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OVERVIEW OF DIFFERENTIATION OF MESENCHYMAL DERIVED STEM CELL INTO INSULIN PRODUCING CELLS AND THEIR CLINICAL ISSUES IN TRANSPLANTATION

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ABSTRACT

Diabetes mellitus is one of chronic disorder it has various subclasses such as type 1diabetes which is insulin dependent, gestational diabetes and type 2diabetes. At present there is no proper therapeutic drug for the cure of diabetes. Transplantation of the differentiated stem cells which are derived from adipose tissue, bone marrow, placenta, umbilical cord, dental pulp etc. but the transplantation may also lead to rejection. This review article explains different types of mesenchymal derived stem cells that differentiated into insulin producing cells and clinical issues in their transplantation.

KEYWORDS: Mesenchymal stem cells, chronic disorder, transplantation, clinical issues.

INTRODUCTION

Type 1 Diabetes Mellitus outcomes from the autoimmune destruction of β cells of the endocrine pancreas. The progression of autoimmune destruction receipts place in genetically susceptible individuals under the prompting effect of one or more environmental factors and regularly growths over an age of many months to years, throughout that period patients are asymptomatic and euglycemic, nonetheless positive for relevant autoantibodies. Symptomatic hyperglycemia and frank diabetes happen subsequently a long inexpression period, which imitates the great percentage of β cells that essential to be devastated earlier unconcealed diabetes become obvious. In T1DM, connotations with exact HLA alleles or haplotypes refer to class II region, as this is the case for the majority of autoimmune diseases. The ability of class II molecules to current antigens is reliant on on their alpha- and beta-chain amino acid arrangement. Replacements at one or two critical sites can pointedly increase or decrease the binding ability of the relevant autoantigens. Symptomatic hyperglycemia and diabetes interrupt after a long dormancy period, which imitates the large percentage of β cells that need to be devastated or dysfunctional first before obvious diabetes become apparent.[1] Vitamin D, vitamin D receptor (VDR), vitamin D-binding protein (DBP) and genetic polymorphisms linked with vitamin D metabolism have distinctly been advocated to effect the risk of T1D development. No studies have jointly analyzed vitamin D, DBP and genetic polymorphisms, which is necessary to relate any, or all, of these factors to T1D risk. Reported an association between 25 (OH) D in early childhood and advanced islet autoimmunity which be contingent on VDR genotype. VDR binding sites are overrepresented close to genetic regions accompanying with T1D and numerous single nucleotide polymorphisms (SNP) in or nearby genes tangled in the vitamin D pathway (CYP2R1, CYP27B1 and DHCR7) have been accompanying with T1D.[2] Type 2 diabetes, or adult-onset diabetes, incorporates individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency At least initially, and often through their lifetime, these individuals do not require insulin treatment to survive. There are possibly several different sources of this form of diabetes. While the specific etiologies are not known, autoimmune destruction of cells does not occur, and patients do not have any of the other causes of diabetes listed above or below. Most patients with this system of diabetes are obese, and obesity the situation causes some grade of insulin resistance. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ ethnic subgroups. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1diabetes. However, the genetics of this form of diabetes are complex and not clearly defined.[3] Moreover, type 2 diabetes (T2D) has become the leading cause of death

