TOPIC HIGHLIGHT

Benefits of healthy adipose tissue in the treatment of diabetes

Subhadra C Gunawardana

Subhadra C Gunawardana, Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center, Nashville, TN 37232, United States
Author contributions: Gunawardana SC solely contributed to this paper.
Correspondence to: Subhadra C Gunawardana, PhD, Research Assistant Professor, Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center, 1211 Medical Center Dr, Nashville, TN 37232,
United States. subhadra.gunawardana@vanderbilt.edu
Telephone: +1-615-3229710   Fax: +1-615-3227236
Received: December 17, 2013 Revised: May 19, 2014
Accepted: May 31, 2014
Published online: August 15, 2014

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.

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.

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 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 auto-immune 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 aforementioned approaches 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 dipeptidyl peptidase-4 (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 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 AMP-activated protein kinase and the peroxisome proliferator-activated receptor-α 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]. Numer-

ous 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, and pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukins 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 dysregulation, 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-inflammatory 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 thiazolidinediones 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 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 replacement therapy, such as hypoglycemia unawareness and the need for invasive surgery and/or immunosuppresive therapy. The subcutaneous 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 monotherapy 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 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 interleukin 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 expressed in BAT, leads to increased energy expenditure 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 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 or cardiac natriuretic peptides, 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 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.

REFERENCES

1   **Gruessner RW**, Gruessner AC. The current state of pancreas transplantation. *Nat Rev Endocrinol* 2013; **9**: 555-562 [PMID: 23897173 DOI: 10.1038/nrendo.2013.138]

2   **Margreiter C**, Resch T, Oberhuber R, Aigner F, Maier H, Sucher R, Schneeberger S, Ulmer H, Bösmüller C, Margreiter R, Pratschke J, Öllinger R. Combined pancreas-kidney transplantation for patients with end-stage nephropathy caused by type-2 diabetes mellitus. *Transplantation* 2013; **95**: 1030-1036 [PMID: 23407544 DOI: 10.1097/TP.0b013e3182861945]

3   **Friedman AL**, Friedman EA. Pancreas transplantation for type 2 diabetes at U.S. Transplant centers. *Diabetes Care* 2002; **25**: 1896 [PMID: 12351511]

4   **Tavakoli A**, Liong S. Pancreatic transplant in diabetes. *Adv*

Exp Med Biol 2012; **771**: 420-437 [PMID: 23393694]

5   **Barlow AD**, Hosgood SA, Nicholson ML. Current state of pancreas preservation and implications for DCD pancreas transplantation. *Transplantation* 2013; **95**: 1419-1424 [PMID: 23579769 DOI: 10.1097/TP.0b013e318285558f]

6   **Vardanyan M**, Parkin E, Gruessner C, Rodriguez Rilo HL. Pancreas vs. islet transplantation: a call on the future. *Curr Opin Organ Transplant* 2010; **15**: 124-130 [PMID: 20009930 DOI: 10.1097/MOT.0b013e32833553f8]

7   **Maffi P**, Scavini M, Socci C, Piemonti L, Caldara R, Gremizzi C, Melzi R, Nano R, Orsenigo E, Venturini M, Staudacher C, Del Maschio A, Secchi A. Risks and benefits of transplantation in the cure of type 1 diabetes: whole pancreas versus islet transplantation. A single center study. *Rev Diabet Stud* 2011; **8**: 44-50 [PMID: 21720672]

8   **Ramesh A**, Chhabra P, Brayman KL. Pancreatic islet transplantation in type 1 diabetes mellitus: an update on recent developments. *Curr Diabetes Rev* 2013; **9**: 294-311 [PMID: 23721158]

9   **Deters NA**, Stokes RA, Gunton JE. Islet transplantation: factors in short-term islet survival. *Arch Immunol Ther Exp* (Warsz) 2011; **59**: 421-429 [PMID: 21984594 DOI: 10.1007/s00 005-011-0143-0]

10   **Plesner A**, Verchere CB. Advances and challenges in islet transplantation: islet procurement rates and lessons learned from suboptimal islet transplantation. *J Transplant* 2011; **2011**: 979527 [PMID: 22235361 DOI: 10.1155/2011/979527]

11   **Kawahara T**, Kin T, Shapiro AM. A comparison of islet auto-transplantation with allotransplantation and factors elevating acute portal pressure in clinical islet transplantation. *J Hepatobiliary Pancreat Sci* 2012; **19**: 281-288 [PMID: 21879320 DOI: 10.1007/s00534-011-0441-2]

12   **Kawahara T**, Kin T, Kashkoush S, Gala-Lopez B, Bigam DL, Kneteman NM, Koh A, Senior PA, Shapiro AM. Portal vein thrombosis is a potentially preventable complication in clinical islet transplantation. *Am J Transplant* 2011; **11**: 2700-2707 [PMID: 21883914 DOI: 10.1111/j.1600-6143.2011.03717.x]

13   **O'Connell PJ**, Cowan PJ, Hawthorne WJ, Yi S, Lew AM. Transplantation of xenogeneic islets: are we there yet? *Curr Diab Rep* 2013; **13**: 687-694 [PMID: 23922060 DOI: 10.1007/s11892-013-0413-9]

14   **Elliott RB**, Escobar L, Tan PL, Muzina M, Zwain S, Buchanan C. Live encapsulated porcine islets from a type 1 diabetic patient 9.5 yr after xenotransplantation. *Xenotransplantation* 2007; **14**: 157-161 [PMID: 17381690]

15   **Tudurí E**, Bruin JE, Kieffer TJ. Restoring insulin production for type 1 diabetes. *J Diabetes* 2012; **4**: 319-331 [PMID: 22429761 DOI: 10.1111/j.1753-0407.2012.00196.x]

