**DIABETES MELLITUS**

**A. Clinical Response:** Clinical response demonstrates a decrease in blood glucose as well as the differentiation of stem cells into B-cells. In addition to physical examinations prior to stem cell treatment and 6 months post-treatment, laboratory test results serve as evidence of repair process. Internationally recognized lab tests for monitoring Diabetes Mellitus include:
- Complete Blood Count
- Complete Metabolic Panel
- HbA1c (Glycosylated hemoglobin)
- Fasting Blood glucose
- Oral glucose tolerance tests

**PRELIMINARIES**

**A. Background:** Diabetes results from the insufficient production of insulin by the pancreas. This is caused by genetic predisposition as well as sometimes caused by destruction of pancreas by pancreatitis. Insulin allows glucose to enter the cells where it is converted to energy for metabolism. When there is an insulin deficiency, cells do not receive insulin and thus high blood sugar and high urine sugar occurs. The latter causes dehydration. Severe blood sugar is life threatening. Initially, the affected will have a large appetite which will diminish with time. As the disease advances and is not treated, lethargy, loss of appetite, vomiting, dehydration and ultimately coma will occur. Cataracts are a common occurrence and eventually all organs are affected. There are two types of Diabetes: Diabetes type 1 caused by a predisposition to the disease and Diabetes type 2 caused by a pre-existing condition which leads to diabetes [1].

**B. Types of diabetes:**
- **Prediabetes:** is a condition in which blood glucose levels are higher than normal but not high enough for a diagnosis of diabetes. This condition is sometimes called impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Patients with prediabetes are at increased risk of developing Diabetes Mellitus Type 2. Prediabetes usually does not present with symptoms, although some patients may present with acanthosis nigricans.
- **Diabetes Mellitus Type 1:** is a disease of glucose metabolism secondary to destruction of insulin-producing beta cells in islets of Langerhans. The exact pathophysiology is unknown, but evidence exists for an autoimmune variant and a non-autoimmune variant (also unknown).
- **Diabetes Mellitus Type 2:** is a group of disorders with insulin resistance, defective insulin secretion, decreased insulin receptors and increased glucose production by liver.
- **Gestational Diabetes:** is a condition “caused by the hormonal changes and metabolic demands of pregnancy together with genetic and environmental factors” [1].

**c. Causes:**

**Diabetes Mellitus Type 1:** Type 1 diabetes is “caused by a lack of insulin due to the destruction of insulin-producing beta cells in the pancreas” [1].

Genetic Susceptibility  Autoimmune Destruction of Beta Cells  Environmental Factors

**Diabetes Mellitus Type 2:** is a group of disorders with insulin resistance, defective insulin secretion, decreased insulin receptors and increased glucose production by liver. [1]

- Genetic Susceptibility
- Obesity and Physical Inactivity
- Insulin Resistance
- Abnormal Glucose Production by the Liver
- Metabolic Syndrome
- Cell Signaling & Regulation Issues
- Beta Cell Dysfunction

**Gestational Diabetes:**
- Insulin Resistance and Beta Cell Dysfunction
- Family History
- Future Risk of Type 2 Diabetes

**d. Treatment options:** Management of Diabetes is best provided by a multidisciplinary team of health professionals with expertise in diabetes, working. Management of Diabetes is best provided by a multidisciplinary team of health professionals with expertise in diabetes, working in collaboration with the patient and family. Early initiation of pharmacologic therapy is associated with improved glycemic control and reduced long-term complications in type 2 diabetes: in collaboration with the patient and family. Early initiation of pharmacologic therapy is associated with improved glycemic control and reduced long-term complications in type 2 diabetes:
Drug classes used for the treatment of type 2 diabetes include the following:
- Biguanides
- Insulins
- Sulfonylureas
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- Amylinomimetics
- Infusion of adipose derived stem cells

**POTENTIAL BENEFITS OF STEM CELL TREATMENT**

Mesenchymal Stem Cells (MSCs) found in several bodily tissues, such as bone marrow and adipose tissue, have the capacity to differentiate and migrate to the site of damage and secrete growth factors or cytokines. In type 1 diabetes the insulin producing cells, B-cells within the pancreatic islets are being destroyed by the immune system. Mesenchymal stem cells have shown an increase in insulin secretion and an increase in the number of islet cells in the pancreas (Pileggi, 2012). Some studies have also shown the ability of human derived mesenchymal stem cells to differentiate into B-cells which expressed the insulin gene (Timper, et al., 2006), therefore having the ability to reverse diabetes mellitus. Furthermore, mesenchymal stem cells have been shown to travel to the site of injury, in this case to pancreatic islets and the liver where they may contribute to tissue repair and remodeling, as well as improving metabolic function (Pileggi, 2012). Diabetes type 2 studies have shown a reduction of glucose levels in the blood when stem cell therapy was done (Renitha, et al., 2011).

