

WJD 5th Anniversary Special Issues (1): Insulin**Adipose stem cell-based regenerative medicine for reversal of diabetic hyperglycemia**

Hyun Joon Paek, Courtney Kim, Stuart K Williams

Hyun Joon Paek, Courtney Kim, Biologics, Tissue Genesis Institute, LLC, Honolulu, HI 96813, United States

Stuart K Williams, Cardiovascular Innovation Institute, University of Louisville, Louisville, KY 40202, United States

Author contributions: Paek HJ wrote the manuscript; Kim C and Williams SK reviewed and revised it.

Correspondence to: Hyun Joon Paek, PhD, Director, Biologics, Tissue Genesis Institute, LLC, 810 Richards Street, Suite 1000, Honolulu, HI 96813,

United States. jpaek@tissuegenesis.com

Telephone: +1-808-7725590 Fax: +1-808-5595339

Received: December 12, 2013 Revised: January 30, 2014

Accepted: May 8, 2014

Published online: June 15, 2014

Abstract

Diabetes mellitus (diabetes) is a devastating disease that affects millions of people globally and causes a myriad of complications that lead to both patient morbidity and mortality. Currently available therapies, including insulin injection and beta cell replacement through either pancreas or pancreatic islet transplantation, are limited by the availability of organs. Stem cells provide an alternative treatment option for beta cell replacement through selective differentiation of stem cells into cells that recognize glucose and produce and secrete insulin. Embryonic stem cells, albeit pluripotent, face a number of challenges, including ethical and political concerns and potential teratoma formation. Adipose tissue represents an alternative source of multipotent mesenchymal stem cells, which can be obtained using a relatively simple, non-invasive, and inexpensive method. Similarly to other adult mesenchymal stem cells, adipose-derived stem cells (ADSCs) are capable of differentiating into insulin-producing cells. They are also capable of vasculogenesis and angiogenesis, which facilitate engraftment of donor pancreatic islets when co-transplanted. Additionally, anti-inflammatory and immunomodulatory effects of ADSCs can protect donor

islets during the early phase of transplantation and subsequently improve engraftment of donor islets into the recipient organ. Although ADSC-therapy is still in its infancy, the potential benefits of ADSCs are far reaching.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

Key words: Diabetes mellitus; Diabetes; Insulin; Stem cells; Adipose; Pancreas; Beta-cells; Differentiation

Core tip: Adipose-derived stem cells (ADSCs) can provide a promising cell therapy for treatment of diabetes and associated complications. ADSCs' multipotency allows differentiation into insulin-producing β -cells. Anti-inflammatory and immunomodulatory capabilities of ADSCs can facilitate enhanced engraftment of transplanted donor islets. Although many challenges lie ahead for ADSC-based cell therapies are used clinically to treat diabetic hyperglycemia, ADSCs represent a novel treatment option to many diabetic patients worldwide.

Paek HJ, Kim C, Williams SK. Adipose stem cell-based regenerative medicine for reversal of diabetic hyperglycemia. *World J Diabetes* 2014; 5(3): 235-243 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v5/i3/235.htm> DOI: <http://dx.doi.org/10.4239/wjd.v5.i3.235>

INTRODUCTION

Diabetes mellitus (diabetes) is a chronic disease, affecting over 347 million people globally^[1-8]. Due to diets with high fat and high sugar accompanied by sedentary lifestyles, the global epidemic of diabetes is expected to rise. Furthermore, the economic burden imposed by diabetes and its complications easily exceeds \$100 billion annually^[9].

The most common treatment for type 1 and some type 2 diabetes is insulin therapy. Intensive insulin treat-

ment can maintain normoglycemia, and control acute hypoglycemia as well as long-term complications^[10,11], however, fails to achieve normal hemoglobin A1c levels. Advancements in commercial glucose monitors, insulin formulation, and insulin pumps are also providing improved control of diabetic symptoms^[10,12]. However, even with widely available insulin therapy, the life expectancy of diabetic patients is approximately 12 years shorter on average than that of non-diabetic individuals^[9,13]. Additionally, those with child-onset type 1 diabetes have a significantly increased risk of retinopathy, nephropathy, neuropathy, and various cardio-, cerebro- and peripheral vascular diseases^[5,6,9,10,14-21].

More definitive treatment options for type 1 diabetes, which is characterized by autoimmune destruction of insulin-producing β -cells in pancreatic islets of Langerhans, are pancreas or pancreatic islet transplantation^[22-26]. Over a century ago, pancreas extracts were the first transplants tested in diabetic patients^[27]. Modern-day pancreas and pancreatic islet transplantations are relatively effective in normalizing fasting and postprandial blood glucose levels, hemoglobin A1c levels as well as restoring insulin and C-peptide production^[9]. However, the severe shortage of available donors limit the widespread adoption of this form of therapy^[10,28], and thus, appear to only benefit less than 0.5% of type 1 diabetics^[28]. Additionally, life-long requirement of immunosuppression and adverse effects caused by immunosuppressants, such as nephrotoxicity, hypertension, and hypersensitivity to infection, often leads to patient non-compliance^[10,28,29]. Lastly, reoccurring autoimmunity against pancreatic β -cells continues to be a major challenge associated with transplantation therapies^[9].

Recent advancements in stem cell isolation and differentiation methodologies have resulted in production of cell lines with the capability to synthesize, package, and subsequently secrete insulin in response to glucose. Albeit pluripotent, embryonic stem (ES) cell differentiation often leads to the development of multiple cell lineages, resulting in a mixed population of cells along with target cells^[9]. Definitive endodermal markers are also absent in ES cells, and undifferentiated teratogenic ES cells may pose serious risks as well^[9,28]. Due to ethical and legal concerns and risks of teratoma formation, embryonic stem cells face austere challenges in becoming a clinically viable solution although cellular isolation device may provide a method to implant embryonic stem cells with insulin producing capabilities^[30].

Multipotent progenitor cells are now known to be localized in many different organs^[31]. Although multipotent, adult stem cells provide a relatively reliable source of mesenchymal stem cells for cell-based therapies. Recently, adult stem cells from bone marrow, umbilical cord blood, pancreatic duct, periosteum, and adipose tissue have shown a capacity to differentiate into insulin-producing cells^[32-43].

Among the many tissue sources for adult stem cells, adipose tissue is particularly attractive based on its stem cell abundance and ease of tissue procurement through a minimally invasive and relatively inexpensive proce-

dures^[44-48]. Mesenchymal stem cells from bone marrow and adipose tissue share similar cell populations, along with cell characteristics^[49-51]. Adipose tissue has also been reported to contain a significantly greater number of mesenchymal stem cells than bone marrow per unit weight^[6,52-54]. In this review, adipose-derived stem cells will be specifically examined for their utility in developing treatments for diabetes and diabetic complications.

Direct differentiation into pancreatic hormone producing cells

Kodama *et al.*^[55] proposed four mechanisms of pancreatic regeneration: (1) replication of mature β -cells; (2) differentiation of stem cells; (3) cell fusion; and (4) transdifferentiation of one stem cell type to another. Most studies on cell-based therapies focus on direct differentiation of stem cells into insulin-producing β -cells.