16   **Ham DS**, Shin J, Kim JW, Park HS, Cho JH, Yoon KH. Generation of functional insulin-producing cells from neonatal porcine liver-derived cells by PDX1/VP16, BETA2/NeuroD and MafA. *PLoS One* 2013; **8**: e79076 [PMID: 24260156 DOI: 10.1371/journal.pone.0079076]

17   **Bhonde RR**, Sheshadri P, Sharma S, Kumar A. Making surrogate β-cells from mesenchymal stromal cells: perspectives and future endeavors. *Int J Biochem Cell Biol* 2014; **46**: 90-102 [PMID: 24275096 DOI: 10.1016/j.biocel.2013.11.006]

18   **Zhao Y**, Jiang Z, Zhao T, Ye M, Hu C, Yin Z, Li H, Zhang Y, Diao Y, Li Y, Chen Y, Sun X, Fisk MB, Skidgel R, Holterman M, Prabhakar B, Mazzone T. Reversal of type 1 diabetes via islet β cell regeneration following immune modulation by cord blood-derived multipotent stem cells. *BMC Med* 2012; **10**: 3 [PMID: 22233865 DOI: 10.1186/1741-7015-10-3]

19   **Han MX**, Craig ME. Research using autologous cord blood - time for a policy change. *Med J Aust* 2013; **199**: 288-299 [PMID: 23984789]

20   **Chhabra P**, Brayman KL. Stem cell therapy to cure type 1 diabetes: from hype to hope. *Stem Cells Transl Med* 2013; **2**: 328-336 [PMID: 23572052 DOI: 10.5966/sctm.2012-0116]

21   **Molitch ME**. Current state of type 2 diabetes management.

Am J Manag Care 2013; **19**: S136-S142 [PMID: 23844829]

22   **Corathers SD**, Peavie S, Salehi M. Complications of diabetes therapy. *Endocrinol Metab Clin North Am* 2013; **42**: 947-970 [PMID: 24286957 DOI: 10.1016/j.ecl.2013.06.005]

23   **Meneghini LF**. Intensifying insulin therapy: what options are available to patients with type 2 diabetes? *Am J Med* 2013; **126**: S28-S37 [PMID: 23953077 DOI: 10.1016/j.am-jmed.2013.06.011]

24   **Kalaitzidis RG**, Sarafidis PA, Bakris GL. Effects of thiazoli-dinediones beyond glycaemic control. *Curr Pharm Des* 2009; **15**: 529-536 [PMID: 19199979]

25   **Rizos CV**, Elisaf MS, Mikhailidis DP, Liberopoulos EN. How safe is the use of thiazolidinediones in clinical practice? *Expert Opin Drug Saf* 2009; **8**: 15-32 [PMID: 19236215 DOI: 10.1517/14740330802597821]

26   **Moore EM**, Mander AG, Ames D, Kotowicz MA, Carne RP, Brodaty H, Woodward M, Boundy K, Ellis KA, Bush AI, Faux NG, Martins R, Szoeke C, Rowe C, Watters DA. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. *Diabetes Care* 2013; **36**: 2981-2987 [PMID: 24009301 DOI: 10.2337/dc13-0229]

27   **Harwood HJ**. The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. *Neuropharmacology* 2012; **63**: 57-75 [PMID: 22200617 DOI: 10.1016/j.neuropharm.2011.12.010]

28   **Kim W**, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev* 2008; **60**: 470-512 [PMID: 19074620 DOI: 10.1124/pr.108.000604]

29   **Cho YM**, Fujita Y, Kieffer TJ. Glucagon-like peptide-1: glucose homeostasis and beyond. *Annu Rev Physiol* 2014; **76**: 535-559 [PMID: 24245943 DOI: 10.1146/annurev-physi-ol-021113-170315]

30   **De Marinis YZ**, Salehi A, Ward CE, Zhang Q, Abdulkader F, Bengtsson M, Braha O, Braun M, Ramracheya R, Amisten S, Habib AM, Moritoh Y, Zhang E, Reimann F, Rosengren AH, Shibasaki T, Gribble F, Renström E, Seino S, Eliasson L, Rorsman P. GLP-1 inhibits and adrenaline stimulates glucagon release by differential modulation of N- and L-type Ca2+ channel-dependent exocytosis. *Cell Metab* 2010; **11**: 543-553 [PMID: 20519125 DOI: 10.1016/j.cmet.2010.04.007]

31   **Dardevet D**, Moore MC, Neal D, DiCostanzo CA, Snead W, Cherrington AD. Insulin-independent effects of GLP-1 on canine liver glucose metabolism: duration of infusion and involvement of hepatoportal region. *Am J Physiol Endocrinol Metab* 2004; **287**: E75-E81 [PMID: 15026303]

32   **Knauf C**, Cani PD, Perrin C, Iglesias MA, Maury JF, Bernard E, Benhamed F, Grémeaux T, Drucker DJ, Kahn CR, Girard J, Tanti JF, Delzenne NM, Postic C, Burcelin R. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. *J Clin Invest* 2005; **115**: 3554-3563 [PMID: 16322793]

33   **Ishibashi Y**, Matsui T, Takeuchi M, Yamagishi S. Glucagon-like peptide-1 (GLP-1) inhibits advanced glycation end product (AGE)-induced up-regulation of VCAM-1 mRNA levels in endothelial cells by suppressing AGE receptor (RAGE) expression. *Biochem Biophys Res Commun* 2010; **391**: 1405-1408 [PMID: 20026306]