among people under the age of 60. These alarming data are becoming increasingly serious both for medicine and the national health care system. Many strategies have been recently proposed to minimize health-related consequences of metabolic syndrome and diabetes. They involve new drug development, including, e.g., glucagon-like peptide (GLP-1) mimetic, dipeptidyl-peptidase-4 (DPP-4) inhibitors, sodium glucose transporter-2 (SGLT2) inhibitors, but also surgical gastric correction, diet-related therapy, such as calorie restriction and finally mesenchymal stem cells application.[4] Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. Although uncomplicated GDM with less severe fasting hyperglycemia has not been associated with increased perinatal mortality, GDM of any severity increases the risk of fetal macrosomia. Neonatal hypoglycemia, jaundice, polycythemia, and hypocalcemia may complicate GDM as well. GDM is associated with an increased frequency of maternal hypertensive disorders and the need for cesarean delivery.[5] Although the risks associated with gestational diabetes are well recognized, it remains uncertain whether screening and treatment to reduce maternal glucose levels reduce these risks. Given this uncertainty, professional groups disagree on whether to recommend routine screening, selective screening based on risk factors for gestational diabetes, or no screening; some recommend screening, whereas others do not. There have been repeated calls for well-designed, randomized trials to determine the efficacy of screening, diagnosis, and management of gestational diabetes.[6] Most patients with autoimmune disease have a near-normal life expectancy. Nevertheless, some patients suffer severe, therapy-resistant progressive autoimmunity. Haematopoietic-cell transplantation (HCT) is a potential therapy for people with such severe refractory diseases. HCT involves the administration of haematopoietic stem cells (HSC), which are self-renewing and capable of giving rise to all mature haematopoietic cell types and possibly to some non-haematopoietic cell types. The recipient is prepared for the transplant by potent immunosuppressive treatment, usually by chemotherapy and/or radiotherapy. This may then be followed by the transfer of autologous haematopoietic cells. Thus, the real potential of tissue regeneration from HSC to cure autoimmune disease is controversial and remains an area of intense investigation.[7] Mesenchymal Stem Cells (MSCs) can be described as a heterogeneous subset of multipotent stromal cells that proliferate in vitro as plastic-adherent cells with a fibroblast-like morphology with the ability to differentiate into various types of cells. MSCs can be isolated from various tissues for example bone marrow, umbilical cord blood, adipose tissue.[8] Islet allotransplantation is a capable therapy to treat severe type 1 diabetes (T1D) patients with the goal to accomplish independence of exogenous insulin administration. Though, transplanted islets surrender to an early phase of rejection and to an advanced loss of graft function because of inflammatory and immune reactions. Regulatory B cells endorse transplantation forbearance and a role for regulatory B cells in tolerance induction in an allogenic islet transplantation.[9]

Differentiation Of Adipose Derived Mesenchymal Stem Cells

Adipose derived mesenchymal cells are multipotent cells and they are fibroblast and non-haematopoietic and they are capable of differentiation into adipocyte, chondrocyte, osteocyte and endocrine pancreatic progenitors. Human adipose tissue have the potent to espouse phenotype of pancreatic endocrine than the other types of mesenchymal stem cells. Specific stem cell markers such as nestin and ABCG2 have the capability to activate the development of pancreatic genes. In animals genes like insulin and Ipf-1 have potential to reverse the hyperglycemia. Adipocytes has the ability to release somatostatin which regulates the synthesis of glucagon and insulin with the help of G-protein.[10] Normally adipocytes are present in different parts and show different gene expression patterns. The precursor cells present in the subcutaneous fat deposits of the tissues has specific metabolic characteristics which may lead the precursor cells to differentiate.[12,13] The overexpression of the MafA high ability for differentiation of adipose mesenchymal stem cells (AMSCs) into functional insulin producing cells (IPCs).[14] The differentiation effect is high in the presence of PVA nanofibers and PRP. When the PRP is stimulated it produces the growth hormones includes EGF, BFGF, HGF, VEGF-A and fibronectin which are responsible for the differentiation of stem cells into insulin producing cells (IPCs).[15] When HDACi (histone deacetylase inhibitor) is used it effectively enhance the differentiation of adipose derived mesenchymal stem cells (AMSCs) into insulin producing pancreatic beta cells.[16] With the help of paracrinem effects adipose derived stem cells produce growth factors, cytokines and bioactive molecules which are responsible for the mechanism of regeneration of adipose derived stem cells into insulin producing cells (IPCs).[17] Exendine-4 and activin showed increased GLUT-2 expression which is involved in the detection of glucose and insulin -4 and secretion mechanism. Exendine-4 and activing shows high efficiency in the proliferation of adipose derived stem cells.[18] In the differentiation of adipose derived mesenchymal stem cells the presence of exendine-4 increases the expression of Pdx-1 which is responsible for the stimulation of transcription of insulin gene and it also mediates the maturation of promoters such as beta cells, glucose transpoter-2(GLUT-2) and glucokinase.[19] Factors such hepatocyte growth factor and pentagastrin also have high efficient to beta cell differentiation. Of all other types of mesenchymal stem cell differentiation

adipose derived mesenchymal stem cell differentiation is the easy and simple method as regenerative medicine and also for transplantation.[20]