Mesenchymal stem cells derived from adipose tissue exhibit unique characteristics well suited for transdifferentiation into a pancreatic endocrine lineage, which is of the endodermal origin. Freshly isolated adipose-derived stem cells (ADSCs) also expressed stem cell factor (SCF) and its receptor (c-kit)^[44,56], but not ABCG2, nestin, Thy-1, and Isl-1. Lin *et al.*^[6] reported that ADSCs constitutively expressed glucagon and NeuroD as well as insulin. The proliferative ADSCs, on the other hand, expressed the transcription factor Isl-1 and Pax-6, which are critical transcription factors required for β cell development^[44,56], as a previous study showed that formation of insulin- and glucagon-positive cells were found inhibited during development of Isl-1 knock-out mice^[57]. Therefore, the intrinsic expression of Isl-1 in ADSCs provides a considerable advantage for generating insulin-producing cells. Proliferative ADSCs also express stem cell markers nestin, ABCG2, SCF, and Thy-1. Nestin was originally thought to be a neural stem/progenitor cell marker but was recently reported to be a multipotent pancreatic stem cell marker as well, detected within pancreatic islets^[16,58]. ABCG2 has also shown to be associated with pancreatic islet-derived precursor cells and neural stem cells^[10,59]. Kojima *et al.*^[60] demonstrated that extrapancreatic insulin-producing cells, which were positive for proinsulin and insulin, were present in the adipose tissue of streptozotocin-induced diabetic rodents. Based on these intrinsic characteristics, ADSCs can serve as a promising source of pancreatic hormone-producing cells following differentiation.

Derivation of insulin producing cells from stem cells is made possible through the understanding of key steps during embryonic development and the coordinated activation of intracellular transcription factors. Similar to embryonic stem cells^[61-65], derivation of insulin-producing cells from ADSC is executed through a progressive multi-stage differentiation protocol: starting from definitive endoderm into pancreatic endoderm and finally into pancreatic hormone-expressing cell^[2,44,56,66-68]. Outlines the culture conditions used by various groups to stimulate ADSCs into an insulin-producing cell lineage.

All of the differentiated cell populations reported

were stained positively for dithizone, indicating the presence of endogenous insulin. Furthermore, these stem cell-derived insulin producing cells exhibited abundant expression of Pdx-1, C-peptide, insulin, glucagon, somatostatin, pancreatic polypeptide, and Glut-2^[2,44,56]. Enhanced expression of Isl-1, Pax-4, Ngn-3, Ipf-1, Pax-6, Nkx-2.2, Nkx-6.1, FoxA2, GLP-1 receptor, and glucokinase was also confirmed in differentiated cells, implicating pancreatic lineage^[2,16,44,56,69]. Interestingly, transcription of leptin and adiponectin was also well maintained in differentiated cells, still demonstrating adipose tissue characteristics. Additionally, expression of visfatin, which activates insulin receptors and has a blood glucose lowering effect similar to insulin, was significantly upregulated following differentiation into an insulin producing phenotype^[44].

Following transplantation of human ADSC-derived insulin producing cells into streptozotocin-induced diabetic mice, a significant level of human C-peptide was detected in subjects, demonstrating successful insulin production *in vivo*. Although these differentiated cells demonstrated a capacity to lower blood glucose levels, the insulin secretion level compared to mature pancreatic islets was significantly lower, and they failed to restore normoglycemia in STZ-induced diabetic mice^[6,44,67].

The ability of ADSCs to differentiate into insulin-producing cells akin to mature native pancreatic cells also remains under question. Dor *et al*^[70] used a genetic lineage tracing method to determine whether pancreatic stem cells contribute to pancreatic β -cell replenishment during adult life. In this study, they demonstrated that terminally differentiated mature β -cells maintain their proliferative capacity and serve as a major source of new β -cells in mice, contrary to previously reported studies^[71-74]. Although this study directly rejected pluripotent adult stem cells' role in replacing β -cells *in vivo* following partial pancreatectomy, it does not directly refute the utility of insulin-producing cells, differentiated from adult stem cells *in vitro*, as a potential new treatment option for diabetes as demonstrated by a number of studies previously reported^[71-74].

Engraftment of transplanted islets

Success of pancreatic islet transplantation depends on successful engraftment into the recipient liver where donor islets are transfused through the hepatic portal vein. However, apoptosis, inflammation and ischemia frequently interfere with successful engraftment^[75], and therefore two or more pancreata are frequently required to procure sufficient numbers of islets for each transplant. This is a major limitation to the widespread use of this therapy, considering the acute shortage of donor organs. Due to unavoidable destruction of native islet structures, including intraislet vasculature, during isolation, islet engraftment could take up to several weeks^[76,77]. Further deterioration of islets and β -cell death can occur due to ischemia and inflammation, ultimately leading to graft failure^[78,79]. A mean to improve engraftment of transplanted islets

will lead to a reduction of the required number of pancreata and more positive clinical outcomes.

Adipose-derived stem cells have been reported to possess inherent regenerative angiogenic potential and anti-apoptotic capability through their secretion of trophic factors^[80-82]. ADSCs also have anti-inflammatory and immunomodulatory properties, including suppression of T-cell proliferation^[82-88]. Therefore, ADSCs can potentially allow improved engraftment of transplanted islets with enhanced vascularization and suppression of inflammation.

Ohmura *et al*^[79] tested hybrid islet transplantation by co-transplanting allogeneic mouse pancreatic islets along with autologous ADSC under the kidney capsule of recipient mice and demonstrated that autologous murine ADSCs were able to significantly prolong allogeneic islet survival and achieve normoglycemia for up to 14 d. Allogeneic islets alone could not survive under the kidney capsule for longer than 2 d, and normoglycemia was never achieved. The islets following hybrid transplantation showed well-preserved islet architecture and were surrounded by endothelial cells compared to islet grafts transplanted without ADSCs, suggesting vascularization had been improved. Infiltration by CD4⁺/CD8⁺ T cells and CD68⁺ macrophages were also markedly reduced, suggesting successful anti-inflammation and immunomodulation by ADSCs and prolonged graft islet retention when ADSCs were co-transplanted with donor islets^[79]. Although it is still uncertain whether this hybrid transplantation method will work in a clinical model, which utilizes the hepatic portal vein route for islet transplantation rather than the kidney capsule, the potentially enormous benefits of ADSCs in islet engraftment is clearly promising.

Veriter *et al*^[89] also showed the utility of ADSCs by co-encapsulating xenogeneic porcine islets with autologous primate ADSCs in semipermeable capsules and transplanting them in primates. Compared to islets encapsulated alone, improved oxygenation, graft survival and function, and glycated hemoglobin correction, as well as greater vasculogenesis were observed in co-encapsulated implants, consequently reducing the cellular stress immediately following transplantation^[89].

It is widely accepted that a significantly large number of pancreatic islets are lost during the first 10-14 d following infusion into human liver through the portal vein^[90], even in the presence of immunosuppression. Furthermore, 60% of transplanted islets were reported to die during this period even in syngeneic animal models^[91]. An ability to prevent such early death immediately following transplantation, as demonstrated by Ohmura *et al*^[79], Veriter *et al*^[89] and Cavallari *et al*^[92], using ADSCs, may prove to be enormously beneficial to the successful engraftment of transplanted islets.