34   **Hattori Y**, Jojima T, Tomizawa A, Satoh H, Hattori S, Kasai K, Hayashi T. A glucagon-like peptide-1 (GLP-1) analogue, lira-glutide, upregulates nitric oxide production and exerts anti-inflammatory action in endothelial cells. *Diabetologia* 2010; **53**: 2256-2263 [PMID: 20593161 DOI: 10.1007/s00125-010-1831-8]

35   **Bloomgarden ZT**. Incretin concepts. *Diabetes Care* 2010; **33**: e20-e25 [PMID: 20103551]

36   **Ussher JR**, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012; **33**: 187-215 [PMID: 22323472 DOI: 10.1210/er.2011-1052]

37   **Sivertsen J**, Rosenmeier J, Holst JJ, Vilsbøll T. The effect of glucagon-like peptide 1 on cardiovascular risk. *Nat Rev Cardiol* 2012; **9**: 209-222 [PMID: 22290234 DOI: 10.1038/nrcar-

dio.2011.211]

38 **Gu W**, Lloyd DJ, Chinookswong N, Komorowski R, Sivits G, Graham M, Winters KA, Yan H, Boros LG, Lindberg RA, Véniant MM. Pharmacological targeting of glucagon and glucagon-like peptide 1 receptors has different effects on energy state and glucose homeostasis in diet-induced obese mice. *J Pharmacol Exp Ther* 2011; **338**: 70-81 [PMID: 21471191 DOI: 10.1124/jpet.111.179986]

39 **Garber AJ**. Incretin therapy--present and future. *Rev Diabet Stud* 2011; **8**: 307-322 [PMID: 22262069 DOI: 10.1900/RDS.2011.8.307]

40 **Cernea S**. The role of incretin therapy at different stages of diabetes. *Rev Diabet Stud* 2011; **8**: 323-338 [PMID: 22262070 DOI: 10.1900/RDS.2011.8.323]

41 **Spellman CW**. Incorporating glucagon-like peptide-1 receptor agonists into clinical practice. *J Am Osteopath Assoc* 2012; **112**: S7-15 [PMID: 22267302]

42 **Scheen AJ**. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. *Diabetes Metab* 2012; **38**: 89-101 [PMID: 22197148 DOI: 10.1016/j.diabet.2011.11.001]

43 **Dupre J**. Glycaemic effects of incretins in Type 1 diabetes mellitus: a concise review, with emphasis on studies in humans. *Regul Pept* 2005; **128**: 149-157 [PMID: 15780434]

44 **Ahrén B**. The future of incretin-based therapy: novel avenues--novel targets. *Diabetes Obes Metab* 2011; **13** Suppl 1: 158-166 [PMID: 21824270]

45 **Suen CS**, Burn P. The potential of incretin-based therapies in type 1 diabetes. *Drug Discov Today* 2012; **17**: 89-95 [PMID: 21920456 DOI: 10.1016/j.drudis.2011.08.017]

46 **Delfino M**, Motola D, Benini A, Franzè GP, Barotto M, Campi A, Monda VM. Incretin-mimetics associated pancreatitis: evidence from the spontaneous adverse drug reactions reporting in Italy. *Expert Opin Drug Saf* 2014; **13**: 151-156 [PMID: 24219498 DOI: 10.1517/14740338.2014.853036]

47 **Cohen D**. Reports of pancreatitis are 20-30 times more likely with GLP-1 drugs, analysis finds. *BMJ* 2013; **346**: f2607 [PMID: 23613543 DOI: 10.1136/bmj.f2607]

48 **Hansen JB**, Kristiansen K. Regulatory circuits controlling white versus brown adipocyte differentiation. *Biochem J* 2006; **398**: 153-168 [PMID: 16898874]

49 **Kajimura S**, Seale P, Spiegelman BM. Transcriptional control of brown fat development. *Cell Metab* 2010; **11**: 257-262 [PMID: 20374957 DOI: 10.1016/j.cmet.2010.03.005]

50 **Billon N**, Dani C. Developmental origins of the adipocyte lineage: new insights from genetics and genomics studies. *Stem Cell Rev* 2012; **8**: 55-66 [PMID: 21365256 DOI: 10.1007/s12015-011-9242-x]

51 **Wronska A**, Kmiec Z. Structural and biochemical characteristics of various white adipose tissue depots. *Acta Physiol* (Oxf) 2012; **205**: 194-208 [PMID: 22226221 DOI: 10.1111/j.1748-1716.2012.02409.x]

52 **Bjørndal B**, Burri L, Staalesen V, Skorve J, Berge RK. Different adipose depots: their role in the development of metabolic syndrome and mitochondrial response to hypolipidemic agents. *J Obes* 2011; **2011**: 490650 [PMID: 21403826 DOI: 10.1155/2011/490650]

53 **Wozniak SE**, Gee LL, Wachtel MS, Frezza EE. Adipose tissue: the new endocrine organ? A review article. *Dig Dis Sci* 2009; **54**: 1847-1856 [PMID: 19052866 DOI: 10.1007/s10620-008-0585-3]

54 **Ouchi N**, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011; **11**: 85-97 [PMID: 21252989 DOI: 10.1038/nri2921]

55 **Falcão-Pires I**, Castro-Chaves P, Miranda-Silva D, Lourenço AP, Leite-Moreira AF. Physiological, pathological and potential therapeutic roles of adipokines. *Drug Discov Today* 2012; **17**: 880-889 [PMID: 22561894 DOI: 10.1016/j.drudis.2012.04.007]

56 **Tishinsky JM**, Robinson LE, Dyck DJ. Insulin-sensitizing

properties of adiponectin. *Biochimie* 2012; **94**: 2131-2136 [PMID: 22314192 DOI: 10.1016/j.biochi.2012.01.017]