Differentiation Of Bone Marrow Derived Mesenchymal Stem Cells

Bone marrow derived mesenchymal cells (BMMSCs) induce the proliferation of insulin producing pancreatic beta cells through IGF-1 (insulin like growth factor-1) and via its downstream signalling pathways of Akt (protein kinase B) and ERK (extracellular signal regulated kinases). Co transplantation of MSCs along with ICCs (islet like cell clusters) highly increase the efficient of the proliferation and function of insulin producing pancreatic beta cells.[21] The GCK which is responsible for the initiation of glucose induced insulin secretion, glucose sensing and glucose transporter GLUT-2 and its concentration can be varied depending on the blood glucose level during the sampling if the expression of the GCK is maintained in correct proportion the percentage of the insulin producing cells are relatively high. All the pancreatic genes are well expressed, level of the glucose tolerance curve shows that these cells derived from bone marrow are capable of insulin secreting.[22] The change of energy cycle from the glycolysis metabolism to aerobic metabolism should be high and predominantly essential for the differentiation of the mesenchymal stem cells which is relatively high in bone marrow derived mesenchymal stem cells (BMMSCs) when compared to other types.[23] SSEA-1 positive cells isolated from the bone marrow derived mesenchymal stem cells (BMMSCs) have the capability to differentiate into insulin producing pancreatic cells. SSEA-1 have expressed Pdx-1, Ngn3, insulin-1 and insulin-2 delivering that it have potent to produce functional insulin producing pancreatic cells. Pdx-1 plays a major role in the maturation of insulin secreting cells, in the developing of the insulin secreting cells it co express the Pdx-1 which in turn supress the V- maf musculo aponeurotic fibrosarcoma oncogene homolog B (MafB) and MafA also required for the maturation of insulin secreting cells. Pdx-1 play an important role in encoding of insulin and somatostatin and repression of glucagon which is clear that it favours to produce insulin secreting cells rather than production of glucagon.[24] COUP-TFI is one of the notable negative regulator which supress the ins-2 which repress the transcription of beta cells. MafA have high efficiency to activate the ins-2 promoter but its efficiency in bone marrow derived mesenchymal stem cells activate ins-2 is low. Ins-2 is activated with co-transfection of MafA and siCOUP-TFI in the BMMSCs. Repression of the negative regulator and overexpression MafA induces the efficiency of BMMSCs to differentiate into insulin producing cells.[25] Bone marrow derived stem cells have negative phenotype for the cells such as CD34, CD14 and CD-45 which indicate that they are hematopoietic do not have the potential to differentiate into insulin producing cells while CD-106, CD-44 and CD-29 have the capability to differentiate into insulin producing cells and have positive phenotype. Nicotinamide and activin A plays a major role. Nicotinamide induces the differentiation and preserves the viability of the cells via poly ADP – ribose polymerase (PARP). Activin A regulates neogenesis of the beta cell and the member of transforming growth factor.[26] In bone marrow derived mesenchymal cells Pdx-1 gene creates a major change in the human mesodermal tissue and that leads to the differentiation of the beta cells. It leads to the autologous cell therapy which is not feasible further without the manipulation of cell growth by telomerase[27] Based on the phenotype of the bone marrow derived mesenchymal cells (BMMSCs) can be prompted to transdifferentiate into insulin producing cells and it can also be functionally controlled by its intrinsic genetic program and surrounding micro-environment in in vitro condition. Pancreatic tissue extract can effectively improve the trans-differentiation efficiency and maturity of insulin producing cells (IPCs) by the traditional induction. In response to the glucose stimulation the derived insulin producing cells have the capability to produce insulin. BMMSCs were induced with DMDM/F12 medium containing BFGF, EGF, and B27 into nestin-positive cells, and nerve stem cells were amplified with BFGF and EGF as a mitogen combination. Activin-A, β cell regulin, hepatocyte growth factor, nicotinamide and other cytokines were enhanced with serum-free high-glucose medium. As the glucose concentration is crucial in the induction and differentiation process, glucose can increase insulin synthesis, while it could inhibit β-cell differentiation. Fetal pancreatic cell differentiation and increase in the beta cell quantity were stimulated by nicotinamide. The production of insulin is also promoted by nicotinamide. Mesenchymal stem cells (MSCs) differentiation into β-cell is induced by activing –A and BTC. The injured pancreatic tissue extract endorse bone marrow derived mesenchymal stem cells (BMMSCs) differentiate into islet-like cells, which expressively increase the insulin producing cells (IPCs) ability of secreting insulin. BMMSCs were induced with a traditional two-stage protocol. EGF, BFGF, HGF, BTC, activing- A and high glucose combined with nicotinamide could not effectively induce the formation of insulin producing cells (IPCs).[28]