Challenges and opportunities for ADSCs in diabetes

Several uncertain factors in stem cell-based cell therapy for diabetes still remain: (1) the absence of gold-standard,

reproducible differentiation protocol for generating insulin-producing cells from adult stem cells; (2) an exact dosage of stem cell-derived β -cells to reverse diabetic conditions and feasibility of producing such dosage *in vitro*; (3) proliferative capacity and maintenance of differentiated insulin-producing cells; (4) sensitivity to counter-regulatory hormones; (5) potential adverse effects of undifferentiated adult stem cells; and (6) potential *in vivo* migration of differentiated cells following implantation^[8,15]. Consensus of investigators on the criteria for transdifferentiation and plasticity to avoid confusion with cell fusion, contaminating stem cell populations, and to prevent over interpretation of the data, is necessary^[8,93-95].

A major challenge also lies in imitating the physiological mechanism of insulin secretion. Insulin secretion occurs through complex regulatory systems, involving multiple hormonal feedback mechanisms and neurological stimulation, within the islet of Langerhans. For instance, insulin secretion by β -cells can inhibit glucagon secretion by α -cells^[96]. Somatostatin secreted by δ -cells also regulates insulin secretion by β -cell^[97]. In order to mimic normal or near normal metabolic control, differentiated cells must be able to interact with existing pancreatic endocrine cells. Another mechanism of controlling insulin release is through the secretion of incretin hormones, including glucose-dependent insulinotropic peptide and glucagon-like peptide 1^[10,98-101]. These intestinal tract signaling hormones have shown to be responsible for up to 70% of glucose-induced postprandial insulin secretion^[99,100]. An ability to respond to these signals is also a critical characteristic that stem cell-derived β -cells need to possess in order to closely mimic physiological processes. Lastly, insulin secretion is a pulsatile rather than a constant release, and such pulsatility may be significant in its action^[102]. Stem cells differentiated into a pancreatic lineage that simply produces insulin, even in a glucose-responsive manner, without capability to accommodate these complex interactions, will unavoidably fail to reverse diabetic conditions.

The general architecture of natural pancreatic islets also poses another challenge for the efficacy of differentiated insulin-producing cells. Individual islets are highly vascularized and innervated. The endothelial cells comprising the microvasculatures of pancreatic islets of Langerhans may even be glucose responsive^[10,103]. Stem cell-derived islet-like structures thus far have not shown to contain any intrinsic vascularity within them when derived *in vitro*, and therefore rely on the circulation external to the cell aggregates. The distance between β -cells and capillaries can potentially affect the kinetics of insulin release, and non-physiological integration of islet-like structures to circulation may in turn affect the engraftment, survival, and efficacy of implants^[104]. Insulin release by β -cells is affected not only by increased blood glucose level but also by nervous control (cephalic phase) mostly through cholinergic neurons during meal ingestion^[10,105]. Even with whole organ or pancreatic islet transplantation, complete restoration of the cephalic phase of in-

ulin secretion will fail due to a lack of innervation^[106,107]. These structural challenges are critical to overcome for stem cell-derived β -cells or islets to be clinically viable in the future.

Nearly all of the insulin-producing cells derived from adult stem cells co-express glucagon, somatostatin, pancreatic polypeptide along with insulin, all of which are characteristic of immature pancreatic islets of Langerhans. This suggests an incomplete differentiation of stem cells, and could be one of the main reasons why these cells were unable to achieve normoglycemia in diabetic animals. Further differentiation and maturation are required to achieve a more mature substitute capable of functioning similarly to a normal pancreas. However, others also argue that terminally differentiated mature β -cells might not be required for treatment of diabetes. Konno *et al.*^[108] and Kajiyama *et al.*^[109] reported that transplantation of adipose-derived stem cells overexpressing Pdx-1 ameliorated hyperglycemia and improved survival rate. Furthermore, ecto-pancreatic transplantation enabled normalization of hemoglobin A1c levels and subsequently attenuated or partially reversed nerve and kidney damages caused by diabetes^[10,110,111]. Achieving normal hemoglobin A1c levels may also prove to be critical for future stem cell-based therapies.

Diabetic conditions present a uniquely detrimental environment to various cell types. The proliferative capability of mesenchymal stem cells isolated from adipose tissue of streptozotocin-induced type 1 and 2 diabetic rats was reported to be compromised^[112]. When ADSCs were exposed to high glucose concentration *in vitro* prior to implantation into a hindlimb ischemia model, their proliferative capacity and ability to reverse hindlimb ischemia were significantly and irreversibly reduced, compared to ADSCs cultured at a normal glucose concentration^[112]. In type 1 diabetic patients, however, autoimmunity did not seem to fundamentally influence the regenerative capability of islets and their progenitor cells^[54,113]. Hess *et al.*^[114] demonstrated that bone marrow derived stem cells initiated pancreatic regeneration and reversed hyperglycemia by stimulating proliferation of the recipient's innate pancreatic progenitor cells and β -cells. It is highly possible the same mechanism can be utilized for ADSCs, and therefore, warrants further investigation as well. Improving the relative regenerative capacity of pancreatic islets using ADSCs would potentially benefit diabetic patients.

Transplantation of islet-like cells or pancreas-like tissues generated from stem cells *in vitro* may be accompanied by graft rejection, graft hypertrophy with subsequent chronic hypoglycemia, and potentially malignant transformation. The intrinsic immunomodulatory capabilities of ADSCs have shown to enhance engraftment of multiple types of tissues when co-transplanted^[115-117]. Vanikar *et al.*^[115] reported that transfusion of ADSCs may reduce the need of immunosuppression during renal transplantations. The ability to reduce the required dosage of immunosuppressants would subsequently minimize complications caused by these agents and improve the clinical

outcome of islet transplantation.

Approximately 90% of people with diabetes are suffering from type 2 diabetes. However, only a few cases of stem cell-based research were performed recently^[118-122] to develop a therapeutic option for type 2 diabetes, as type 1 diabetes has stood as the forefront. Deriving insulin-secreting β -cells from stem cells for treatment of type 1 diabetes seems relatively straightforward compared to developing an alternative treatment option for type 2 diabetes. Further research on the complex disease mechanisms of type 2 diabetes in association with the potential utility of stem cells may improve the quality of life for hundreds of millions patients.

CONCLUSION

It is now undeniable that the utility of ADSCs in the treatment of diabetes is extremely promising. The abundance of available source tissue, high frequency and multipotency of adipose-derived mesenchymal stem cells, its trophic and regenerative capabilities, all serve as valuable solutions to the ever-increasing diabetic population and associated health crises observed around the world. Understanding of ADSCs and the development of ADSC-based treatments for diabetes are still considered to be in their infancy, and numerous challenges and opportunities still lie ahead. The exact mechanism of generating insulin-producing cells from ADSCs as well as further maturation of those cells into functional pancreatic islets still needs to be further explored. Sustainability of differentiated insulin-producing cells is still under investigation. Autoimmune attack on β -cells, which is a fundamental disease mechanism of type 1 diabetes, has not been completely resolved and can make any future cell-based therapy unfeasible.