57 **Wolfson N**, Gavish D, Matas Z, Boaz M, Shargorodsky M. Relation of adiponectin to glucose tolerance status, adiposity, and cardiovascular risk factor load. *Exp Diabetes Res* 2012; **2012**: 250621 [PMID: 22253614 DOI: 10.1155/2012/250621]

58 **Pereira RI**, Snell-Bergeon JK, Erickson C, Schauer IE, Bergman BC, Rewers M, Maahs DM. Adiponectin dysregulation and insulin resistance in type 1 diabetes. *J Clin Endocrinol Metab* 2012; **97**: E642-E647 [PMID: 22278421 DOI: 10.1210/jc.2011-2542]

59 **Miller RA**, Chu Q, Le Lay J, Scherer PE, Ahima RS, Kaestner KH, Foretz M, Viollet B, Birnbaum MJ. Adiponectin suppresses gluconeogenic gene expression in mouse hepatocytes independent of LKB1-AMPK signaling. *J Clin Invest* 2011; **121**: 2518-2528 [PMID: 21606593 DOI: 10.1172/JCI45942]

60 **Dridi S**, Taouis M. Adiponectin and energy homeostasis: consensus and controversy. *J Nutr Biochem* 2009; **20**: 831-839 [PMID: 19716279 DOI: 10.1016/j.jnutbio.2009.06.003]

61 **Gardener H**, Sjoberg C, Crisby M, Goldberg R, Mendez A, Wright CB, Elkind MS, Sacco RL, Rundek T. Adiponectin and carotid intima-media thickness in the northern Manhattan study. *Stroke* 2012; **43**: 1123-1125 [PMID: 22198981 DOI: 10.1161/STROKEAHA.111.641761]

62 **Tian L**, Luo N, Zhu X, Chung BH, Garvey WT, Fu Y. Adiponectin-AdipoR1/2-APPL1 signaling axis suppresses human foam cell formation: differential ability of AdipoR1 and AdipoR2 to regulate inflammatory cytokine responses. *Atherosclerosis* 2012; **221**: 66-75 [PMID: 22227293 DOI: 10.1016/j.atherosclerosis.2011.12.014]

63 **Carlton ED**, Demas GE, French SS. Leptin, a neuroendocrine mediator of immune responses, inflammation, and sickness behaviors. *Horm Behav* 2012; **62**: 272-279 [PMID: 22561456 DOI: 10.1016/j.yhbeh.2012.04.010]

64 **Kitazawa M**, Nagano M, Masumoto KH, Shigeyoshi Y, Natsume T, Hashimoto S. Angiopoietin-like 2, a circadian gene, improves type 2 diabetes through potentiation of insulin sensitivity in mice adipocytes. *Endocrinology* 2011; **152**: 2558-2567 [PMID: 21586562 DOI: 10.1210/en.2010-1407]

65 **Xu A**, Lam MC, Chan KW, Wang Y, Zhang J, Hoo RL, Xu JY, Chen B, Chow WS, Tso AW, Lam KS. Angiopoietin-like protein 4 decreases blood glucose and improves glucose tolerance but induces hyperlipidemia and hepatic steatosis in mice. *Proc Natl Acad Sci USA* 2005; **102**: 6086-6091 [PMID: 15837923]

66 **Kim MK**, Lee JH, Kim H, Park SJ, Kim SH, Kang GB, Lee YS, Kim JB, Kim KK, Suh SW, Eom SH. Crystal structure of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase, free and in complex with the anti-cancer agent FK-866. *J Mol Biol* 2006; **362**: 66-77 [PMID: 16901503]

67 **Sun Q**, Li L, Li R, Yang M, Liu H, Nowicki MJ, Zong H, Xu J, Yang G. Overexpression of visfatin/PBEF/Nampt alters whole-body insulin sensitivity and lipid profile in rats. *Ann Med* 2009; **41**: 311-320 [PMID: 19263259 DOI: 10.1080/07853890902729760]

68 **LeRoith D**, Yakar S. Mechanisms of disease: metabolic effects of growth hormone and insulin-like growth factor 1. *Nat Clin Pract Endocrinol Metab* 2007; **3**: 302-310 [PMID: 17315038]

69 **Bremer AA**, Devaraj S, Afify A, Jialal I. Adipose tissue dysregulation in patients with metabolic syndrome. *J Clin Endocrinol Metab* 2011; **96**: E1782-E1788 [PMID: 21865369 DOI: 10.1210/jc.2011-1577]

70 **Hammarstedt A**, Graham TE, Kahn BB. Adipose tissue dysregulation and reduced insulin sensitivity in non-obese individuals with enlarged abdominal adipose cells. *Diabetol Metab Syndr* 2012; **4**: 42 [PMID: 22992414 DOI: 10.1186/1758-5996-4-42]

71 **McGown C**, Birerdinc A, Younossi ZM. Adipose tissue as an endocrine organ. *Clin Liver Dis* 2014; **18**: 41-58 [PMID:

24274864 DOI: 10.1016/j.cld.2013.09.012]

72   **Gerner RR**, Wieser V, Moschen AR, Tilg H. Metabolic inflammation: role of cytokines in the crosstalk between adipose tissue and liver. *Can J Physiol Pharmacol* 2013; **91**: 867-872 [PMID: 24117253 DOI: 10.1139/cjpp-2013-0050]

73   **Lafontan M**. Adipose tissue and adipocyte dysregulation. *Diabetes Metab* 2014; **40**: 16-28 [PMID: 24139247 DOI: 10.1016/j.diabet.2013.08.002]