Differentiation Of Umbilical Cord Derived Mesenchymal Stem Cells

HUMSCs in Wharton's Jelly of the umbilical cord as a foundation for cellular differentiation into insulin-producing cells (IPCs) under de novo culture environments. HUMSCs in Wharton's Jelly of the umbilical cord are effortlessly obtained when related with embryonic and other stem cells. Islet-like cell clusters were shown to contain human C-peptide and release insulin in response to physiological glucose levels. The enrichment of insulin and other pancreatic β-cell-related genes, such as *Pdx1*, *Hlxb9*, *Nkx2.2*, *Nkx6.1*, and *Glut-2* in these islet-like cell clusters are also disclosed by the study of real time RT-PCR. HUMSCs in Wharton's Jelly of the umbilical cord denote rich

foundation of large quantities of stem cells which are very safe. And they are easily manipulated and free of ethical problems. HUMSCs in Wharton's Jelly of the umbilical cord have been established to have genetic and surface markers of mesenchymal stem cells: positive for CD10, CD13, CD29, CD44, and CD90 and negative for CD14, CD33, CD56, CD31, CD34, CD45, and HLA-DR. The lack of HLA-DR may be the one of cause that differentiated human umbilical cord derived mesenchymal cells (HUMSCs) can endure in the course of xenotransplantation, and suggests that the differentiated human umbilical cird derived mesenchymal stem cells (HUMSCs) can look imperceptible to the possessions of the fundamental autoimmunity. Differentiated human umbilical cord derived mesenchymal cells (HUMSCs) into mature islet-like cell clusters that retain insulin-producing ability *in vitro* and *in vivo*. HUMSCs in Wharton's Jelly of the umbilical cord appear to be a constructive basis of stem cells for renovation into insulin-producing cells, due to its large prospective donor pool, rapid availability, absence of discomfort to the donor, and low risk of rejection (39). Adult stem cells are initiate in most tissues, where they are thought to contribute in natural turnover and regeneration. Under defined conditions, some of these cells can also be significantly expanded and differentiated along specific lineages. Adult stem cells with the potential to differentiate into insulin-producing cells. Actions of pancreatic development, as well as in the attainment of beta cell properties, Pdx1 has been widely used as a tool for the differentiation of stem cells. The pre-treated the cells with 5-AZA to inhibit DNA methylation, which has been recognized in important differentiation processes. The capacity of 5-AZA to alter gene expression and to transform cell phenotypes has been known for a long time. However, a recent report showed that 5-AZA can also cause the direct phenotype conversion of human skin fibroblasts into insulin-secreting cells. New protocol that combines 5-Aza, activin A, RA, and Nicotinamide that can induce chicken UCMSCs to differentiate into beta-like cells over a short-time period. Our results indicate that RA and Nicotinamide signals are critical for pancreatic beta cell development and maturation.[30] The MSC numbers in bone marrow and umbilical cord blood are low and require multiple *ex vivo* expansion. Extra-embryonic tissue such as fetal membrane and umbilical cord Wharton's jelly has the stem ness phenotype, immune privileged properties, and faster proliferation than adult MSCs and is considered as unlimited source for tissue engineering and regenerative medicine. The WJ-MSCs express HLA-G6 isoform, the unique ability which is important in immune modulation. The effects of RA are achieved through RA binding and activation of retinoic acid receptors such as RARα, RARβ, and RAR. Over expression of RARβ was detected in early stage of pancreases differentiation and absence of RARβ impaired the terminal differentiation of α and β-cells. In vitamin-A deficiency, pancreatic islet function was Impaired. RA directly induces Pdx1 expression in ESCs and Pdx1 is an important transcription factor in the early development of pancreatic progenitors and bud expansion. The retinoic acid response element is located at upstream of the transcription start site of Pdx1. Retinoie Acid Receptor (RARβ) expression is depended on epigenetic regulation. Hyper methylation of the RARβ2 promoter was reported in pancreatic cancer, and diabetes. Therefore, it is postulated that the epigenetic silencing of RARβ, combined with vitamin A deficiency, may play a role in pathogenesis of diabetes. Differentiation of WJ-MSCs to form IPCs needs further optimization for clinical practice. To overcome this problem, addition of growth factors, extracellular matrix and/or culturing the cells in three dimensional environments are suggestive.[31] Nestin-positive cells were then transformed into insulin-producing cells (IPCs) under the medium containing high glucose, high insulin, nicotinamide, and B27, well along developing the islet-like cell clusters. Nicotinamide is a poly (ADP-ribose) synthetase inhibitor known to differentiate and increase β-cell mass in cultured human fetal pancreatic cells as well as to protect β-cells for desensitization induced by prolonged exposure to large amounts of glucose. The immune cyto chemical study presented that stage 4 islet-like cell clusters do not direct nestin, inferring that these cell clusters are non-neuronal. Susceptibility for type 1 diabetes is largely inherited by genes predominantly in the HLA genotypes DR and DQ. Both high risk and protective HLA haplotypes have been identified .These susceptibility genes are thought to be important regulators of the cellular immune response. The human umbilical cord derived mesenchymal stem cells (HUMSCs) in Wharton's Jelly of the umbilical cord have been revealed to have genetic and surface markers of mesenchymal stem cells: positive for CD10, CD13, CD29, CD44, and CD90 and it is negative for CD14, CD56, CD31, CD45, CD33, CD56 and HLA-DR. the upkeep of regularised blood glucose level during transplantation may need the construction of fused liver cells (human insulin and nuclei-positive staining and contained secretory granules) through a possible cell fusion pathway.[32] Purified CD133+ cells articulated *CD133, OCT4* and *NANOG* genes which confirmed their stem potential. They easily formed islet-like colonies at the end of the differentiation process. The colonies expressed insulin and C-peptide at the protein level but were not functional and could not increase insulin production and release in response to high glucose concentrations. Pancreatic stromal niche on generating IPCs from UCB-CD133+ cells by using a co-cultured system. Our finding showed no significant differences between cells cultured in the presence or absence of rat PMCs, however in direct culture the number of colonies increased. Other studies have also confirmed that rat pancreas extract could stimulate phenotypic pancreatic differentiation. As our differentiated cells did not significantly express specific protein markers (insulin and C-peptide) and were unresponsive to high glucose concentrations, thus we proposed that pancreatic stromal cells might not be