**TREATMENT & DELIVERY METHOD REQUIRED**

A. Typical Recommended Treatment: Adipose Derived Stem Cells
B. Typical Delivery Method Required: Autologous Ad-SVF containing adult stem cells are infused in 5-10 ml normal saline intravenously with aslowbolus push.
C. Recommended dosing: Recommended repeat dosing MSC’s every 2-3 months and based on patient’s symptoms.

**POTENTIAL RISKS OF STEM CELL INJECTION**

There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of any results, excellent results can be attained. The medical professional provides services in the most responsible, professional, and diligent manner; always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Low-grade fever
- Itching at injection site
- Nerve/muscle injury
- Dizziness
- Swelling of joints
- Hot flashes
- Pain in joints
- Malaise
- Vascular spasm or obstruction
- Bruising
- Allergic reaction
- Nausea

**FREQUENTLY ASKED QUESTIONS**

1. **What are adult stem cells and how do they work?**

   They are undifferentiated cells found in tissues in the body, responsible for maintaining and repairing surrounding cells. These tissues include but are not limited to adipose tissue (fat tissue) and bone marrow. It has been found over recent years that adipose tissue is far superior to bone marrow containing 500 times more adult stem cells. They have the ability to differentiate into various cell types in a diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

2. **How can stem cell therapy help treat Diabetes Mellitus?**

   In diabetes mellitus, two things may happen: 1) B-cells responsible for insulin secretion are being destroyed by the immune system or 2) there is insulin resistance, and an increase of glucose in the blood. Mesenchymal stem cell therapy has shown a reduction in blood glucose levels and stem cell differentiation to B-cells.
2. How can stem cell therapy help treat Diabetes Mellitus?
In diabetes mellitus, two things may happen: 1) B-cells responsible for insulin secretion are being destructed by the immune system or 2) there is insulin resistance, and an increase of glucose in the blood. Mesenchymal stem cell therapy has shown a reduction in blood glucose levels and stem cell differentiation to B-cells.

3. How long do you think it would be before I see some improvement?
Stem cells therapy for diabetes mellitus is still an ongoing research topic and the results are not guaranteed. However, the response to the treatment varies from patient to patient. Studies have shown patients’ improvement3-6 months after a stem cell therapy.

4. How will the stem cells be administered?
For diabetes mellitusisolated stem cells will be resuspended in 0.5ml of saline and administered intravenously.

5. Does smoking or drinking affect the therapy?
Smoking and the consumption of alcohol has been shown to be harmful to stem cells. We advise that people do not smoke or drink during their treatment, and it must absolutely be avoided the week following the treatment.

6. Will anyone follow up with me after the procedure?
A team member will follow up with you 1 day, 1 week, 3 months, 6 months and 1 year after the procedure. Follow ups help us evaluate the effectiveness of our treatment, and improve treatment protocols. We will be monitoring your progress closely. We are happy to address any issues or questions at anytime.

SUPPORTING ARTICLES

1. Mesenchymal stem cells for the treatment of diabetes
Authors: Antonello Pileggi
Abstract:
The field of regenerative medicine is rapidly evolving, paving the way for novel therapeutic interventions through cellular therapies and tissue engineering approaches that are reshaping the biomedical field. The remarkable plasticity of different cell subsets obtained from human embryonic and adult tissues from disparate sources (including bone marrow, umbilical cord, amniotic fluid, placenta, and adipose tissue) has sparked research endeavors evaluating use of these cells for numerous conditions, including diabetes and its complications (1). A readily accessible source for multipotent stem cells is the bone marrow, which comprises progenitors of hematopoietic, endothelial, and mesenchymal stem cells (MSCs). Unfractioned and fractioned bone marrow-derived stem cells have been used in experimental and clinical settings to improve diabetes and diabetes complications. Bone marrow-derived MSCs are stromal, nonhematopoietic cells generally obtained from iliac crest aspirates following enrichment based on their preferential adhesion on culture vessels in defined media. MSC characterization relies on expression of specific surface markers and on their ability to differentiate into fat, bone, and cartilage when exposed to appropriate culture conditions.
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2. Human adipose tissue-derived mesenchymal stem cells differentiate into insulin, somatostatin, and glucagon expressing cells
Authors: Katharina Timper, DalmaSeboek, Michael Eberhardt, Philippe Linscheid, Mirjam Christ-Crain, Ulrich Keller, Beat Mu`ller, HenrykZulewski
Abstract:
Mesenchymal stem cells (MSC) from mouse bone marrow were shown to adopt a pancreatic endocrine phenotype in vitro and to reverse diabetes in an animal model. MSC from human bone marrow and adipose tissue represent very similar cell populations with comparable phenotypes. Adipose tissue is abundant and easily accessible and could thus also harbor cells with the potential to differentiate in insulin producing cells. We isolated human adipose tissue-derived MSC from four healthy donors. During the proliferation period, the cells expressed the stem cell markers nestin, ABCG2, SCF, Thy-1 as well as the pancreatic endocrine transcription factor Isl-1. The cells were induced to differentiate into a pancreatic endocrine phenotype by defined culture conditions within 3 days. Using quantitative PCR a down-regulation of ABCG2 and up-regulation of pancreatic developmental transcription factors Isl1, Pdx-1, and Ngn3 were observed together with induction of the islet hormones insulin, glucagon, and somatostatin.
Biochemical and Biophysical Research Communications 341 (2006) 1135–1140
3. Can multiple intramuscular injections of mesenchymal stromal cells overcome insulin resistance offering an alternative mode of cell therapy for type 2 diabetes?