74   **Snell-Bergeon JK**, West NA, Mayer-Davis EJ, Liese AD, Marcovina SM, D'Agostino RB, Hamman RF, Dabelea D. Inflammatory markers are increased in youth with type 1 diabetes: the SEARCH Case-Control study. *J Clin Endocrinol Metab* 2010; **95**: 2868-2876 [PMID: 20371668 DOI: 10.1210/jc.2009-1993]

75   **Verrijn Stuart AA**, Schipper HS, Tasdelen I, Egan DA, Prakken BJ, Kalkhoven E, de Jager W. Altered plasma adipokine levels and in vitro adipocyte differentiation in pediatric type 1 diabetes. *J Clin Endocrinol Metab* 2012; **97**: 463-472 [PMID: 22112811 DOI: 10.1210/jc.2011-1858]

76   **Gervois P**, Fruchart JC, Staels B. Inflammation, dyslipidaemia, diabetes and PPars: pharmacological interest of dual PPARalpha and PPARgamma agonists. *Int J Clin Pract Suppl* 2004; (**143**): 22-29 [PMID: 16035393]

77   **Hammarstedt A**, Andersson CX, Rotter Sopasakis V, Smith U. The effect of PPARgamma ligands on the adipose tissue in insulin resistance. *Prostaglandins Leukot Essent Fatty Acids* 2005; **73**: 65-75 [PMID: 15936183]

78   **Schwanstecher C**, Schwanstecher M. Targeting type 2 diabetes. *Handb Exp Pharmacol* 2011; (**203**): 1-33 [PMID: 21484565 DOI: 10.1007/978-3-642-17214-4_1]

79   **Conway B**, Miller RG, Costacou T, Fried L, Kelsey S, Evans RW, Orchard TJ. Adiposity and mortality in type 1 diabetes. *Int J Obes* (Lond) 2009; **33**: 796-805 [PMID: 19451912 DOI: 10.1038/ijo.2009.75]

80   **de Vries L**, Bar-Niv M, Lebenthal Y, Tenenbaum A, Shalitin S, Lazar L, Cohen A, Phillip M. Changes in weight and BMI following the diagnosis of type 1 diabetes in children and adolescents. *Acta Diabetol* 2014; **51**: 395-402 [PMID: 24158774]

81   **Gunawardana SC**, Piston DW. Reversal of type 1 diabetes in mice by brown adipose tissue transplant. *Diabetes* 2012; **61**: 674-682 [PMID: 22315305 DOI: 10.2337/db11-0510]

82   **Gunawardana SC**. Adipose tissue, hormones, and treatment of type 1 diabetes. *Curr Diab Rep* 2012; **12**: 542-550 [PMID: 22814676 DOI: 10.1007/s11892-012-0300-9]

83   **Gunawardana SC**, Piston DW. Insulin-independent reversal of type-1 diabetes with brown adipose tissue transplants: Involvement of IGF-1. International Pancreas and Islet Transplant Association, 2013: Abstract 244

84   **Lindberg S**, Jensen JS, Bjerre M, Pedersen SH, Frystyk J, Flyvbjerg A, Galatius S, Jeppesen J, Mogelvang R. Adiponectin, type 2 diabetes and cardiovascular risk. *Eur J Prev Cardiol* 2013; Epub ahead of print [PMID: 24265290]

85   **Yadav A**, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta* 2013; **417**: 80-84 [PMID: 23266767 DOI: 10.1016/j.cca.2012.12.007]

86   **Gökşen D**, Levent E, Kar S, Ozen S, Darcan S. Serum adiponectin and hsCRP levels and non-invasive radiological methods in the early diagnosis of cardiovascular system complications in children and adolescents with type 1 diabetes mellitus. *J Clin Res Pediatr Endocrinol* 2013; **5**: 174-181 [PMID: 24072086 DOI: 10.4274/Jcrpe.1003]

87   **Gokulakrishnan K**, Aravindhan V, Amutha A, Abhijit S, Ranjani H, Anjana RM, Unnikrishnan R, Miranda P, Narayan KM, Mohan V. Serum adiponectin helps to differentiate type 1 and type 2 diabetes among young Asian Indians. *Diabetes Technol Ther* 2013; **15**: 696-702 [PMID: 23902401 DOI: 10.1089/dia.2012.0306]

88   **Al-Azzam SI**, Khabour OF, Alzoubi KH, Mukattash TL, Ghanma M, Saleh H. The role of adiponectin gene variants in glycemic control in patients with Type 2 diabetes. *Endocr Res* 2014; **39**: 13-17 [PMID: 23772547]

89   **Hu X**, She M, Hou H, Li Q, Shen Q, Luo Y, Yin W. Adiponectin decreases plasma glucose and improves insulin sensitivity in diabetic Swine. *Acta Biochim Biophys Sin* (Shanghai) 2007; **39**: 131-136 [PMID: 17277888]

90   **Fukushima M**, Hattori Y, Tsukada H, Koga K, Kajiwara E, Kawano K, Kobayashi T, Kamata K, Maitani Y. Adiponectin gene therapy of streptozotocin-induced diabetic mice using hydrodynamic injection. *J Gene Med* 2007; **9**: 976-985 [PMID: 17868184]

91   **Park S**, Kim DS, Kwon DY, Yang HJ. Long-term central infusion of adiponectin improves energy and glucose homeostasis by decreasing fat storage and suppressing hepatic gluconeogenesis without changing food intake. *J Neuroendocrinol* 2011; **23**: 687-698 [PMID: 21599766 DOI: 10.1111/j.1365-2826.2011.02165.x]

92   **Ohashi K**, Kihara S, Ouchi N, Kumada M, Fujita K, Hiuge A, Hibuse T, Ryo M, Nishizawa H, Maeda N, Maeda K, Shibata R, Walsh K, Funahashi T, Shimomura I. Adiponectin replenishment ameliorates obesity-related hypertension. *Hypertension* 2006; **47**: 1108-1116 [PMID: 16651465]

