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STEM CELL THERAPY FOR DIABETES COMPLICATIONS: CURRENT EVIDENCE AND POTENTIAL ROLE IN DIABETIC NEPHROPATHY

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Abstract

A metabolic condition known as diabetes is characterized by elevated blood sugar levels, brought on by deviations in insulin synthesis, and action. The kidney condition known as diabetic nephropathy (DN) often appears among individuals with diabetes for 10 to 20 years. Diabetes nephropathy may be treatable with stem cell therapy. It is critical to discover a novel therapeutic approach to treat DN because existing treatments, such as hyperglycemia and blood pressure management, can only partially halt the development of the disease. Adipose-derived stem cell (ADSC) transplantation has been established to enhance the capacity for cell repair and restoration, and adult mesenchymal stem cells (MS) have been attributed to the reduction of DN. There is evidence that oxidative stress is an underlying process in the progression of diabetic problems.

Keywords- Diabetes Mellitus, Diabetes Nephropathy, hyperglycemia, Stem cells, CVD

1. Introduction

As the world's elderly population grows, as does the occurrence of diabetes, kidney disorders cardiovascular disease, and hypertension are becoming increasingly serious worldwide public health issues.[1] A metabolic condition known as diabetes is characterized by elevated blood sugar levels, which are brought on by deviations in insulin synthesis, and action. Chronically elevated blood sugar from diabetes has been linked to abnormalities, damage, and failure of several organs such as kidneys, eyes, nerves, heart, and blood vessels.[2]

Diabetes prevalence in Chinese people has increased to 9.7% in recent years.[3] A significant percentage of people across the world are affected by diabetes. Changes in renal and lipid parameters due to diabetes are important risk factors for diabetic complications including diabetic nephropathy and cardiovascular illnesses.[4]

End-stage renal disease is mostly brought on by diabetic nephropathy (DN), a major consequence of diabetes that has a death rate of 30–40%. Renal fibrosis and increasing abnormalities in renal function are features of DN. It is critical to discover a novel therapeutic approach to treat DN because existing treatments, such as hyperglycemia and blood pressure management, can only partially halt the development of the disease.[5]

In complicated genetic illnesses, several more genes may contribute to nephropathy's development. Two distinct methods—case-control association studies and family studies—represent the strategy used to find genes.[6] Currently, there are roughly 200 million diabetic patients worldwide, and by 2025, there will be 3 billion DN sufferers. In Western societies, DN is also a key risk factor for end-stage renal disease (ESRD), which affects those 65 and older and whose prevalence is rising as the population ages faster.[7] The main clinical symptoms of this condition which has become a prevalent chronic consequence of diabetes, are increasing renal failure and elevated urine protein levels. Glomerulosclerosis, renal fibrosis, and glomerular basement membrane thickening are the major characteristics of renal pathology in patients with DN. At this time, DN incidence is still gradually rising. Although there are numerous DN treatments available.[8]

Elevated blood lipids, smoking, and the quantity and source of dietary protein also are risk factors for this disease.[9] The observed proteinuria in glomerular disorders is said to be caused by the loss of the glomerular filtration barrier's size-selective or charge-selective features.[10] The transforming growth factor (TGF-) receptor signalling is an established mechanism that results in DN. As the most potent profibrogenic cytokine, TGF-1 promotes ECM build up, which is usually regarded as one of the most significant pathogenic features of DN.[11]

However, the precise molecular pathways driving the advancement of DN are still not completely understood. As a result, there aren't many effective drugs for treating DN. angiotensin receptor blockers, ACE inhibitors, or aldosterone blockers are being used as the mainstays of DN treatment to ensure that the renin-angiotensin-aldosterone (RAAS) system is kept under optimal control (spironolactone or finerenone).[12] In the complicated genetic illness known as diabetic nephropathy, several more genes may contribute to the nephropathy's development. Two distinct methods—case-control association studies and family studies—represent the strategy used to find genes.[13]

1.1 Stem Cells:

Stem cell therapy for cardiac illness is predicated on the hypothesis that the body's own self-repair mechanisms, although capable of renewing the myocardium, may be insufficient to fully repair the damaged heart muscle after infarction.[14] The human body is brimming with undifferentiated cells called stem cells. Treatments based on stem cells have developed into a highly sophisticated and promising research field in recent years.[15] These cells can be divided into various categories according to their ability to differentiate.[16] Despite the fact that stem cells have been promised to cure human diseases, there are still various obstacles to be overcome.[17] Stem cells were first found by Becker et al. (1963), who injected bone marrow cells into treated mice and saw that a proportional number of nodules grew in the spleens of the animals.[18]