Current therapies for diabetes ranging from insulin injection to pancreatic islet transplantation are not truly the best options for patients. Stem cells that are theoretically limitless in numbers and multipotent will provide hopes and viable therapies for millions of diabetic patients in the future. However, if all stem cell-based therapies only eliminate the need for glucose monitoring and insulin injection for convenience and modestly improve diabetic symptoms, it would not justify the adoption of these therapies in the future. Therefore, stem cell-based therapies must be able to provide fundamentally improved multifaceted metabolic controls and concomitantly improve long-term prognosis in diabetic patients to be widely accepted as a clinically viable therapy.

REFERENCES

- 1 Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011; **378**: 31-40 [PMID: 21705069 DOI: 10.1016/S0140-6736(11)60679-X]

- 2 Dhanasekaran M, Indumathi S, Harikrishnan R, Mishra R, Lissa RP, Rajkumar JS, Sudarsanam D. Human omentum fat-derived mesenchymal stem cells transdifferentiates into pancreatic islet-like cluster. *Cell Biochem Funct* 2013; **31**: 612-619 [PMID: 23315589 DOI: 10.1002/cbf.2948]
- 3 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**: e442 [PMID: 17132052]
- 4 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047-1053 [PMID: 15111519]
- 5 Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. *Diabetes Care* 2006; **29**: 2114-2116 [PMID: 16936162]
- 6 Lin G, Wang G, Liu G, Yang LJ, Chang LJ, Lue TF, Lin CS. Treatment of type 1 diabetes with adipose tissue-derived stem cells expressing pancreatic duodenal homeobox 1. *Stem Cells Dev* 2009; **18**: 1399-1406 [PMID: 19245309 DOI: 10.1089/scd.2009.0010]
- 7 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; **414**: 782-787 [PMID: 11742409]
- 8 Ansari MJ, Fiorina P, Dada S, Guleria I, Ueno T, Yuan X, Trikudanathan S, Smith RN, Freeman G, Sayegh MH. Role of ICOS pathway in autoimmune and alloimmune responses in NOD mice. *Clin Immunol* 2008; **126**: 140-147 [PMID: 17889619]
- 9 Ramiya V, Schatz D. Islet replacement vs. regeneration: hope or hype? *Pediatr Diabetes* 2004; **5** Suppl 2: 45-56 [PMID: 15601374]
- 10 Lechner A. Stem cells and regenerative medicine for the treatment of type 1 diabetes: the challenges lying ahead. *Pediatr Diabetes* 2004; **5** Suppl 2: 88-93 [PMID: 15601379]
- 11 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; **329**: 977-986 [PMID: 8366922]
- 12 Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery-the path to physiological glucose control. *Adv Drug Deliv Rev* 2004; **56**: 125-144 [PMID: 14741112]
- 13 Manuel DG, Schultz SE. Using linked data to calculate summary measures of population health: Health-adjusted life expectancy of people with Diabetes Mellitus. *Popul Health Metr* 2004; **2**: 4 [PMID: 15038828]
- 14 Wei AH, Wang WJ, Mu XP, Li HM, Yan WQ. Enhanced differentiation of human adipose tissue-derived stromal cells into insulin-producing cells with glucagon-like peptide-1. *Exp Clin Endocrinol Diabetes* 2012; **120**: 28-34 [PMID: 21915820 DOI: 10.1055/s-0031-1280807]
- 15 Harvey JN, Allagoa B. The long-term renal and retinal outcome of childhood-onset Type 1 diabetes. *Diabet Med* 2004; **21**: 26-31 [PMID: 14706050]
- 16 Zulewski H. Stem cells with potential to generate insulin-producing cells in man. *Swiss Med Wkly* 2007; **137** Suppl 155: 60S-67S [PMID: 17874504]
- 17 Venturini M, Fiorina P, Maffi P, Losio C, Vergani A, Secchi A, Del Maschio A. Early increase of retinal arterial and venous blood flow velocities at color Doppler imaging in brittle type 1 diabetes after islet transplant alone. *Transplantation* 2006; **81**: 1274-1277 [PMID: 16699454]
- 18 Maffi P, Bertuzzi F, De Taddeo F, Magistretti P, Nano R, Fiorina P, Caumo A, Pozzi P, Socci C, Venturini M, del Maschio A, Secchi A. Kidney function after islet transplant alone in type 1 diabetes: impact of immunosuppressive therapy on progression of diabetic nephropathy. *Diabetes Care* 2007; **30**: 1150-1155 [PMID: 17259471]
- 19 Paroni R, Fermo I, Fiorina P, Cighetti G. Determination of asymmetric and symmetric dimethylarginines in plasma