93   **Kandasamy AD**, Sung MM, Boisvenue JJ, Barr AJ, Dyck JR. Adiponectin gene therapy ameliorates high-fat, high-sucrose diet-induced metabolic perturbations in mice. *Nutr Diabetes* 2012; **2**: e45 [PMID: 23446660 DOI: 10.1038/nutd.2012.18]

94   **Ma Y**, Liu D. Hydrodynamic delivery of adiponectin and adiponectin receptor 2 gene blocks high-fat diet-induced obesity and insulin resistance. *Gene Ther* 2013; **20**: 846-852 [PMID: 23425917 DOI: 10.1038/gt.2013.8]

95   **Nan MH**, Park JS, Myung CS. Construction of adiponectin-encoding plasmid DNA and gene therapy of non-obese type 2 diabetes mellitus. *J Drug Target* 2010; **18**: 67-77 [PMID: 19708766 DOI: 10.3109/10611860903225719]

96   **Yu X**, Park BH, Wang MY, Wang ZV, Unger RH. Making insulin-deficient type 1 diabetic rodents thrive without insulin. *Proc Natl Acad Sci USA* 2008; **105**: 14070-14075 [PMID: 18779578 DOI: 10.1073/pnas.0806993105]

97   **Wang MY**, Chen L, Clark GO, Lee Y, Stevens RD, Ilkayeva OR, Wenner BR, Bain JR, Charron MJ, Newgard CB, Unger RH. Leptin therapy in insulin-deficient type I diabetes. *Proc Natl Acad Sci USA* 2010; **107**: 4813-4819 [PMID: 20194735 DOI: 10.1073/pnas.0909422107]

98   **Naito M**, Fujikura J, Ebihara K, Miyanaga F, Yokoi H, Kusakabe T, Yamamoto Y, Son C, Mukoyama M, Hosoda K, Nakao K. Therapeutic impact of leptin on diabetes, diabetic complications, and longevity in insulin-deficient diabetic mice. *Diabetes* 2011; **60**: 2265-2273 [PMID: 21810600 DOI: 10.2337/db10-1795]

99   **Kruger AJ**, Yang C, Lipson KL, Pino SC, Leif JH, Hogan CM, Whalen BJ, Guberski DL, Lee Y, Unger RH, Greiner DL, Rossini AA, Bortell R. Leptin treatment confers clinical benefit at multiple stages of virally induced type 1 diabetes in BB rats. *Autoimmunity* 2011; **44**: 137-148 [PMID: 20695765 DOI: 10.3109/08916934.2010.482116]

100   **Chen H**, Zheng C, Zhang X, Li J, Li J, Zheng L, Huang K. Apelin alleviates diabetes-associated endoplasmic reticulum stress in the pancreas of Akita mice. *Peptides* 2011; **32**: 1634-1639 [PMID: 21762740 DOI: 10.1016/j.peptides.2011.06.025]

101   **Day RT**, Cavaglieri RC, Feliers D. Apelin retards the progression of diabetic nephropathy. *Am J Physiol Renal Physiol* 2013; **304**: F788-F800 [PMID: 23303408 DOI: 10.1152/ajprenal.00306.2012]

102   **Acerini CL**, Patton CM, Savage MO, Kernell A, Westphal O, Dunger DB. Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997; **350**: 1199-1204 [PMID: 9652560]

103   **Hadjiyanni I**, Baggio LL, Poussier P, Drucker DJ. Exendin-4 modulates diabetes onset in nonobese diabetic mice. *Endocrinology* 2008; **149**: 1338-1349 [PMID: 18063685]

104 **Pugazhenthi U**, Velmurugan K, Tran A, Mahaffey G, Pugazhenthi S. Anti-inflammatory action of exendin-4 in human islets is enhanced by phosphodiesterase inhibitors: potential therapeutic benefits in diabetic patients. *Diabetologia* 2010; **53**: 2357-2368 [PMID: 20635178 DOI: 10.1007/s00125-010-1849-y]

105 **Hari Kumar KV**, Shaikh A, Prusty P. Addition of exenatide or sitagliptin to insulin in new onset type 1 diabetes: a randomized, open label study. *Diabetes Res Clin Pract* 2013; **100**: e55-e58 [PMID: 23490599 DOI: 10.1016/j.diabres.2013.01.020]

106 **Hendarto H**, Inoguchi T, Maeda Y, Ikeda N, Zheng J, Takei R, Yokomizo H, Hirata E, Sonoda N, Takayanagi R. GLP-1 analog liraglutide protects against oxidative stress and albuminuria in streptozotocin-induced diabetic rats via protein kinase A-mediated inhibition of renal NAD(P)H oxidases. *Metabolism* 2012; **61**: 1422-1434 [PMID: 22554832 DOI: 10.1016/j.metabol.2012.03.002]

107 **García-Robles MJ**, Segura-Ortega JE, Fafutis-Morris M. The biology of leptin and its implications in breast cancer: a general view. *J Interferon Cytokine Res* 2013; **33**: 717-727 [PMID: 23869900 DOI: 10.1089/jir.2012.0168]

108 **Yuan Y**, Zhang J, Cai L, Ding C, Wang X, Chen H, Wang X, Yan J, Lu J. Leptin induces cell proliferation and reduces cell apoptosis by activating c-myc in cervical cancer. *Oncol Rep* 2013; **29**: 2291-2296 [PMID: 23588620 DOI: 10.3892/or.2013.2390]

109 **Lowell BB**, Flier JS. Brown adipose tissue, beta 3-adrenergic receptors, and obesity. *Annu Rev Med* 1997; **48**: 307-316 [PMID: 9046964]