1.1.1 Types of Stem cells: (Figure A.1)

Adipose-derived stem cell (ADSC) transplantation has been found to enhance the capacity for cell repair and redevelopment, hence reducing the severity of acute kidney injury.[19] The gut has recently gained significant attention as a model system for stem cell research. To identify intestinal stem cells a specific marker gene, Lgr5, can be used. Miniature organoids encompassing all intestine cell types were generated using a transgenic mouse model in which intestinal stem cells expressed green fluorescent protein, allowing for their identification, separation, molecular characterization, and use in the production of organoids.[20]

The reduction of diabetic nephropathy (DN) has been attributed to mesenchymal stem cells (MSCs); however, the precise mediator of this effect and its function have not been fully described. According to some theories, the primary mechanism of action of MSC treatment for DN involves the different paracrine actions of the trophic substances produced by MSCs.[21] PSCs or Pluripotent stem cells possess the capacity to proliferate endlessly and create cells in all three germ layers. For the treatment of a broad variety of diseases and injuries, PSCs are desirable sources of cell therapies for a wide range of illnesses and injuries.[22]

In 1998, the first human embryonic stem cell lines (HESCs) were established. Due to their capacity to differentiate between all cell types and their pluripotent nature, they have been considered a cell source for regenerative medicine. Since then, extensive research has been conducted on the variables that regulate differentiation and pluripotency.[23] The bone marrow contains both mesenchymal stem cells, which can differentiate into fat, bone, and cartilage, and hematopoietic stem cells, which can differentiate into both red and white blood cells.[24] The constant replenishment of adult differentiated cells from the stem cell compartment is essential to preserve the structural and functional reliability of many tissues and organs, including the haematological system, gut, and epidermis.[25]

Mature mammalian neural stem cells are unique in that they can differentiate, self-renew, and quiesce, and they only exist in the subgranular zone and subventricular zone of the hippocampus's dentate gyrus, two separate niches.[26] Human amniotic epithelium, unlike other components of the placenta, is produced from pluripotent epiblasts. A tiny hollow form within the blastocyst's inner cell mass from the 14th day of pregnancy.[27] Melanocyte stem cells (MeSCs) renew the pigment-producing melanocytes that give our skin and hair their unique colours, epidermal stem cells (EpSCs) regenerate the epidermis that covers us, and hair follicle stem cells (HFSCs) fuel the cyclic development of the hair follicle to make hair shafts.[28]

The regeneration of skeletal muscle is a coordinated process that triggers a variety of cellular and molecular responses. Satellite cells are essential to this process as they are skeletal muscle stem cells. Self-renewing satellite cell proliferation also produces a large number of myogenic cells, which multiply, differentiate, fuse, and generate new myofibers to restore a functional contractile apparatus. The intricate activity of satellite cells during skeletal muscle regeneration is tightly regulated by the dynamic interaction between internal variables in satellite cells and exterior components that comprise the muscle stem cell niche or microenvironment.[29] Somatic stem cell populations help their host tissues grow and regenerate. Because stem cells are contained in skeletal and non-muscle stem cell populations, skeletal muscle can regenerate entirely. Its regenerating capability, however, is diminished in severe myopathic disorders like Duchenne Muscular Dystrophy.[30]

1.2 Pathophysiology of Disease:

The true cost of diabetes, in terms of both dollars and human misery, is not in day-to-day care, but in the disease's numerous consequences.[31] The pathogenesis of diabetic complications has been linked to oxidative stress caused by the excessive generation of reactive oxygen species (ROS).[32] There are three types of complications, each with its own mechanism of development, while some variables are shared by all. Elevated blood glucose levels are the one thing that all problems have in common. Complications are classified into three types: macrovascular, microvascular, and neurologic.[31]

Genetics and obesity play significant roles in the development of diabetes in people over the age of 40. The hypothesis that there are two forms of human diabetes mellitus indicates that the pathophysiology of the diabetic syndrome is not the same in all individuals.[33]

Autoimmune breakdown of pancreatic β-cells produces type 1 diabetes. A steady decrease in endogenous insulin synthesis characterizes the natural course of this condition. This is affected by both hereditary and the surrounding environment.[34]

