

Stem Cell Therapy: A Breakthrough in Diabetes Mellitus

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Abstract

Diabetes mellitus regardless of the type, its associated complications and the tendency to inherit the condition due to genetic reasons have affected world wide and is increasing at a rapid pace. Although there are effective ways to manage this condition, none of them stops the progressive decline of the beta cell functioning. The existing treatment modalities only delays the complications. Pancreatic islet transplantation have been promising with patients being insulin independent for initial few years post transplant, but over the period of time they restart their daily insulin injections. Even though stem cell therapy for diabetes is currently being investigated, its recent progress has been assuring one. Stem cell therapy does not face risk like graft rejection requiring immunosuppression or complications associated with the procedure and post transplant unlike the pancreatic islet transplantation, since they can withdrawn from the diabetic patient and injected back, thus eliminating issues like lack of donors. This review shows the potential of hematopoietic stem cell and mesenchymal stem cell therapy as a good alternative approach in treating diabetes.

Keywords: diabetes, alternative approaches, hematopoietic stem cells, mesenchymal stem cells

1) Introduction and scope

Diabetes and its associated complications has contributed to “1.6 million deaths and was the seventh leading cause of death” according WHO report “in 2016”. [1] The increase in population affected by the diabetes which arose due to number of reasons such as the genetic component, modern sedentary life style that gradually lead to overweight there by contributing to more complications such as uncontrolled hyper-hypo glycemc episodes. T2DM (type 2 diabetes mellitus) is more prevalent in general population. [2] Though both the types have similar symptoms T1DM (type 1 diabetes mellitus) arises mostly due to

unknown reasons or autoimmune destruction of pancreatic islets of which the cause is unknown. Then there is T3c DM (type 3c diabetes mellitus) which occurs due to chronic pancreatitis.[3] Regardless of the type of diabetes, the unregulated high levels of blood glucose for prolonged period damages all the vital organs; which leads to the complications such as the blindness due to diabetic retinopathy, diabetic neuropathy that eventually leads to diabetic foot ulcer, infection thereby the need for limb amputation, two-three fold increased risk of heart attacks, strokes and kidney failure. Complications and presence of diabetes contributes greatly to the poor prognosis of patients especially when they encounter with severe infections. Even active TB (tuberculosis) in the presence of diabetes mellitus along with close contact of TB during childhood were found to be associated in Kerala, the southern Indian state.[4] Diabetic foot infections being one of the most common complications of uncontrolled diabetes which have poor outcomes due to factors such as “age, hypoalbuminemia, hyponatremia, peripheral vascular disease, positive bone structure and previous amputations” leads to decrease in quality of life of diabetic patients.[5]

Though there are several conventional methods of management such as oral hypoglycemic agents, even with more new class of compounds being developed in recent years like “glucagon-like peptide (GLP-1) mimetics, dipeptidyl-peptidase-4 (DPP-4) inhibitors, sodium glucose transporter-2 (SGLT2) inhibitors”; these on the long run loses its efficacy; there by having administration of daily injections of exogenous insulin to regulate blood glucose, with common side effect as hypoglycemia.[6],[7] Despite the arrival of the newer pharmacological agents; the increasing trend of gestational diabetes where these mostly goes away after pregnancy; but in recent years it has been observed that the pregnant mothers who had gestational diabetes end being diagnosed with T2DM within few years or after 10-15 years post pregnancy and the baby born to them have higher risk of developing diabetes in future; this in return increases the tendency to inherit diabetes. Since the current management does not stop the progressive decline of pancreatic β -cell function, the need for more targeted permanent solutions is demanding. The Edmonton protocol that became successful by introduction of transplant of pancreatic islets from cadaveric donors has helped to achieve increased insulin production, insulin independence, normal blood glucose

though this has drawbacks like the inevitable prolong usage of immunosuppressants that comes with the complications notably infections due to low immunity ; which has given inspiration to the development of incorporation of stem cells in treating diabetes, that has the capability to differentiate, is a promising breakthrough; though it comes with the price of possibility for cancer cells.[8] This review will primarily cover on the stem cells: their potential, progress, benefits, risks and challenges in treating diabetes. Also very briefly on existing conventional therapies: their limitations, current alternatives and newer approaches.