- of hyperhomocysteinemic subjects. *Amino Acids* 2005; **28**: 389-394 [PMID: 15827687]
- 20 **Astorri E**, Fiorina P, Gavaruzzi G, Astorri A, Magnati G. Left ventricular function in insulin-dependent and in non-insulin-dependent diabetic patients: radionuclide assessment. *Cardiology* 1997; **88**: 152-155 [PMID: 9096915]
- 21 **Folli F**, Guzzi V, Perego L, Coletta DK, Finzi G, Placidi C, La Rosa S, Capella C, Soggi C, Lauro D, Tripathy D, Jenkinson C, Paroni R, Orsenigo E, Cighetti G, Gregorini L, Staudacher C, Secchi A, Bachi A, Brownlee M, Fiorina P. Proteomics reveals novel oxidative and glycolytic mechanisms in type 1 diabetic patients' skin which are normalized by kidney-pancreas transplantation. *PLoS One* 2010; **5**: e9923 [PMID: 20360867]
- 22 **Sutherland DE**, Gruessner RW, Dunn DL, Matas AJ, Humar A, Kandaswamy R, Mauer SM, Kennedy WR, Goetz FC, Robertson RP, Gruessner AC, Najarian JS. Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann Surg* 2001; **233**: 463-501 [PMID: 11303130]
- 23 **Shapiro AM**, Ryan EA, Lakey JR. Clinical islet transplant-state of the art. *Transplant Proc* 2001; **33**: 3502-3503 [PMID: 11750497]
- 24 **Ryan EA**, Lakey JR, Paty BW, Imes S, Korbutt GS, Kneteman NM, Bigam D, Rajotte RV, Shapiro AM. Successful islet transplantation: continued insulin reserve provides long-term glycemic control. *Diabetes* 2002; **51**: 2148-2157 [PMID: 12086945]
- 25 **Ryan EA**, Paty BW, Senior PA, Bigam D, Alfadhi E, Kneteman NM, Lakey JR, Shapiro AM. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005; **54**: 2060-2069 [PMID: 15983207]
- 26 **Vergani A**, D'Addio F, Jurewicz M, Petrelli A, Watanabe T, Liu K, Law K, Schuetz C, Carvello M, Orsenigo E, Deng S, Rodig SJ, Ansari JM, Staudacher C, Abdi R, Williams J, Markmann J, Atkinson M, Sayegh MH, Fiorina P. A novel clinically relevant strategy to abrogate autoimmunity and regulate alloimmunity in NOD mice. *Diabetes* 2010; **59**: 2253-2264 [PMID: 20805386 DOI: 10.2337/db09-1264]
- 27 **Williams PW**. Notes on diabetes treated with extract and by grafts of sheep's pancreas. *BMJ* 1894; **2**: 1303-1304
- 28 **Miszta-Lane H**, Mirbolooki M, James Shapiro AM, Lakey JR. Stem cell sources for clinical islet transplantation in type 1 diabetes: embryonic and adult stem cells. *Med Hypotheses* 2006; **67**: 909-913 [PMID: 16762516]
- 29 **Hirshberg B**, Rother KI, Digon BJ, Lee J, Gaglia JL, Hines K, Read EJ, Chang R, Wood BJ, Harlan DM. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: the National Institutes of Health experience. *Diabetes Care* 2003; **26**: 3288-3295 [PMID: 14633816]
- 30 **Krishnan L**, Touroo J, Reed R, Boland E, Hoying JB, Williams SK. Vascularization and cellular isolation potential of a novel electrospun cell delivery vehicle. *J Biomed Mater Res A* 2014; **102**: 2208-2219 [PMID: 23913805 DOI: 10.1002/jbm.a.34900]
- 31 **Wagers AJ**, Weissman IL. Plasticity of adult stem cells. *Cell* 2004; **116**: 639-648 [PMID: 15006347]
- 32 **Zalzman M**, Gupta S, Giri RK, Berkovich I, Sappal BS, Karnieli O, Zern MA, Fleischer N, Efrat S. Reversal of hyperglycemia in mice by using human expandable insulin-producing cells differentiated from fetal liver progenitor cells. *Proc Natl Acad Sci USA* 2003; **100**: 7253-7258 [PMID: 12756298]
- 33 **Hori Y**, Gu X, Xie X, Kim SK. Differentiation of insulin-producing cells from human neural progenitor cells. *PLoS Med* 2005; **2**: e103 [PMID: 15839736]
- 34 **Kodama S**, Kührtreiber W, Fujimura S, Dale EA, Faustman DL. Islet regeneration during the reversal of autoimmune diabetes in NOD mice. *Science* 2003; **302**: 1223-1227 [PMID: 14615542]
- 35 **Ianus A**, Holz GG, Theise ND, Hussain MA. In vivo derivation of glucose-competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. *J Clin Invest* 2003; **111**: 843-850 [PMID: 12639990]
- 36 **Tang DQ**, Cao LZ, Burkhardt BR, Xia CQ, Litherland SA, Atkinson MA, Yang LJ. In vivo and in vitro characterization of insulin-producing cells obtained from murine bone marrow. *Diabetes* 2004; **53**: 1721-1732 [PMID: 15220196]
- 37 **Ramiya VK**, Maraist M, Arfors KE, Schatz DA, Peck AB, Cornelius JG. Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic stem cells. *Nat Med* 2000; **6**: 278-282 [PMID: 10700229]
- 38 **Bonner-Weir S**, Taneja M, Weir GC, Tatarikiewicz K, Song KH, Sharma A, O'Neil JJ. In vitro cultivation of human islets from expanded ductal tissue. *Proc Natl Acad Sci USA* 2000; **97**: 7999-8004 [PMID: 10884429]
- 39 **Fiorina P**, Voltarelli J, Zavazava N. Immunological applications of stem cells in type 1 diabetes. *Endocr Rev* 2011; **32**: 725-754 [PMID: 21862682 DOI: 10.1210/er.2011-0008]
- 40 **Francesse R**, Fiorina P. Immunological and regenerative properties of cord blood stem cells. *Clin Immunol* 2010; **136**: 309-322 [PMID: 20447870 DOI: 10.1016/j.clim.2010.04.010]
- 41 **Parekh VS**, Joglekar MV, Hardikar AA. Differentiation of human umbilical cord blood-derived mononuclear cells to endocrine pancreatic lineage. *Differentiation* 2009; **78**: 232-240 [PMID: 19664871 DOI: 10.1016/j.diff.2009.07.004]
- 42 **Ende N**, Chen R, Reddi AS. Effect of human umbilical cord blood cells on glycemia and insulinitis in type 1 diabetic mice. *Biochem Biophys Res Commun* 2004; **325**: 665-669 [PMID: 15541340]
- 43 **Fedyunina IA**, Rzhabinova AA, Kirienko EE, Goldshtein DV. Isolation of insulin-producing cells from different populations of multipotent stromal cells of the umbilical cord and human adipose tissue. *Bull Exp Biol Med* 2011; **151**: 114-120 [PMID: 22442815]
- 44 **Chandra V**, G S, Phadnis S, Nair PD, Bhonde RR. Generation of pancreatic hormone-expressing islet-like cell aggregates from murine adipose tissue-derived stem cells. *Stem Cells* 2009; **27**: 1941-1953 [PMID: 19544426 DOI: 10.1002/stem.117]
- 45 **Zuk PA**, Zhu M, Ashjian P, De Ugarte DA, Huang JL, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 2002; **13**: 4279-4295 [PMID: 12475952]
- 46 **Schäffler A**, Büchler C. Concise review: adipose tissue-derived stromal cells--basic and clinical implications for novel cell-based therapies. *Stem Cells* 2007; **25**: 818-827 [PMID: 17420225]
- 47 **Doi K**, Tanaka S, Iida H, Eto H, Kato H, Aoi N, Kuno S, Hirohi T, Yoshimura K. Stromal vascular fraction isolated from lipo-aspirates using an automated processing system: bench and bed analysis. *J Tissue Eng Regen Med* 2013; **7**: 864-870 [PMID: 22438241 DOI: 10.1002/term.1478]
- 48 **Gimble JM**, Guilak F, Bunnell BA. Clinical and preclinical translation of cell-based therapies using adipose tissue-derived cells. *Stem Cell Res Ther* 2010; **1**: 19 [PMID: 20587076 DOI: 10.1186/scri19]
- 49 **De Ugarte DA**, Morizono K, Elbarbary A, Alfonso Z, Zuk PA, Zhu M, Dragoo JL, Ashjian P, Thomas B, Benhaim P, Chen I, Fraser J, Hedrick MH. Comparison of multi-lineage cells from human adipose tissue and bone marrow. *Cells Tissues Organs* 2003; **174**: 101-109 [PMID: 12835573]
- 50 **Lee RH**, Kim B, Choi I, Kim H, Choi HS, Suh K, Bae YC, Jung JS. Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue. *Cell Physiol Biochem* 2004; **14**: 311-324 [PMID: 15319535]
- 51 **Dicker A**, Le Blanc K, Aström G, van Harmelen V, Götherström C, Blomqvist L, Arner P, Rydén M. Functional studies of mesenchymal stem cells derived from adult human adipose tissue. *Exp Cell Res* 2005; **308**: 283-290 [PMID: 15925364]
- 52 **Fraser J**, Wulur I, Alfonso Z, Zhu M, Wheeler E. Differences in stem and progenitor cell yield in different subcutaneous adipose tissue depots. *Cytotherapy* 2007; **9**: 459-467 [PMID:

- 17786607]
- 53 **Strem BM**, Hicok KC, Zhu M, Wulur I, Alfonso Z, Schreiber RE, Fraser JK, Hedrick MH. Multipotential differentiation of adipose tissue-derived stem cells. *Keio J Med* 2005; **54**: 132-141 [PMID: 16237275]
 - 54 **Nakao N**, Nakayama T, Yahata T, Muguruma Y, Saito S, Miyata Y, Yamamoto K, Naoe T. Adipose tissue-derived mesenchymal stem cells facilitate hematopoiesis in vitro and in vivo: advantages over bone marrow-derived mesenchymal stem cells. *Am J Pathol* 2010; **177**: 547-554 [PMID: 20558580 DOI: 10.2353/ajpath.2010.091042]
 - 55 **Kodama S**, Faustman DL. Routes to regenerating islet cells: stem cells and other biological therapies for type 1 diabetes. *Pediatr Diabetes* 2004; **5 Suppl 2**: 38-44 [PMID: 15601373]
 - 56 **Timper K**, Seboek D, Eberhardt M, Linscheid P, Christ-Crain M, Keller U, Müller B, Zulewski H. Human adipose tissue-derived mesenchymal stem cells differentiate into insulin, somatostatin, and glucagon expressing cells. *Biochem Biophys Res Commun* 2006; **341**: 1135-1140 [PMID: 16460677]
 - 57 **Ahlgren U**, Pfaff SL, Jessell TM, Edlund T, Edlund H. Independent requirement for ISL1 in formation of pancreatic mesenchyme and islet cells. *Nature* 1997; **385**: 257-260 [PMID: 9000074]
 - 58 **Lechner A**, Leech CA, Abraham EJ, Nolan AL, Habener JF. Nestin-positive progenitor cells derived from adult human pancreatic islets of Langerhans contain side population (SP) cells defined by expression of the ABCG2 (BCRP1) ATP-binding cassette transporter. *Biochem Biophys Res Commun* 2002; **293**: 670-674 [PMID: 12054520]
 - 59 **Cai J**, Cheng A, Luo Y, Lu C, Mattson MP, Rao MS, Furu-kawa K. Membrane properties of rat embryonic multipotent neural stem cells. *J Neurochem* 2004; **88**: 212-226 [PMID: 14675165]
 - 60 **Kojima H**, Fujimiya M, Matsumura K, Nakahara T, Hara M, Chan L. Extrapancratic insulin-producing cells in multiple organs in diabetes. *Proc Natl Acad Sci USA* 2004; **101**: 2458-2463 [PMID: 14983031]
 - 61 **Lumelsky N**, Blondel O, Laeng P, Velasco I, Ravin R, McKay R. Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets. *Science* 2001; **292**: 1389-1394 [PMID: 11326082]
 - 62 **Hori Y**, Rulifson IC, Tsai BC, Heit JJ, Cahoy JD, Kim SK. Growth inhibitors promote differentiation of insulin-producing tissue from embryonic stem cells. *Proc Natl Acad Sci USA* 2002; **99**: 16105-16110 [PMID: 12441403]
 - 63 **Soria B**, Roche E, Berná G, León-Quinto T, Reig JA, Martín F. Insulin-secreting cells derived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice. *Diabetes* 2000; **49**: 157-162 [PMID: 10868930]
 - 64 **Paek HJ**, Morgan JR, Lysaght MJ. Sequestration and synthesis: the source of insulin in cell clusters differentiated from murine embryonic stem cells. *Stem Cells* 2005; **23**: 862-867 [PMID: 15888689]
 - 65 **Paek HJ**, Moise LJ, Morgan JR, Lysaght MJ. Origin of insulin secreted from islet-like cell clusters derived from murine embryonic stem cells. *Cloning Stem Cells* 2005; **7**: 226-231 [PMID: 16390258]
 - 66 **Dave SD**, Vanikar AV, Trivedi HL. Ex vivo generation of glucose sensitive insulin secreting mesenchymal stem cells derived from human adipose tissue. *Indian J Endocrinol Metab* 2012; **16 Suppl 1**: S65-S69 [PMID: 22701849 DOI: 10.4103/2230-8210.94264]
 - 67 **Chandra V**, Swetha G, Muthyala S, Jaiswal AK, Bellare JR, Nair PD, Bhonde RR. Islet-like cell aggregates generated from human adipose tissue derived stem cells ameliorate experimental diabetes in mice. *PLoS One* 2011; **6**: e20615 [PMID: 21687731 DOI: 10.1371/journal.pone.0020615]
 - 68 **Zhang S**, Dai H, Wan N, Moore Y, Dai Z. Promoting long-term survival of insulin-producing cell grafts that differentiate from adipose tissue-derived stem cells to cure type 1 diabetes. *PLoS One* 2011; **6**: e29706 [PMID: 22216347 DOI: 10.1371/journal.pone.0029706]
 - 69 **Lee J**, Kim SC, Kim SJ, Lee H, Jung EJ, Jung SH, Han DJ. Differentiation of human adipose tissue-derived stem cells into aggregates of insulin-producing cells through the over-expression of pancreatic and duodenal homeobox gene-1. *Cell Transplant* 2013; **22**: 1053-1060 [PMID: 23031216 DOI: 10.3727/096368912X657215]
 - 70 **Dor Y**, Brown J, Martinez OI, Melton DA. Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. *Nature* 2004; **429**: 41-46 [PMID: 15129273]
 - 71 **Baeyens L**, De Breuck S, Lardon J, Mfopou JK, Rooman I, Bouwens L. In vitro generation of insulin-producing beta cells from adult exocrine pancreatic cells. *Diabetologia* 2005; **48**: 49-57 [PMID: 15616797]
 - 72 **Minami K**, Okuno M, Miyawaki K, Okumachi A, Ishizaki K, Oyama K, Kawaguchi M, Ishizuka N, Iwanaga T, Seino S. Lineage tracing and characterization of insulin-secreting cells generated from adult pancreatic acinar cells. *Proc Natl Acad Sci USA* 2005; **102**: 15116-15121 [PMID: 16210247]
 - 73 **Seaberg RM**, Smukler SR, Kieffer TJ, Enikolopov G, Asghar Z, Wheeler MB, Korbitt G, van der Kooy D. Clonal identification of multipotent precursors from adult mouse pancreas that generate neural and pancreatic lineages. *Nat Biotechnol* 2004; **22**: 1115-1124 [PMID: 15322557]
 - 74 **Zulewski H**, Abraham EJ, Gerlach MJ, Daniel PB, Moritz W, Müller B, Vallejo M, Thomas MK, Habener JF. Multipotential nestin-positive stem cells isolated from adult pancreatic islets differentiate ex vivo into pancreatic endocrine, exocrine, and hepatic phenotypes. *Diabetes* 2001; **50**: 521-533 [PMID: 11246871]
 - 75 **Korsgren O**, Lundgren T, Felldin M, Foss A, Isaksson B, Permert J, Persson NH, Rafael E, Rydén M, Salmela K, Tibell A, Tufveson G, Nilsson B. Optimising islet engraftment is critical for successful clinical islet transplantation. *Diabetologia* 2008; **51**: 227-232 [PMID: 18040664]
 - 76 **Lifson N**, Lassa CV, Dixit PK. Relation between blood flow and morphology in islet organ of rat pancreas. *Am J Physiol* 1985; **249**: E43-E48 [PMID: 2409813]
 - 77 **Carlsson PO**, Liss P, Andersson A, Jansson L. Measurements of oxygen tension in native and transplanted rat pancreatic islets. *Diabetes* 1998; **47**: 1027-1032 [PMID: 9648824]
 - 78 **Barshes NR**, Wyllie S, Goss JA. Inflammation-mediated dysfunction and apoptosis in pancreatic islet transplantation: implications for intrahepatic grafts. *J Leukoc Biol* 2005; **77**: 587-597 [PMID: 15728243]
 - 79 **Ohmura Y**, Tanemura M, Kawaguchi N, Machida T, Tanida T, Deguchi T, Wada H, Kobayashi S, Marubashi S, Eguchi H, Takeda Y, Matsuura N, Ito T, Nagano H, Doki Y, Mori M. Combined transplantation of pancreatic islets and adipose tissue-derived stem cells enhances the survival and insulin function of islet grafts in diabetic mice. *Transplantation* 2010; **90**: 1366-1373 [PMID: 21076379 DOI: 10.1097/TP.0b013e3181f1fba31]
 - 80 **Moon MH**, Kim SY, Kim YJ, Kim SJ, Lee JB, Bae YC, Sung SM, Jung JS. Human adipose tissue-derived mesenchymal stem cells improve postnatal neovascularization in a mouse model of hindlimb ischemia. *Cell Physiol Biochem* 2006; **17**: 279-290 [PMID: 16791003]
 - 81 **Kim Y**, Kim H, Cho H, Bae Y, Suh K, Jung J. Direct comparison of human mesenchymal stem cells derived from adipose tissues and bone marrow in mediating neovascularization in response to vascular ischemia. *Cell Physiol Biochem* 2007; **20**: 867-876 [PMID: 17982269]
 - 82 **Rehman J**, Traktuev D, Li J, Merfeld-Clauss S, Temm-Grove CJ, Bovenkerk JE, Pell CL, Johnstone BH, Considine RV, March KL. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation* 2004; **109**: 1292-1298 [PMID: 14993122]
 - 83 **Ghannam S**, Bouffi C, Djouad F, Jorgensen C, Noël D. Im-