DN is more likely to strike close relatives, suggesting a hereditary risk and the extent of genetic similarity to the proband are correlated. HLA gene variations confer 50 to 60 percent of the genetic risk by altering HLA protein binding to antigenic peptides and antigen presentation to T cells.[35] Alcohol has an inhibiting effect on both gluconeogenesis and glycogenolysis in the liver. With these physiological processes disrupted, in an individual with diabetes blood glucose concentrations can decline for several hours after consuming alcohol and, eventually, can become life-threatening, especially when combined with insulin therapy.[36]

A complicated network of risk factors influences the prevalence of DN, including genetic, metabolic, and environmental factors. Epidemiology studies have indicated that addressing the key modifiable risk factors, such as obesity, inactivity, and poor nutrition, may prevent many cases of DN.[37] Recent research has shown that foetal sex plays an essential role in pregnancy for predicting the possibility of acquiring gestational diabetes mellitus and the subsequent risk of developing T2DM after pregnancy. Women carrying a boy in their first pregnancy have a 3 to 4% increased risk of GDM, and a 7% increased risk in their second pregnancy. Mothers carrying a girl child during the first pregnancy are at lower risk of developing GDM.[38]

The illness progresses at a faster rate, leading to the development of the cooccurrence of diseases at a younger age, emphasizing the importance of early identification at the stage of pre-diabetes. There are various flaws

in the existing management strategy. Insofar as the passage from insulin resistance to T2DM is a continuum; a fundamental challenge is determining how to avoid or treat IR early.[39] (Figure A.2)

Notably, published information on the possibility of avoiding development from normal to micro-albuminuria in T2D is more consistent than in T1D. A preliminary study in a small group of hypertensive type 2 normoalbuminuric diabetes found that 3 years of ACE inhibitor therapy slightly improved GFR and reduced the risk of progression to microalbuminuria, which is consistent with experimental evidence that early ACE inhibition therapy, i.e., at the stage of diabetes induction, may completely prevent the onset of nephropathy.[40]

Only a small percentage of DN cases are diagnosed with a kidney biopsy, although the usual histological findings are defined in an international categorization system. Classifications I through IV are distinguished by glomerular basement membrane thickness, mesangial expansion, nodular sclerosis (Kimmelstiel-Wilson lesion), and severe glomerulosclerosis, respectively. In addition to these distinctive glomerular characteristics, interstitial fibrosis and tubular atrophy (IFTA), interstitial fibrosis, arteriolar hyalinosis, and arteriosclerosis is usually present. [41]

The natural course of diabetic nephropathy yielded just a 5–7-year survival rate. Several developments in treatment and lifestyle have happened during the last several decades. The prognosis of diabetic nephropathy with stronger management of blood pressure (including increasing use of long-term renin-angiotensin system inhibition), lipids, and glycemia, as well as decreased smoking and other lifestyle and treatment developments, has not been well studied. [42]

Oxidative stress is increased by hyperglycemia and thus the production of reactive oxygen species, which have a vital role in the pathophysiology of DN.[43] Recent findings suggest that hyperglycemia makes target organs to blood pressure-induced damage and that local renin-angiotensin systems play a role in the genesis and progression of diabetic nephropathy.[44]

1.3 Epidemiology:

According to global diabetes mellitus statistics from 2013, over 382 million people worldwide have this condition, with type 2 diabetes accounting for approximately 90% of cases. Both men and women are affected equally (8.3% of the adult population) by this. Diabetes was the eighth biggest cause of death in the globe in 2012 and 2013, killing 1.5-5.1 million people per year.[45] Type 1 diabetes represents 7%-12% of the global diabetes burden.[46]

Persistent microalbuminuria, with an albumin excretion rate between 20 and 200 g/min or 30-300 mg/24 h, or a spot urine albumin to creatinine ratio between 30-300 mg/g (3.5-35 mg/mmol) in men and 20 and 200 mg/g (2.5 and 25 mg/mmol) in females, may be indicative of early diabetic nephropathy (DN). Proteinuria above 500 mg/24 h or albuminuria over 300 mg/24 h is diagnostic with overt DN. Overt DN may also show as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m2. [47]

Diabetes nephropathy (DN) is a kind of chronic kidney disease that worsens with time and is most common in those who have had diabetes for ten to twenty years. In a minority of people with modest diabetes-induced renal impairment, DN may remain clinically asymptomatic for the remainder of their lives.[48]