2) Conventional therapies: Limitations and drawbacks

In general when a patient is diagnosed with T2DM, they are in most cases overweight or obese.[9] Hence they are always advised to begin with life style changes like including physical activity such as brisk walking and making modifications in diet, which include high protein, less carbohydrate, less fats and high amounts of fibre. Depending upon the results of diagnostic tests such as the fasting blood glucose, HbA1C (Glycated hemoglobin), postprandial glucose test and several other factors like age, comorbidities, vascular complications, psychological status, economic issues, risk of hypoglycemia etc the oral pharmacological agents and/or insulin injections are decided.[10] Common limitation in most of the oral hypoglycemic agents is the loss of efficacy over period of time due to the progressive decline of β cell function. Though each of the agents have their own specific limitations and drawbacks. In case of metformin despite being the most preferred drug due to least side effects like hypoglycemia or weight gain, also have certain issues. This agent cannot be given in patients suffering from liver disease, renal dysfunction, acute heart failure. Metformin is avoided in patients with eGFR (estimated glomerular filtration rate) 30-60ml/min and when serum creatinine level is above 1.4mg/dl in women and 1.5mg/dl in men.[11] While for the insulin secretagogues ie, sulfonyl ureas and meglitinides weight gain is an inevitable known side effect.[12] Increased cardiovascular risk along with hypoglycemia which worsens in patients who have CKD (chronic kidney disease) and loss of efficacy makes this class of drugs less desirable.[13],[14] Compared to above mentioned class of drugs, the alpha-glucosidase inhibitors tend to cause compliance issues due to abdominal pain, flatulence and diarrhea. Also they are to be avoided in

patients with intestinal obstructions and ulcers, hernia, asymptomatic elevation of liver enzymes and low creatinine clearance.[15] As for thiazolidinediones, the major side effect is heart failure and weight gain.[16] When it comes to iDPP4 (dipeptidyl peptidase-4 inhibitors); more studies are required to confirm its side effects. Since the chance of usual adverse effects in iDPP4 observed is very low when compared to any other oral hypoglycemic agents ; even though elevation of liver enzymes that causes hepatic dysfunction and heart failure as an increased risk is a cause of concern.[17] In iSGLT2 (sodium glucose co-transporter-2 inhibitor) possible side effect due to its mechanism are orthostatic hypotension and increased glucosuria that cause infections in urogenital tract especially in women where they are prone to vulvovaginal candidiasis, vulvitis, vulvovaginitis etc.[18]

For an individual when diagnosed with T1DM they are started on insulin therapy unlike in T2DM patients, due to the complete destruction of the β cells producing insulin, there by requiring exogenous source of insulin. While for T2DM, they are gradually put into insulin, due to uncontrolled elevated blood glucose levels for a prolong period despite taking oral pharmacological agents. By the initiation of insulin therapy, though both types of diabetic patients achieve good glycemic control, this comes with side effects like hypoglycemia and weight gain which are the major ones compared to oral agents.[19] Although the incidence of hypoglycemia is lower in T2DM patients especially at the initiation of the therapy but tend to increase with the duration of both disease and treatment compared to T1DM patients.[20],[21],[22]

3) Current alternatives and newer approaches

Alternative approach to treat diabetes mellitus has gained immense importance in recent years. There is diversity in these alternative approaches that include bariatric surgery, yoga, acupuncture, aromatherapy etc. The bariatric surgery shows good glycemic control along with the weight loss by the alteration of gastrointestinal anatomy that leads to decreased food intake; there by also causes improved metabolic status.[23],[24] Yoga has proven significant improvements in patients with lifestyle diseases and is quiet recommended to patients with diabetes. It has been found that patients who have diabetes who practice yoga daily have shown decreased insulin resistance and increased insulin sensitivity.[25] Acupuncture, an integral part of traditional chinese medicine, commonly known to provide pain relief, also can used for

many other conditions, they can enhance insulin synthesis.[26] Aromatherapy is known to help cope the stress of chronic conditions such like diabetes.[27] Vitamin E can influence the insulin sensitivity and secretion.[28] Then there a lot of medicinal herbs that help along such as the bitter melon that lower the blood sugar.[29] Fenugreek known to have the potential to be antidiabetic agent that decrease the post prandial glucose level.[30] Neem leaves doesn't only reduce the elevated glucose level in blood but capable of preventing adrenaline and glucose induced hyperglycemia.[31]

Since diabetes and its associated complications are spreading at a rapid pace, the scientists are driven to find a cure or more effective treatments whether its new class of oral pharmacological agents or innovative ideas like oral insulin, transplant of islet cells from cadavers and even the possibility of the stem cells. There are several oral insulin that are currently undergoing human clinical trials that promises to have better glycemic control than the existing parenterals since they would undergo first pass metabolism they are expected to lower glycogenolysis and to lower the risk of hypoglycemia.[32] In the initial experimentation of transplant of islet cells from cadavers caused the patients condition to deteriorate, where insulin supplement became necessary at the first five years post transplant. But in the recent transplants with patients, has shown improved long term results; where patients became insulin independent for five years. With the development of pluripotent adult stem cells which is capable of differentiation into other cells, these have given hope to the possibility of producing islet cell that can secrete insulin according to the change in blood glucose, although its current progress has been therapeutically very minimal.[33]