110 **Villarroya J**, Cereijo R, Villarroya F. An endocrine role for brown adipose tissue? *Am J Physiol Endocrinol Metab* 2013; **305**: E567-E572 [PMID: 23839524 DOI: 10.1152/ajpendo.00250.2013]

111 **Lee H**, Lee IS, Choue R. Obesity, inflammation and diet. *Pediatr Gastroenterol Hepatol Nutr* 2013; **16**: 143-152 [PMID: 24224147]

112 **Rolland C**, Hession M, Broom I. Effect of weight loss on adipokine levels in obese patients. *Diabetes Metab Syndr Obes* 2011; **4**: 315-323 [PMID: 21887104 DOI: 10.2147/DMSO.S22788]

113 **Raghow R**. Bariatric surgery-mediated weight loss and its metabolic consequences for type-2 diabetes. *World J Diabetes* 2013; **4**: 47-50 [PMID: 23772272 DOI: 10.4239/wjd.v4.i3.47]

114 **Viardot A**, Lord RV, Samaras K. The effects of weight loss and gastric banding on the innate and adaptive immune system in type 2 diabetes and prediabetes. *J Clin Endocrinol Metab* 2010; **95**: 2845-50 [PMID:20375213 DOI: 10.1210/jc.2009-2371]

115 **Schneck AS**, Iannelli A, Patouraux S, Rousseau D, Bonnafous S, Bailly-Maitre B, Le Thuc O, Rovere C, Panaia-Ferrari P, Anty R, Tran A, Gual P, Gugenheim J. Effects of sleeve gastrectomy in high fat diet-induced obese mice: respective role of reduced caloric intake, white adipose tissue inflammation and changes in adipose tissue and ectopic fat depots. *Surg Endosc* 2014; **28**: 592-602 [PMID: 24196540 DOI: 10.1007/s00464-013-3211-1]

116 **Santos J**, Salgado P, Santos C, Mendes P, Saavedra J, Baldaque P, Monteiro L, Costa E. Effect of bariatric surgery on weight loss, inflammation, iron metabolism, and lipid profile. *Scand J Surg* 2014; **103**: 21-25 [PMID: 24177986]

117 **Zhang H**, Wang Y, Zhang J, Potter BJ, Sowers JR, Zhang C. Bariatric surgery reduces visceral adipose inflammation and improves endothelial function in type 2 diabetic mice. *Arterioscler Thromb Vasc Biol* 2011; **31**: 2063-2069 [PMID: 21680898 DOI: 10.1161/ATVBAHA.111.225870]

118 **Fisher G**, Hyatt TC, Hunter GR, Oster RA, Desmond RA, Gower BA. Markers of inflammation and fat distribution following weight loss in African-American and white women. *Obesity* (Silver Spring) 2012; **20**: 715-720 [PMID: 21527894 DOI: 10.1038/oby.2011.85]

119 **Kadomatsu T**, Tabata M, Oike Y. Angiopoietin-like proteins: emerging targets for treatment of obesity and related metabolic diseases. *FEBS J* 2011; **278**: 559-564 [PMID: 21182596 DOI: 10.1111/j.1742-4658.2010.07979.x]

120 **Clemmons DR**. Metabolic actions of insulin-like growth factor-I in normal physiology and diabetes. *Endocrinol Metab Clin North Am* 2012; **41**: 425-43, vii-viii [PMID: 22682639 DOI: 10.1016/j.ecl.2012.04.017]

121 **Cummings BP**. Leptin therapy in type 2 diabetes. *Diabetes Obes Metab* 2013; **15**: 607-612 [PMID: 23216672 DOI: 10.1111/dom.12048]

122 **Cummings BP**, Bettaieb A, Graham JL, Stanhope KL, Dill R, Morton GJ, Haj FG, Havel PJ. Subcutaneous administration of leptin normalizes fasting plasma glucose in obese type 2 diabetic UCD-T2DM rats. *Proc Natl Acad Sci USA* 2011; **108**: 14670-14675 [PMID: 21873226 DOI: 10.1073/pnas.1107163108]

123 **Nakano M**, Asakawa A, Inui A. Long-term correction of type 1 and 2 diabetes by central leptin gene therapy independent of effects on appetite and energy expenditure. *Indian J Endocrinol Metab* 2012; **16**: S556-S561 [PMID: 23565490 DOI: 10.4103/2230-8210.105572]

124 **Tran TT**, Kahn CR. Transplantation of adipose tissue and stem cells: role in metabolism and disease. *Nat Rev Endocrinol* 2010; **6**: 195-213 [PMID: 20195269]

125 **Gavrilova O**, Marcus-Samuels B, Graham D, Kim JK, Shulman GI, Castle AL, Vinson C, Eckhaus M, Reitman ML. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest* 2000; **105**: 271-278 [PMID: 10675352]

126 **Klebanov S**, Astle CM, DeSimone O, Ablamunits V, Harrison DE. Adipose tissue transplantation protects ob/ob mice from obesity, normalizes insulin sensitivity and restores fertility. *J Endocrinol* 2005; **186**: 203-211 [PMID: 16002549]

127 **Ablamunits V**, Klebanov S, Giese SY, Herold KC. Functional human to mouse adipose tissue xenotransplantation. *J Endocrinol* 2012; **212**: 41-47 [PMID: 22007021 DOI: 10.1530/JOE-11-020]

128 **Foster MT**, Softic S, Caldwell J, Kohli R, de Kloet AD, Seeley RJ. Subcutaneous Adipose Tissue Transplantation in Diet-Induced Obese Mice Attenuates Metabolic Dysregulation While Removal Exacerbates It. *Physiol Rep* 2013; **1**: pii: e00015 [PMID: 23914298]