1.4 Risk factors:

The major risk factors for the onset of diabetes are blood pressure, lipid parameters like cholesterol triglycerides, HDL, LDL, heart rate, body weight, and uric acid.[49] Those who are elderly, fat, and sedentary are at the greatest risk for developing DN. Minority populations are much more susceptible to danger, because of the history of their family and genetics as well as their capacity to adapt to the impacts of the American environment, such as their bad eating and lack of physical exercise habits.[50] As a result, identifying and managing risk factors for diabetic nephropathy, as well as rapid diagnosis and management of the disease, are critical for effective therapy.[51]

When it comes to persons who have diabetes, cardiovascular disease is still the main cause of both morbidity and mortality. The mortality rate almost doubles when diabetes mellitus is combined with myocardial infarction or stroke, resulting in a 12-year reduction in life expectancy.[52]

Hypertension, blood pressure, and lipids are examples of classical CVD risk variables that have been shown to have a strong correlation with both overall CVD and major adverse cardiovascular events (MACE). Mean

HbA1c was also responsible for this, however, it was less effective than other independent risks, with the exception of LDL for total CVD. An insulin sensitivity-determined metric GDR was found to be more significantly associated with total CVD than LDL or GFR in alternative models. Insulin sensitivity may be a greater predictor of milder CVD endpoints in type 1 diabetes since the model with GDR revealed a worse fit for MACE than the main model with HbA1c.[53]

New therapeutic and preventative approaches must be developed in response to the T2DM epidemic in order to slow the spread of this crippling condition. There is evidence connecting the circadian system to several pathophysiological and therapeutic facets of diabetes.[54] The type of stem cells, their proliferation capacity, differentiation status the route of administration, the intended location, in vitro culture and other manipulation steps, irreversibility of treatment, the need for concurrent tissue regeneration in case of irreversible tissue loss, and long-term survival of engrafted cells, all influence the risk profile of stem cell-based pharmaceuticals. These components work together to determine the risk profile of the pharmaceuticals.[55]

1.5 Stem cells therapy in Diabetes Nephropathy:

There are two main characteristics that cells must have in order to be considered "stem cells." Stem cells must first be capable of indefinite self-renewal in order to make clones of their parent cell. Stem cell division is well-regulated, whereas cancer cells divide uncontrollably. As a result, it is crucial to underline that stem cells must also be capable of producing a specialized cell type that will become a member of the healthy animal.[56] (Figure A.3)

To replace the function of injured pancreatic beta cells, islet transplantation is the most widely utilized procedure. But it does have serious boundaries. HPSCs have the ability to create an infinite number of pancreatic cells capable of secreting insulin in response to high blood glucose levels.[57] Regular blood glucose monitoring and numerous insulin injections often with an insulin pump are the current therapies for insulin-dependent persons. The availability of customized insulins, each having a different peak of action, has improved diabetes management.[58]

In addition to Regular injections of insulin and oral hypoglycemic agents, physicians are aiming to improve patient care by employing cell therapies utilizing induced pluripotent stem cells (iPSC), embryonic stem cells (ESC), and mesenchymal stem cells (MSC).[59] Diabetic medications nowadays mostly focus on sensitizing β-cells to produce insulin in order to lower blood glucose levels. However, many medications have undesirable side effects, prompting research into alternate treatments.[60] Among the most intriguing ideas to have arisen in nephrology during the past ten years are therapies addressing kidney injury using stem cells and regenerative medicine.[61]

Renal cells may be differentiated from ESCs in the presence of certain growth factors such as retinoic acid, activin A, BMP-2, BMP-7, and FGF-7. Multiple studies have shown that iPSCs can be effectively differentiated into renal cells, which may be used to enhance DNP properties. In addition, MSCs have been used to heal renal damage and regenerate insulin-secreting cells in an STZ-induced diabetic rat, while the release of stromal cell-derived factor (SDF-1) in the kidneys facilitated the homing of MSCs. [62]

Stem cell therapies for kidney injury have shown promise in pre-clinical models, but stronger evidence of their clinical usefulness is still pending. The tolerability and safety of stem cell therapies, especially those based on MSCs, in people with renal disorders and those who have undergone kidney transplants, have been established via numerous clinical trials. To completely eliminate the chance of cancer and the emergence of anti-HLA antibodies, however, long-term surveillance is advised.[63]

