-like properties to WAT, *i.e.*, cause “browning” of WAT, which results in overall increase of energy expenditure, decrease of weight gain and improvement of glucose homeostasis as reported in rodent studies[141,142,146]. Another recently identified messenger molecule originating from skeletal muscle, irisin, also improves energy expenditure in mice with no changes in movement or food intake, leading to improvements in obesity and glucose homeostasis[143]. Induction of BAT in WAT depots can also be accomplished with other stimuli, such as cyclo-oxygenase 2 (COX2) or cardiac natriuretic peptides (NPs), leading to increased energy expenditure[144-146]. These studies demonstrate the benefits of increasing endogenous BAT content with various techniques, and overt adverse effects are not yet reported.

**CONCLUSION**

Taken together, the aforementioned studies demonstrate the powerful global influence of adipose tissue as an endocrine organ, and its strong potential in combating metabolic disease. Adipose tissue is unique in generating a large number of hormones influencing metabolism and inflammation, which may compensate for the function of other endocrine organs upon their malfunction. Recent studies demonstrate the ability of adipose tissue to replace the function of endocrine pancreas under the appropriate circumstances. Once the underlying mechanisms are documented such therapies would be applicable to other metabolic disorders as well. Specific characteristics of adipose tissue such as its abundance, accessibility, and extensive ability to regenerate, make it a very useful and convenient source for transplantation.

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