sufficient to induce functionally mature pancreatic differentiated cells. Insulin producing cells (IPCs) could have released all of their intracellular insulin and had insufficient time to resynthesize more insulin for release during the incubation period at the higher glucose level. On the other hand, IPCs might not have been mature enough; therefore, the number of glucose receptors was not sufficient, which caused them to lack normal function in response to glucose stimulations. Human UCB-CD133+ cells could differentiate into IPCs *in vitro*. Pancreatic stromal cells might cause an enhancement in the number of immature pancreatic β-cells, but not in the number of mature cells.[33]

Differentiation Of Dental Derived Mesenchymal Stem Cells

The MSCs isolated from human dental pulp, papilla, and follicle tissues exhibited adherent fibroblast like spindle morphology that become homogeneous at passage 3 upon sub culturing . The pulp derived MSCs had higher proliferation rate compared with papilla and follicle derived MSCs as assessed by MTT assay However, the flow cytometric analysis of cell cycle revealed no significant differences among three types of MSCs. The pluripotent markers such as OCT4, SOX2, and NANOG were positively expressed in all three types of MSCs as evaluated by PCR and Western blotting. The expression of cell surface markers was analysed by flow cytometer. AllMSC were positive for the expression ofCD73, CD90, CD105, and vimentin, and were negative for the expression of CD14, CD19, CD34, CD45, and HLA-DR. observed. Differentiated cells expressed pancreatic lineage specific marker genes as evaluated by RT-qPCR. Them RNA levels of pancreatic duodenalhomeobox1 (PDX1), NK6 homeobox 1 (NKX6.1), neurogenin 3 (NGN3), aristaless-related homeobox (ARX), paired box 4 (PAX4), insulin (INS), solute carrier family 2 member 2 (GLUT2), MAF bZIP transcription factor A (MAFA), glucagon (GCG), and somatostatin (SST). Mesenchymal stem cells isolated pulp, papilla, and follicle tissues exhibited largely similar features related to morphology, proliferation, expression of various cell surface, intracellular and pluripotent markers, and differentiation toward mesenchymal lineages such as osteocytes, adipocytes, and chondrocytes. All three types of mesenchymal stem cells (MSCs) exhibited larger capability to transdifferentiate into pancreatic β cell-like cells. Nonetheless, differentiated cells were positively stained for dithizone and concealed insulin upon glucose encounter. However, the expression of pancreatic lineage specific markers and insulin secretion assay revealed that follicle-derived MSCs are prominent sources for cell-based diabetic therapy. When compared with other tissue sources of MSCs, the findings of the present study are particularly very interesting when we considered an extracted tooth samples sourced from routine medical waste.[34] Adult stem cells have yielded controversial results with regard to their ability to secrete insulin invitro and normalize hyperglycemia in vivo. For instance, BM-MSCs, which possess pluripotent differentiation capabilities, are a candidate for stem cell therapy in diabetics let cell replacement. Conversely, other studies have failed to support the ability of BM-MSCs to differentiate into islet cells. Moreover, our group has recently shown that BM-MSCs differentiate into immature islets in vitro, and these islets mature under in vivo conditions upon transplantation. However, this does not disqualify BM-MSCs for the treatment of diabetes.