Important features of HESCs include the theoretical capacity to develop into any cell type and the potential for almost infinite proliferation, so there has been an extensive effort towards emerging protocols to produce β-like cells from HESCs for drug development and transplantation.[64]

Over the last decade, studies have clearly established that replicating embryonic development is the most successful technique to create specific cell types from iPSCs in vitro. This technique was successful, revealing that multiple signalling channels and transcription factors regulate pancreatic embryonic development.[65] (Figure A.4)

1.5.1 Stem cell Therapy in Other Diseases:

Embryonic and adult are the two types of stem cells. These cells may also be classified as totipotent, multipotent, or unipotent. So far, stem cell use in the treatment of numerous blood disorders has been investigated. Alzheimer's disease, Amyotrophic lateral sclerosis, Parkinson's disease, Stroke, Spinal Cord Injury, Radiation Induced Intestinal Injury, Multiple Sclerosis, Inflammatory Bowel Disease, Liver Disease, Duchenne Muscular Dystrophy, Diabetes, Heart Disease, Renal Disease, Bone Disease, Graft-Versus-Host Disease, Sepsis, and respiratory disease are all being studied as potential cell therapy applications.[66]

Heart failure is a major global health problem, and Current treatments simply slow the disease's development. Current clinical trials and laboratory investigations show that cell-based therapy may enhance heart function, and the possibilities for cardiac regeneration are quite exciting. Progenitor cells produced from bone marrow and other progenitor cells may develop into vascular cell types, restoring blood flow. Recent research has demonstrated that resident cardiac stem cells may develop into a variety of cell types seen in the heart, including cardiac muscle cells, demonstrating that the heart is not terminally differentiated.[67]

Under various culturing conditions, human ESC produces insulin. Techniques not requiring murine feeder cells have been devised, allowing for single species ESC multiplication and minimizing the possibility of zoonotic infection of clinically relevant cells.[68]

Clinical trials using stem cells have recently opened up many opportunities for the developing field. Others are working to develop and broaden the role of bone marrow and cord blood stem cells for their cutting-edge applications in immune and blood disorders, while still others are looking to expand the uses of the various stem cell types found in the bone marrow and cord blood, particularly mesenchymal stem cells, to uses other than replacing cells in their own lineage.[69]

HESC expresses well-known pluripotency-associated genes like octamer-binding transcription factor 3/4 (OCT3/4), and NANOG is positive for pluripotent stem cell surface antigens like stage specific embryonic antigens 3 and 4 (SSEA-3 and SSEA-4), TRA-1-60, and TRA-1-81. These markers are used to verify the maintenance of the pluripotent state in mature HESC and the successful isolation of a new HESC line.[70]

Clinical trials of drugs based on cell therapy are now underway, and recent advances in stem cell research have shown encouraging results. Patients at high risk of postoperative acute kidney damage after cardiac surgery were successfully treated with allogeneic mesenchymal stem cells in our phase 1 clinical research. By incorporating biomarkers, current stem cell-based treatments may provide a new set of diagnostic and therapeutic tools for detecting AKI at an earlier stage and treating the condition more effectively.[71]

Preclinical studies have revealed that marrow mesenchymal cell transplantation has the potential to repair hereditary bone, cartilage, and muscle abnormalities.[72] During the past ten years, much progress has been made in recreating pancreatic development in vitro making use of HESCs with the support of the vast information accumulated from studies on pancreatic organogenesis in model animals.[64]

Other options for treating spinal cord damage include recruiting endogenous neural stem cells or transplanting NSCs. These cells are multipotent and can be cultured in vitro; they can differentiate into neurons, astrocytes, oligodendrocytes. The spinal cord may be a source for these cells and have distinct features from NSCs derived from the forebrain.[73]

An alternative antiviral treatment may be established by a combination of genetic modification and HSC transplantation. Altering HSC is a great method for creating infection-resistant immune cell populations since they are the source of all hematopoietic cell types that are vulnerable to HIV infection. Gene therapies based on HSCs have developed as a viable avenue, as these self-renewing progenitor cells may be modified to be resistant to HIV. If the altered HSCs are successfully engrafted, they will produce a steady stream of genetically modified cells with enhanced anti-viral activity or resistance to HIV infection. If all viral reservoirs are eradicated and the host is repopulated with an HIV-resistant hematopoietic system, then the patient will be cured permanently.[74]