- munosuppression by mesenchymal stem cells: mechanisms and clinical applications. *Stem Cell Res Ther* 2010; **1**: 2 [PMID: 20504283 DOI: 10.1186/scrt2]
- 84 **Keyser KA**, Beagles KE, Kiem HP. Comparison of mesenchymal stem cells from different tissues to suppress T-cell activation. *Cell Transplant* 2007; **16**: 555-562 [PMID: 17708345]
- 85 **González MA**, Gonzalez-Rey E, Rico L, Büscher D, Delgado M. Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. *Arthritis Rheum* 2009; **60**: 1006-1019 [PMID: 19333946 DOI: 10.1002/art24405]
- 86 **Constantin G**, Marconi S, Rossi B, Angiari S, Calderan L, Anghileri E, Gini B, Bach SD, Martinello M, Bifari F, Galie M, Turano E, Budui S, Sbarbati A, Krampera M, Bonetti B. Adipose-derived mesenchymal stem cells ameliorate chronic experimental autoimmune encephalomyelitis. *Stem Cells* 2009; **27**: 2624-2635 [PMID: 19676124 DOI: 10.1002/stem.194]
- 87 **Kang JW**, Kang KS, Koo HC, Park JR, Choi EW, Park YH. Soluble factors-mediated immunomodulatory effects of canine adipose tissue-derived mesenchymal stem cells. *Stem Cells Dev* 2008; **17**: 681-693 [PMID: 18717642 DOI: 10.1089/scd.2007.0153]
- 88 **Cui L**, Yin S, Liu W, Li N, Zhang W, Cao Y. Expanded adipose-derived stem cells suppress mixed lymphocyte reaction by secretion of prostaglandin E2. *Tissue Eng* 2007; **13**: 1185-1195 [PMID: 17518704]
- 89 **Vériter S**, Gianello P, Igarashi Y, Beaurin G, Ghyselinck A, Aouassar N, Jordan B, Gallez B, Dufrane D. Improvement of Subcutaneous Bioartificial Pancreas Vascularization and Function by Co-Encapsulation of Pig Islets and Mesenchymal Stem Cells in Primates. *Cell Transplant* 2013; Epub ahead of print [PMID: 23461890 DOI: 10.3727/096368913X663550]
- 90 **Evgenov NV**, Medarova Z, Pratt J, Pantazopoulos P, Leyting S, Bonner-Weir S, Moore A. In vivo imaging of immune rejection in transplanted pancreatic islets. *Diabetes* 2006; **55**: 2419-2428 [PMID: 16936189]
- 91 **Barshes NR**, Lee T, Goodpasture S, Brunnicardi FC, Alejandro R, Ricordi C, Soltes G, Barth M, Hamilton D, Goss JA. Achievement of insulin independence via pancreatic islet transplantation using a remote isolation center: a first-year review. *Transplant Proc* 2004; **36**: 1127-1129 [PMID: 15194393]
- 92 **Cavallari G**, Olivi E, Bianchi F, Neri F, Foroni L, Valente S, La Manna G, Nardo B, Stefoni S, Ventura C. Mesenchymal stem cells and islet cotransplantation in diabetic rats: improved islet graft revascularization and function by human adipose tissue-derived stem cells preconditioned with natural molecules. *Cell Transplant* 2012; **21**: 2771-2781 [PMID: 22472472 DOI: 10.3727/096368912X637046]
- 93 **Terada N**, Hamazaki T, Oka M, Hoki M, Mastalerz DM, Nakano Y, Meyer EM, Morel L, Petersen BE, Scott EW. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature* 2002; **416**: 542-545 [PMID: 11932747]
- 94 **Jiang Y**, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, Reyes M, Lenvik T, Lund T, Blackstad M, Du J, Aldrich S, Lisberg A, Low WC, Largaespada DA, Verfaillie CM. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 2002; **418**: 41-49 [PMID: 12077603]
- 95 **Weissman IL**, Anderson DJ, Gage F. Stem and progenitor cells: origins, phenotypes, lineage commitments, and trans-differentiations. *Annu Rev Cell Dev Biol* 2001; **17**: 387-403 [PMID: 11687494]
- 96 **Ishihara H**, Maechler P, Gjinovci A, Herrera PL, Wollheim CB. Islet beta-cell secretion determines glucagon release from neighbouring alpha-cells. *Nat Cell Biol* 2003; **5**: 330-335 [PMID: 12640462]
- 97 **Kleinman R**, Ohning G, Wong H, Watt P, Walsh J, Brunnicardi FC. Regulatory role of intraislet somatostatin on insulin secretion in the isolated perfused human pancreas. *Pancreas* 1994; **9**: 172-178 [PMID: 7910686]
- 98 **Creutzfeldt W**. The entero-insular axis in type 2 diabetes--incretins as therapeutic agents. *Exp Clin Endocrinol Diabetes* 2001; **109** Suppl 2: S288-S303 [PMID: 11460578]
- 99 **Holst JJ**, Vilsbøll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. *Mol Cell Endocrinol* 2009; **297**: 127-136 [PMID: 18786605 DOI: 10.1016/j.mce.2008.08.012]
- 100 **Holst JJ**, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab* 2004; **287**: E199-E206 [PMID: 15271645]
- 101 **Gault VA**, Kerr BD, Harriott P, Platt PR. Administration of an acylated GLP-1 and GIP preparation provides added beneficial glucose-lowering and insulinotropic actions over single incretins in mice with Type 2 diabetes and obesity. *Clin Sci (Lond)* 2011; **121**: 107-117 [PMID: 21332446 DOI: 10.1042/CS20110006]
- 102 **Pørksen N**. The in vivo regulation of pulsatile insulin secretion. *Diabetologia* 2002; **45**: 3-20 [PMID: 11845219]
- 103 **Suschek C**, Fehsel K, Kröncke KD, Sommer A, Kolb-Bachofen V. Primary cultures of rat islet capillary endothelial cells. Constitutive and cytokine-inducible macrophagelike nitric oxide synthases are expressed and activities regulated by glucose concentration. *Am J Pathol* 1994; **145**: 685-695 [PMID: 7521579]
- 104 **Brissova M**, Fowler M, Wiebe P, Shostak A, Shiota M, Radhika A, Lin PC, Gannon M, Powers AC. Intraislet endothelial cells contribute to revascularization of transplanted pancreatic islets. *Diabetes* 2004; **53**: 1318-1325 [PMID: 15111502]
- 105 **Ahrén B**, Holst JJ. The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. *Diabetes* 2001; **50**: 1030-1038 [PMID: 11334405]
- 106 **Secchi A**, Caldara R, Caumo A, Monti LD, Bonfatti D, Di Carlo V, Pozza G. Cephalic-phase insulin and glucagon release in normal subjects and in patients receiving pancreas transplantation. *Metabolism* 1995; **44**: 1153-1158 [PMID: 7666788]
- 107 **Berthoud HR**, Trimble ER, Siegel EG, Bereiter DA, Jeanrenaud B. Cephalic-phase insulin secretion in normal and pancreatic islet-transplanted rats. *Am J Physiol* 1980; **238**: E336-E340 [PMID: 6769337]
- 108 **Konno M**, Hamabe A, Hasegawa S, Ogawa H, Fukusumi T, Nishikawa S, Ohta K, Kano Y, Ozaki M, Noguchi Y, Sakai D, Kudoh T, Kawamoto K, Eguchi H, Satoh T, Tanemura M, Nagano H, Doki Y, Mori M, Ishii H. Adipose-derived mesenchymal stem cells and regenerative medicine. *Dev Growth Differ* 2013; **55**: 309-318 [PMID: 23452121 DOI: 10.1111/dgd.12049]
- 109 **Kajiyama H**, Hamazaki TS, Tokuhara M, Masui S, Okabayashi K, Ohnuma K, Yabe S, Yasuda K, Ishiura S, Okochi H, Asashima M. Pdx1-transfected adipose tissue-derived stem cells differentiate into insulin-producing cells in vivo and reduce hyperglycemia in diabetic mice. *Int J Dev Biol* 2010; **54**: 699-705 [PMID: 19757377 DOI: 10.1387/ijdb.092953hk]
- 110 **Navarro X**, Sutherland DE, Kennedy WR. Long-term effects of pancreatic transplantation on diabetic neuropathy. *Ann Neurol* 1997; **42**: 727-736 [PMID: 9392572]
- 111 **Fioretto P**, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 1998; **339**: 69-75 [PMID: 9654536]
- 112 **Kim HK**, Kim YJ, Kim JT, Kwon CH, Kim YK, Bae YC, Kim DH, Jung JS. Alterations in the proangiogenic functions of adipose tissue-derived stromal cells isolated from diabetic rats. *Stem Cells Dev* 2008; **17**: 669-680 [PMID: 18788931 DOI: 10.1089/scd.2008.0141]
- 113 **Ryu S**, Kodama S, Ryu K, Schoenfeld DA, Faustman DL. Reversal of established autoimmune diabetes by restoration of endogenous beta cell function. *J Clin Invest* 2001; **108**: 63-72 [PMID: 11435458]
- 114 **Hess D**, Li L, Martin M, Sakano S, Hill D, Strutt B, Thyssen