BM-MSCs as such are a gold standard for allogeneic stem cell transplantation. If one associates the capacity of bone marrow derived mesenchymal cells (BM-MSCs) and DPSCs to differentiate into insulin-producing (IPCs) ICAs in vitro, DPSCs will be a restored choice, because they have ability to differentiate into mature insulin-producing (IPCs) ICAs, whereas BM-MSCs differentiate into immature islets which do not secrete insulin (35). The prospective of DPSCs to differentiate into pancreatic cell lineage reminiscent of islet-like cell aggregates (ICAs). Isolated, propagated, and characterized DPSCs and demonstrated that these could be differentiated into adipogenic, chondrogenic, and osteogenic lineage upon exposure to an appropriate cocktail of differentiating agent. Succeeded in obtaining ICAs from DPSCs. The distinctiveness of ICAs was established as islets by dithiozone-positive staining, as well as by appearance of C-peptide, Pdx-1, Pax4, Pax6, Ngn3, and Isl-1. There were several-fold up-regulations of these transcription factors proportional to days of differentiation as compared with undifferentiated DPSCs. Day 10 ICAs released insulin and C-peptide in a glucose-dependent manner, exhibiting in vitro functionality. DPSCs could be differentiated into pancreatic cell lineage and offer an unconventional and non-controversial source of human tissue that could be used for autologous stem cell therapy in diabetes.[36]

Clinical Issues In Transplantation

Islet transplantation has been discovered as a treatment for patients with type 1 diabetes since the improvement of collagenase digestion of the pancreas. Primarily, it was estimated that the technique for islet isolation that had been advanced for the rodent pancreas could also be functional to the human pancreas with only small amendments. Though, it was not till the advance of an automated technique for islet isolation and continuous density gradients for separating exocrine fragments and islets that the field moved advancing in humans. The current opinion is that the inherent risk of HLA immunization is little after islet transplantation. Nevertheless, later a supplement period of only 3 years, graft function in nearly few patients appears to diminish, and a limited patient have already been re-transplanted after a few years of insulin independence. At current, the islet graft endurance time after transplantation into patients with T1DM is unknown. Recommencement of lesser quantities of insulin is not commonly detected as a failure after islet transplantation due to the reduced risks of metabolic lability or recurrent hypoglycemia. Though,

an expected situation is that in a wide stream of patients, graft function (as observed for other transplanted organs) will gradually disappear ended over some years. In difference to organ transplantation, islet transplantation is not unswervingly life-saving. A patient with broadminded diminishing in islet graft function will at some point of time have to re-initiate insulin treatment and still have to bear the burden of immunosuppression. The patient's aspect the risk of drug-induced kidney dysfunction in adding to the inherent risk due to T1DM. Though, the broadly immunized patient can expect a prolonged waiting time to receive a kidney graft, as well as a reduced graft survival time.[37]

CONCLUSION

Hereby we conclude that there is proper drug for the cure for the diabetes mellitus. One of the sources is transplantation of insulin producing cells but only 50 percentage is success rate. Tissue rejection is the major problem. There are many clinical issues in transplantation.

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