1.6 Conclusion:

Cells derived from human embryos have the important characteristics of infinite proliferation and the potential capacity to differentiate to any cell type, much effort has been made into creating methods for producing β-like cells from HESCs for transplantation and drug development. Treatments for diabetes include islet

transplantation, human pluripotent stem cells (HPSCs), and cell therapies utilizing embryonic stem cells (ESC). Treatments based on stem cells are expected to deliver a totally new group of therapeutic and diagnostic tools. Preclinical studies have revealed that mesenchymal stem cell transplantation has the potential to repair hereditary bone, cartilage, and muscle abnormalities. Other options for treating spinal cord damage include recruiting endogenous neural stem cells or transplanting NSCs. Stem cells have the potential to generate every tissue in the human body, making them ideal for future therapeutic applications in tissue repair and regeneration. Stem cell therapies for kidney injury have shown promise in pre-clinical models, but stronger evidence of their clinical usefulness is still pending.

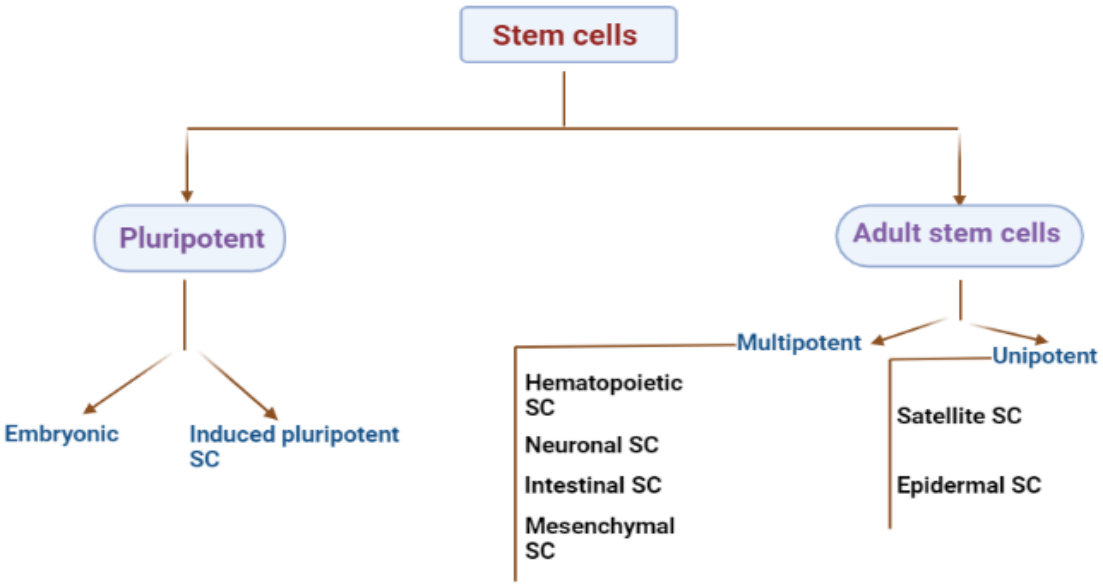

Fig A.1: Types of Stem Cells

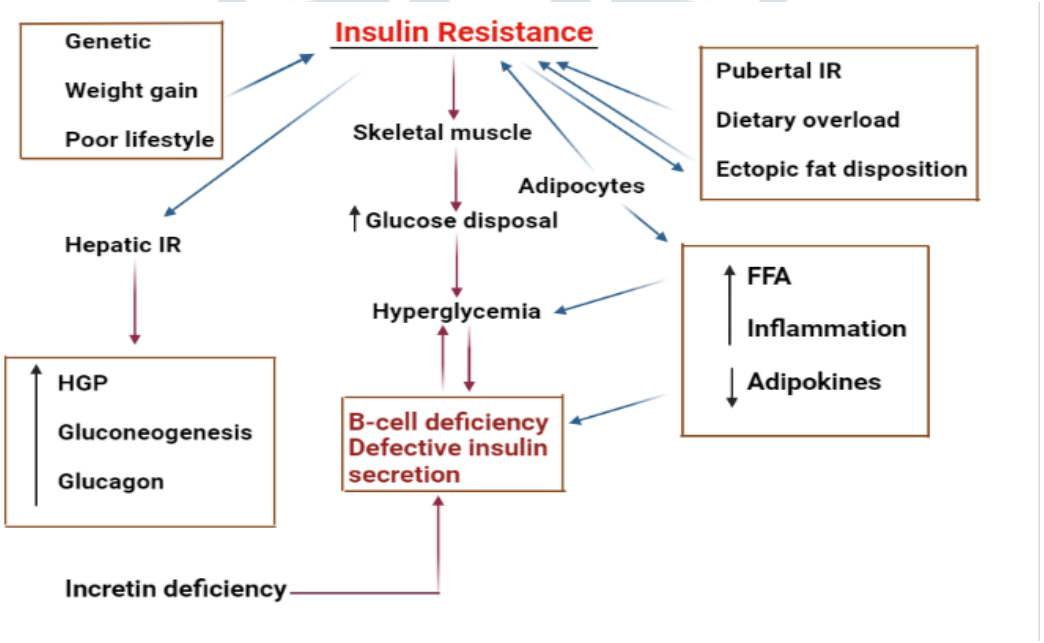

Fig A.2: Insulin resistance in Type 2 diabetes

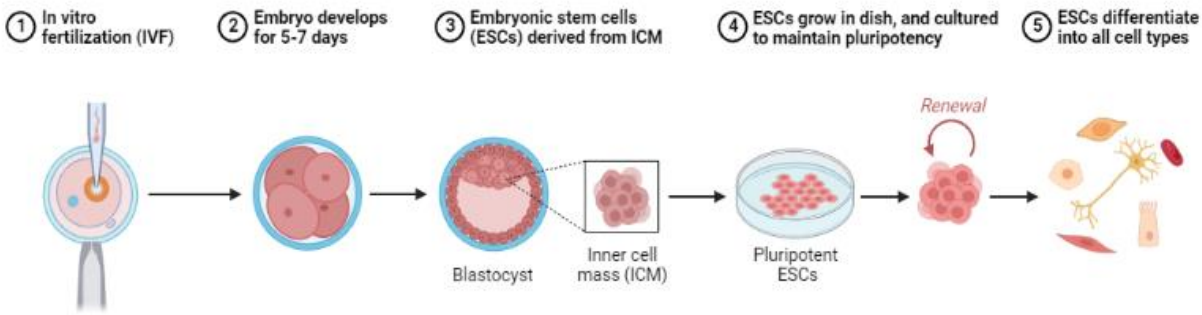

Fig A.3: Stem cell differentiation

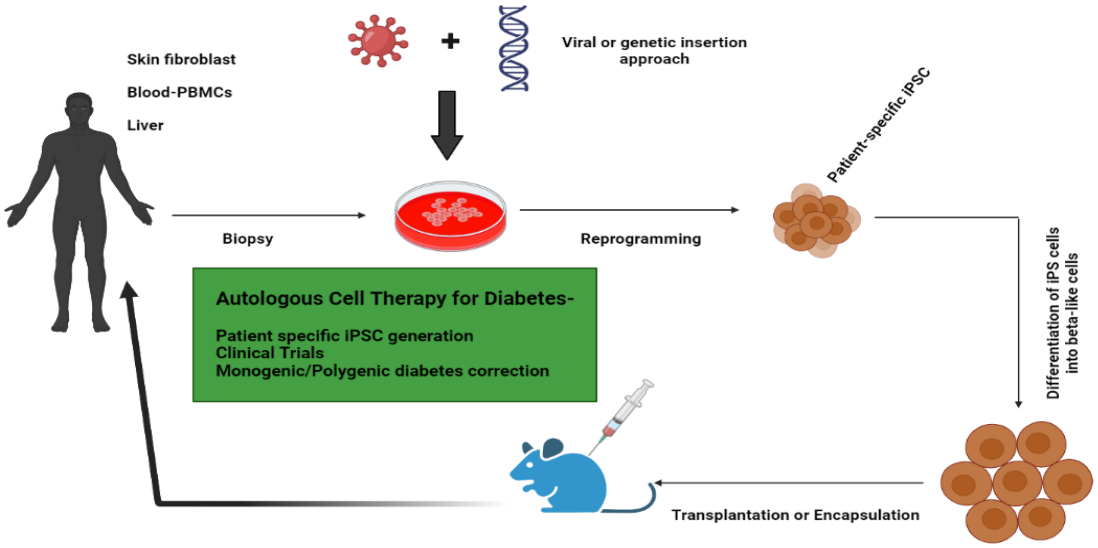

Fig A.4: Autologous cell therapy for diabetes

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