4) MSC and HSC in DM: Potential and progress

Since the discovery of stem cells and its possible sources that include ESC (embryonic stem cells), cord blood stem cells, iPSC (induced pluripotent stem cells) and adult stem cells that can be taken from the adipose tissue, umbilical cord or its blood, fibroblasts, endometrium, liver cells and bone marrow or peripheral blood which is the source of HSC (hematopoietic stem cells) and MSC (mesenchymal stem cells), these has given hope to scientist for treating diabetes especially when it comes to MSC due to their nontumorigenic differentiation potential.[34],[35] These can be good alternative to islet transplant that

overcome issues like lack of sufficient organ donors and usual immunosuppressive regimen that patients have to follow post islet transplant, since these stem cells are initially taken from the patient itself and injected back.[36] With MSC that have immune suppressive qualities; there by reducing the chances of rejection and its isolation can be done through less invasive procedure while retaining the stem cell quality, making it the most preferred source of stem cells.[37] Clinical trials of UC-MSC (Umbilical cord-Mesenchymal stem cells) Therapy in children with T1DM newly diagnosed took place, out which very few children became insulin independent, while the majority had more than 50% reduction in their requirement of daily insulin for 22 months which shows the potential of UC-MSC therapy in treating T1DM.[38] While recently experiments with BM-HSCs (Bone Marrow-Hematopoietic stem cells) has taken place through liver puncture, as a result it was observed there was an increase in the C-peptide levels and a significant decrease in HbA1c levels at first six months post therapy.[39] The key factor to be noted in the therapy outcome was the time of diagnosis, the earlier the diagnosis is established and intervention of stem cell therapy the more likely the insulin independence is achieved. There were no major side effects observed in BM-HSC therapy in T1DM.[40] The HSC transplant along with immunosuppressive regimen taken prior to transplantation has resulted in increased insulin and c-peptide levels and improvement in hyperglycemia and has made autoimmune reaction less severe in diabetic patients.[41]

5) Benefits, risks and challenges

In stem cell therapy, the chance of rejections can be resolved or minimised when the stem cells are withdrawn from and injected back to the same patient but the possibility of difference in the differentiation, insulin secretion or gene profile of non diabetic and diabetic patient is thought provoking. But it has been found that MSC taken from that of a diabetic patient had significantly higher insulin secretion than that of non diabetic donor and there was no notable difference between them.[42] When pancreatic islets can be cultured along with MSC through in vitro experiments, it has ensured the islet survival, reduced inflammation and even prevent the cell apoptosis.[43] In recent systematic and meta analysis review, where all the results of ongoing clinical trials proved that in T1DM, the stem cell therapy has increased C-peptide levels and decreased HbA1C levels but failed to reduce daily insulin requirement. While for the

T2DM, stem cell therapy have reduced HbA1C and daily insulin requirement, though it failed to increase C-peptide. There has been lowering in hyperinsulinemia and decreased insulin resistance when fetal stem cells were used in T2DM treatment.[44]

In the practical application of stem cells, there are lot of risks associated with the therapy. Since currently the MSC are obtained from fetal bovine serum there are chances of allergic reactions and the xenogenic pathogens can contaminate the serum. These stem cells have potential to regenerate, differentiate there by have the possibility to form tumors; there were reports that even the MSC with immunosuppressive effects are causing increased formation of tumors in animals.[45] With MSC already being differentiated than ESCs, it can be a challenge regarding the differentiation into insulin secreting cells.[46] Another challenge of stem cell therapy would be the ideal site for transplantation, though liver has been used so far the possibility of other sites have to be explored, since in recent studies it was found out that the liver might not be suitable due to many factors like the immunologic, anatomic and physiologic.[47] Lastly even if the optimal site is found, there is the issue of the survival of these injected stem cells ie,the duration of these stem cells actively functioning as insulin secreting cells.[48] Favourable clinical outcomes have been observed in diabetic complications like “diabetic foot, diabetic nephropathy and diabetic neuropathy” with the application of MSC.[49],[50],[51]

6) Conclusion

With an increase in the population affected by diabetes and its complications that affects the day to day functions or even making them vulnerable to severe infections , the success of stem cell therapy would alleviate patient’s sufferings hopefully to a greater extent. Over the years with the progress of HSC and MSC therapy, that has been promising and can have therapeutic benefits with some risks accompanied like the possibility of tumor formation, chance of rejection, site of transplant, its durability in vivo and active functioning that could actually produce insulin according to the blood glucose levels in the body of a diabetic patient can be a breakthrough; compared to pancreatic transplantation that has lot of disadvantages such as the lack of donors and where the patients have to undergo immunosuppressive regimen post transplant in order to reduce the graft rejection that in turn is an invitation to infections. Since

a lot of challenges lies ahead of stem cell therapy in diabetes, most of which are the requirement of larger randomized clinical trials, stem cell type to be used, probability of unknown adverse effects of these transplanted stem cells in the long run, etc. A thorough active research along with its safety profile that requires monitoring the patients for long term, will help to determine the efficacy, safety, quality of life of the post stem cell transplant diabetic patients.

Declaration of interest

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