Authors: Renjitha Gopurappilly, Ramesh Bhonde

Abstract:
Insulin resistance is a hallmark of type 2 diabetes (T2D). The mechanisms underpinning β-cell mass expansion and their functionality in insulin-resistant states still remain elusive. It has recently been shown that insulin resistance in skeletal muscles leads to production of myokines that impact negatively on β-cell function. We hypothesize that multiple intramuscular injections (IM) of mesenchymal stromal cells (MSCs) at different sites would aid in countering the insulin resistance in T2D. These IM injections are expected to have dual effects in overcoming muscle insulin resistance. It is likely to modulate the microenvironmental niche of insulin-insensitive myocytes under the influence of paracrine secretions from MSCs, in turn changing the myokine secretion pattern to positively regulate β-cell function. Further, it may stimulate the satellite cell population to generate new myocytes, which would be insulin-sensitive. If our hypothesis proves to be right, it might offer a user-friendly approach to control T2D.

4. Stem cell therapy for diabetes mellitus

Authors: Julio C. Voltarelli, Carlos E.B. Couri, Maria C. Oliveira, Daniela A. Moraes, Ana B.P.L. Stracieri, Fabiano Pieroni, George M.N. Barros, Kelen C.R. Malmegrim, Belinda P. Simoes, Angela M.O. Leal and Milton C. Foss

Abstract:
In this review, we present (1) a brief discussion of hematopoietic stem cell transplantation (HSCT) for severe and refractory autoimmune diseases (AIDs) from its beginning in 1996 through recently initiated prospective randomized clinical trials; (2) an update (up to July 2009) of clinical and laboratory outcomes of 23 patients with newly diagnosed type 1 diabetes mellitus (T1DM), who underwent autologous HSCT at the Bone Marrow Transplantation Unit of the Ribeira™ o Preto Medical School, University of Sa™ o Paulo, Brazil; (3) a discussion of possible mechanisms of action of HSCT in AIDs, including preliminary laboratory data obtained from our patients; and (4) a discussion of future perspectives of stem cell therapy for T1DM and type 2 DM, including the use of stem cell sources other than adult bone marrow and the combination of cell therapy with regenerative compounds.

Kidney International Supplements (2011) 1, 94-98; doi:10.1038/kisup.2011.22


Preconditioning of adipose tissue-derived mesenchymal stem cells with deferoxamine increases the production of pro-angiogenic, neuroprotective and anti-inflammatory factors: Potential application in the treatment of diabetic neuropathy.

Oses C1, Olivares B2, Ezquer M1, Acosta C3, Bosch P4, Donoso M4, Léniz P5, Ezquer F1.

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Abstract:
Diabetic neuropathy (DN) is one of the most frequent and troublesome complications of diabetes mellitus. Evidence from diabetic animal models and diabetic patients suggests that reduced availability of neuroprotective and pro-angiogenic factors in the nerves in combination with a chronic pro-inflammatory microenvironment and high level of oxidative stress, contribute to the pathogenesis of DN. Mesenchymal stem cells (MSCs) are of great interest as therapeutic agents for regenerative purposes, since they can secrete a broad range of cytoprotective and anti-inflammatory factors. Therefore, the use of the MSC secretome may represent a promising approach for DN treatment. Recent data indicate that the paracrine potential of MSCs could be boosted by preconditioning these cells with an environmental or pharmacological stimulus, enhancing their therapeutic efficacy. In the present study, we observed that the preconditioning of human adipose tissue-derived MSCs (AD-MSCs) with 150μM or 400μM of the iron chelator deferoxamine (DFX) for 48 hours, increased the abundance of the hypoxia inducible factor 1 alpha (HIF-1α) in a concentration dependent manner, without affecting MSC morphology and
survival. Activation of HIF-1α led to the up-regulation of the mRNA levels of pro-angiogenic factors like vascular endothelial growth factor alpha and angiopoietin 1. Furthermore, this preconditioning increased the expression of potent neuroprotective factors, including nerve growth factor, glial cell-derived neurotrophic factor and neurotrophin-3, and cytokines with anti-inflammatory activity like IL4 and IL5. Additionally, we observed that these molecules, which could also be used as therapeutics, were also increased in the secretome of MSCs preconditioned with DFX compared to the secretome obtained from non-preconditioned cells. Moreover, DFX preconditioning significantly increased the total antioxidant capacity of the MSC secretome and they showed neuroprotective effects when evaluated in an in vitro model of DN. Altogether, our findings suggest that DFX preconditioning of AD-MSCs improves their therapeutic potential and should be considered as a potential strategy for the generation of new alternatives for DN treatment.

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