- S, Gray DA, Bhatia M. Bone marrow-derived stem cells initiate pancreatic regeneration. *Nat Biotechnol* 2003; **21**: 763-770 [PMID: 12819790]
- 115 **Vanikar AV**, Trivedi HL. Stem cell transplantation in living donor renal transplantation for minimization of immunosuppression. *Transplantation* 2012; **94**: 845-850 [PMID: 22992765 DOI: 10.1097/TP.0b013e3182664000]
- 116 **Kuo YR**, Chen CC, Goto S, Lee IT, Huang CW, Tsai CC, Wang CT, Chen CL. Modulation of immune response and T-cell regulation by donor adipose-derived stem cells in a rodent hind-limb allotransplant model. *Plast Reconstr Surg* 2011; **128**: 661e-672e [PMID: 22094768 DOI: 10.1097/PRS.0b013e318230c60b]
- 117 **Vanikar AV**, Trivedi HL, Feroze A, Kanodia KV, Dave SD, Shah PR. Effect of co-transplantation of mesenchymal stem cells and hematopoietic stem cells as compared to hematopoietic stem cell transplantation alone in renal transplantation to achieve donor hypo-responsiveness. *Int Urol Nephrol* 2011; **43**: 225-232 [PMID: 20084457 DOI: 10.1007/s11255-009-9659-1]
- 118 **Nam JS**, Kang HM, Kim J, Park S, Kim H, Ahn CW, Park JO, Kim KR. Transplantation of insulin-secreting cells differentiated from human adipose tissue-derived stem cells into type 2 diabetes mice. *Biochem Biophys Res Commun* 2014; **443**: 775-781 [PMID: 24148246 DOI: 10.1016/j.bbrc.2013.10.059]
- 119 **Zhao Y**, Jiang Z, Zhao T, Ye M, Hu C, Zhou H, Yin Z, Chen Y, Zhang Y, Wang S, Shen J, Thaker H, Jain S, Li Y, Diao Y, Chen Y, Sun X, Fisk MB, Li H. Targeting insulin resistance in type 2 diabetes via immune modulation of cord blood-derived multipotent stem cells (CB-SCs) in stem cell educator therapy: phase I/II clinical trial. *BMC Med* 2013; **11**: 160 [PMID: 23837842 DOI: 10.1186/1741-7015-11-160]
- 120 **Hao H**, Liu J, Shen J, Zhao Y, Liu H, Hou Q, Tong C, Ti D, Dong L, Cheng Y, Mu Y, Liu J, Fu X, Han W. Multiple intravenous infusions of bone marrow mesenchymal stem cells reverse hyperglycemia in experimental type 2 diabetes rats. *Biochem Biophys Res Commun* 2013; **436**: 418-423 [PMID: 23770360 DOI: 10.1016/j.bbrc.2013.05.117]
- 121 **Jiang R**, Han Z, Zhuo G, Qu X, Li X, Wang X, Shao Y, Yang S, Han ZC. Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. *Front Med* 2011; **5**: 94-100 [PMID: 21681681 DOI: 10.1007/s11684-011-011-z]
- 122 **Estrada EJ**, Valacchi F, Nicora E, Brieva S, Esteve C, Echevarria L, Froud T, Bernetti K, Cayetano SM, Velazquez O, Alejandro R, Ricordi C. Combined treatment of intrapancreatic autologous bone marrow stem cells and hyperbaric oxygen in type 2 diabetes mellitus. *Cell Transplant* 2008; **17**: 1295-1304 [PMID: 19364067]

P- Reviewers: Fiorina P, Panchu P **S- Editor:** Ma YJ
L- Editor: A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

