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Stem cell therapy in Diabetes- Techniques and its therapeutic potential

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I. Introduction:

Obesity and diabetes are the major health challenges that need global attention.Diabetes is one of the top ten leading causes of death worldwide, according to a recent WHO report (1).

The global prevalence of diabetes in 2012 was estimated to be more than 10% among adults. Of the diabetic population 95% are of type 2, and onset is mainly at an adult age (more than 25 years), with the highest prevalence in the Eastern Mediterranean region and the Americas. Diabetes is the leading cause of renal failure and blindness in advanced countries, and the risk of limb amputation is 10 times higher in diabetic patients. In addition, most diabetic patients develop hypertension and cardiovascular diseases, which account for high rates of morbidity and mortality among adult patients. The disease can be initially treated by oral medication, but eventually, some 27% become insulin dependent. Of these, less than one half achieve the recommended HB A1c level(2), since exogenous insulin cannot provide the tight glycemic control exerted by the pancreas-derived insulin secretion. Replacement of and/or improvements in endogenous β cell reserves of the β cells would be an ideal therapeutic option.

A milestone in cell-based therapies for diabetes mellitus has been achieved with the application of islet transplantation from cadaveric donors, and the success of the Edmonton protocol back in 1999(3). As stem cell therapy gained momentum over the past year, efforts to engineer islet-like cells or insulin producing cells from different types of stem cells have offered an appealing alternative to islet transplants. In principle, stem cell therapy avoids some of the serious drawbacks of islet transplantation, most obviously, the shortage of organ donors. Patients can donate their own stem cells to be expanded and differentiated *in vitro* into islet producing cells. The autologous cells can then be injected back into the patient, thus avoiding possibilities and complications of graft rejection, and/or a requirement for and immune suppressive regimen. While islet transplantation in an allogeneic environment may suffer cell exhaustion, stem cell therapies potentially provide sustained source of insulin uncompromised by the many debilitating side effects of the immune suppressive drugs when the transplant is autologous. Sources for stem cell therapies in diabetes mellitus are multiple, including embryonic stem cells (ESCs), cord blood stem cells, iPSCs (induced pluripotent stem cells), and adult stem cells derived from adult tissues.

A small scale prospective study of type 2 diabetic patients undergoing autologous bone marrow stem cell transplantation on the treatment of insulin-dependent type 2 DM with severe progressive insulin dysfunction showed promising results on the safety of the stem cell protocol and a noticeable reduction of insulin requirements. In this study, Bhansali et al. used autologous bone marrow-derived SCs without separation into HSCs or MSCs. The cells were directly injected into the pancreas via the gastro-duodenal artery. It was not clear if these cells helped in regeneration of the β islet cells or they formed insulin producing cells in situ(4). However, large scale studies with more diverse patient populations and long-term followup are still required to determine the feasibility of such an approach.

A different study used highly proliferative progenitor cells obtained from fetal liver to treat insulin dependent diabetes. Fetal liver progenitor cells were genetically manipulated to express the pancreatic duodenal homeobox 1 (Pdx1) gene, a key regulator in insulin secretion(5). Differentiated fetal liver progenitors were transplanted into NOD diabetic mice, the animals became euglycemic, and their serum showed increased levels of human C-peptide.

MSCs derived from a variety of human adult tissues were utilized in an attempt for their differentiation into insulin producing cells. Bone marrow (6-8), adipose tissue (9), umbilical cord or its blood (10-11), fibroblasts (12), endometrium (13), and liver cells(14) are among several others. The richest source for MSCs,

however, is the bone marrow. Bone marrow MSCs have several advantages when used for the purpose of tissue repair. They have a high capacity to self-replicate and differentiate, both *in vitro*and *in vivo*, to bone and fat-forming cells and other tissue cells. They maintain the capacity of multilineage differentiation potential, both within and across lineage barriers. They are easy to cultivate and expand, and maintain pluripotentiality after prolonged culture conditions (15)

II. Techniques:

Many protocols were tried to differentiate MSCs into insulin producing cells (16). Cultures in media with high glucose content were a common feature.

Mesenchymal Stem Cells(MSC) are niche cells. Their traditional role in the bone marrow is the formation of the stroma and facilitation of growth, differentiation, and engraftment of HSCs. It is worth examination whether this niche role is contributing to the normoglycemic effect following their transplant.

MSCs are currently cultured using fetal bovine serum, which can induce xenogeneic and allergic reactions in transplanted patients, in addition to transmission of xenogeneic pathogens that may contaminate the serum. The immune characteristics of MSCs have been generally encouraging for transplantation purposes; however, there are some reports on the increased tumor formation in animals due to the immune suppressive effects of MSC transplants, particularly in the allogeneic setting (17-18). Furthermore, frequent *in vitro* passaging and the long time required for effective differentiation into insulin producing cells can induce mutations and transformations and render the graft unsafe for clinical usage (19). Safety studies must go hand in hand with efficacy studies to ensure safe long term effects of the MSC transplant.

Svensson and colleagues provided evidence that islets grafted into muscle have 3 times more blood vessels than islets at the renal subcapsular site at 2 months aftertransplant(20). They concluded that the intramuscular site can provide an excellent condition for engraftment. Additional tools may also be needed to improve early graft survival: bioengineered matrices, oxygen carriers, and growth factors.

Increasing the number of insulin producing cells and their sustained survival is a high priority in stem cell research. If surrogate β cells could be obtained in sufficient numbers, two additional questions have to be addressedas follows. For how long can these cells maintain their active function *in vivo*? And what is the optimal site for their transplantation? Information regarding the duration of active function is limited by the observation period following transplantation in experimental models, the longest of which is in order of three months before the animals are sacrificed (16). It is abundantly clear that experiments with larger animal models and for more extended periods are required.

Therefore there is a need for understanding, learning the technique and evaluating the stem cell therapy in diabetes. It will be a very rewarding learning experience to take back home as Libya too severely affected by obesity and Type 2 diabetes mellitus.(21)

III. Conclusion:

Diabetes remains a major burden. More than 200 million people are affected worldwide, which represents 6% of the population. The success achieved over the last decade with islet transplantation suggests that diabetes can be cured by the replenishment of deficient beta cells. These observations are proof-of-concept and have intensified interest in treating diabetes not only by cell transplantation but also by stem cells. Regeneration of beta cells from stem and progenitor cells is an attractive method to restore islet cell mass. Pancreatic stem/progenitor cells have been identified, and the formation of new beta cells from pancreatic duct, acinar and liver cells is an active area of investigation. Protocols for the in vitro differentiation of embryonic stem (ES) cells based on normal developmental processes have generated beta-like cells that produce high levels of insulin, even though at low efficiency and without full responsiveness to extracellular levels of glucose. Induced pluripotent stem (iPS) cells can also yield insulin-producing cells following similar approaches.

Therefore studies undertaken in stem cell transplantation techniques, cell therapy and its application will prove very beneficial for our country afflicted with obesity and diabetes mellitus.

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