129 **Foster MT**, Shi H, Seeley RJ, Woods SC. Transplantation or removal of intra-abdominal adipose tissue prevents age-induced glucose insensitivity. *Physiol Behav* 2010; **101**: 282-288 [PMID: 20570685 DOI: 10.1016/j.physbeh.2010.05.014]

130 **Bahr J**, Klöting N, Klöting I, Follak N. Transplantation of adipose tissue protects BB/OK rats from type 1 diabetes development. *Transpl Immunol* 2011; **24**: 238-240 [PMID: 21277980 DOI: 10.1016/j.trim.2011.01.003]

131 **Cohen P**, Levy JD, Zhang Y, Frontini A, Kolodin DP, Svensson KJ, Lo JC, Zeng X, Ye L, Khandekar MJ, Wu J, Gunawardana SC, Banks AS, Camporez JP, Jurczak MJ, Kajimura S, Piston DW, Mathis D, Cinti S, Shulman GI, Seale P, Spiegelman BM. Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch. *Cell* 2014; **156**: 304-316 [PMID: 24439384 DOI: 10.1016/j.cell.2013.12.021]

132 **Stanford KI**, Middelbeek RJ, Townsend KL, An D, Nygaard EB, Hitchcox KM, Markan KR, Nakano K, Hirshman MF, Tseng YH, Goodyear LJ. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. *J Clin Invest* 2013; **123**: 215-223 [PMID: 23221344 DOI: 10.1172/JCI62308]

133 **Zhu Z**, Spicer EG, Gavini CK, Goudjo-Ako AJ, Novak CM, Shi H. Enhanced sympathetic activity in mice with brown adipose tissue transplantation (transBATation). *Physiol Behav* 2014; **125**: 21-29 [PMID: 24291381 DOI: 10.1016/j.physbeh.2013.11.008]

134 **Zafrir B**. Brown adipose tissue: research milestones of a potential player in human energy balance and obesity. *Horm Metab Res* 2013; **45**: 774-785 [PMID: 23803970 DOI: 10.1055/s-0033-1348264]

135 **Cypess AM**, Lehman S, Williams G, Tal I, Rodman D, Gold-

fine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 2009; **360**: 1509-1517 [PMID: 19357406 DOI: 10.1056/NEJMoa0810780]

136 **Saito M**, Okamatsu-Ogura Y, Matsushita M, Watanabe K, Yoneshiro T, Nio-Kobayashi J, Iwanaga T, Miyagawa M, Kameya T, Nakada K, Kawai Y, Tsujisaki M. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. *Diabetes* 2009; **58**: 1526-1531 [PMID: 19401428 DOI: 10.2337/db09-0530]

137 **Cypess AM**, Kahn CR. Brown fat as a therapy for obesity and diabetes. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 143-149 [PMID: 20160646 DOI: 10.1097/MED.0b013e328337a81f]

138 **Ginter E**, Simko V. Brown fat tissue - a potential target to combat obesity. *Bratisl Lek Listy* 2012; **113**: 52-56 [PMID: 22380505]

139 **Gómez-Hernández A**, Otero YF, de las Heras N, Escribano O, Cachofeiro V, Lahera V, Benito M. Brown fat lipoatrophy and increased visceral adiposity through a concerted adipocytokines overexpression induces vascular insulin resistance and dysfunction. *Endocrinology* 2012; **153**: 1242-1255 [PMID: 22253415 DOI: 10.1210/en.2011-1765]

140 **Skarulis MC**, Celi FS, Mueller E, Zemskova M, Malek R, Hugendubler L, Cochran C, Solomon J, Chen C, Gorden P. Thyroid hormone induced brown adipose tissue and amelioration of diabetes in a patient with extreme insulin resistance. *J Clin Endocrinol Metab* 2010; **95**: 256-262 [PMID: 19897683 DOI: 10.1210/jc.2009-0543]

141 **Seale P**, Conroe HM, Estall J, Kajimura S, Frontini A, Ishibashi J, Cohen P, Cinti S, Spiegelman BM. Prdm16 deter-mines the thermogenic program of subcutaneous white adipose tissue in mice. *J Clin Invest* 2011; **121**: 96-105 [PMID: 21123942 DOI: 10.1172/JCI44271]

142 **Ohno H**, Shinoda K, Spiegelman BM, Kajimura S. PPARγ agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein. *Cell Metab* 2012; **15**: 395-404 [PMID: 22405074 DOI: 10.1016/j.cmet.2012.01.019]

143 **Boström P**, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP, Spiegelman BM. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012; **481**: 463-468 [PMID: 22237023 DOI: 10.1038/nature10777]

144 **Vegiopoulos A**, Müller-Decker K, Strzoda D, Schmitt I, Chichelnitskiy E, Ostertag A, Berriel Diaz M, Rozman J, Hrabe de Angelis M, Nüsing RM, Meyer CW, Wahli W, Klingenspor M, Herzig S. Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science* 2010; **328**: 1158-1161 [PMID: 20448152 DOI: 10.1126/science.1186034]

145 **Bordicchia M**, Liu D, Amri EZ, Ailhaud G, Dessì-Fulgheri P, Zhang C, Takahashi N, Sarzani R, Collins S. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *J Clin Invest* 2012; **122**: 1022-1036 [PMID: 22307324 DOI: 10.1172/JCI59701]

146 **Bartelt A**, Heeren J. Adipose tissue browning and metabolic health. *Nat Rev Endocrinol* 2014; **10**: 24-36 [PMID: 24146030 DOI: 10.1038/nrendo.2013.204]

Baishideng®