Review Article

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Holistic Regenerative Medicine and Cell Therapy in Treatment of Diabetes Mellitus: State of The Art Medicine and A Game Changer

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ABSTRACT

Diabetes Mellitus is affecting at least half a billion people globally. Being one of the most common noncommunicable diseases, to many, Diabetes Mellitus is considered to be a death sentence, to others, it means a struggle of survival. Diabetes is associated with increased premature mortality and a number of complications significantly impacting individual's quality of life, such as loss of vision, kidney failure, stroke, heart attack, limb ischemia. In spite of being one of the most widely occurring and well researched diseases Diabetes Mellitus still has no definitive cure. The research and discoveries in cellular biology that were done in the recent years had shed some light upon the aspects of the pathogenesis of Diabetes Mellitus, which may render more promising therapeutic solutions to this disease. Integration of the regenerative and preventive medicine protocols into the treatment paradigms for the Diabetes Mellitus may signify a beginning of a new era in treatment of the Diabetes Mellitus.

Keywords

Diabetes mellitus, Regenerative medicine, Mitochondrial function, Stem cells, Glycaemia, Glucose, Metabolic syndrome, Cell therapy.

List of Abbreviations

IDF: International Diabetes Federation; OGTT: Oral glucose tolerance test; GADA: Glutamate decarboxylase antibodies; BMI: Body mass index; AMPK: Adenosine monophosphate activated protein kinase; ATP: Adenosine triphosphate; AICAR: 5-aminoimidazole-4-carboxamide ribonucleoside; ROS: Reactive oxygen species; NRF-1: Nuclear respiratory factor; SHLP: Small humanin like peptide; PPAR: Peroxisome proliferator-activated receptor.

Introduction

Diabetes Mellitus: via Latin from Greek, literally 'siphon', from diabainein 'go through'; mellitus is from Latin mellitus 'sweet'. Literally, "melting down of flesh and limbs into urine". Clinical symptoms representing Diabetes Mellitus was described as early as 3000 years ago in ancient Egypt. Araetus of Cappodocia (81-133AD) coined the term Diabetes and later, the word mellitus (honey sweet) was added by Thomas Willis (Britain) in 1675 after rediscovering the sweetness of urine and blood of patients suffering from Diabetes Mellitus, which was initially discovered by the ancient Indians. In 1857, Claude Bernard (France) established the role of liver in glycogenesis and the concept that diabetes is due to excessive glucose production. Later on, Mering and Minkowski (Austria) 1889 discovered the pivotal role of pancreas in the pathogenesis of Diabetes Mellitus. These were the important stepping stones for Banting and Best (1921, Canada) to formulate insulin and kick start the clinical usage of it. Trials of first oral anti diabetic agents were successful in 1955 with the marketing of tolbutamide and carbutamide [1].

In present days, the term diabetes encompasses a spectrum of metabolic disorders characterized and identified by the presence of hyperglycaemia in the absence of treatment [2]. The poly-aetio-

pathology includes impairment in insulin secretion, insulin action, or both, and defects in carbohydrate, fat and protein metabolism. A diagnosis of Diabetes Mellitus invariably has multiple implications towards an individual. Health being aside, the potential stigma and how it affects employment, life insurance, driving status, psycho-social implications can be gruesome. Besides, the cultural, ethical and human rights consequences faced by these patients are always undermined [3].

Global burden

The current age stands at the verge of the urgent need of a cure rather than just a control. Diabetes Mellitus is global and found even in the rural and poor socioeconomic communities. The rise in newly diagnosed cases is steady and what is more alarming; the International Diabetes Federation (IDF) estimates about 1.1 million children and adolescents aged 14–19 years with Type 1 Diabetes Mellitus [4]. The World Health Organisation estimates a global disease burden of 629 million by 2045 with seven million deaths each year if no measures are taken to halt the progress. The IDF estimated that a hefty amount of USD 850 billion was spent in 2017 on diabetic healthcare [4]. Inevitably, the 'damage' ranges from individual to a nation's productivity.

Diagnosis and classification

The latest World Health Organisation devised four diagnostic tests for Diabetes Mellitus (2019):

- Measurement of fasting plasma glucose
- 2-hour (2-h) post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT)
- Glycosylated haemoglobin (HbA1c)
- Random blood glucose in the presence of signs and symptoms of diabetes [5].

People who present with fasting plasma glucose value of ≥ 7.0 mmol/L (126 mg/dL), 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dL), HbA1c ≥ 6.5% (48 mmol/mol) or a random blood glucose ≥ 11.1 mmol/L (200 mg/ dL) in the presence of signs and symptoms are diagnosed to have diabetes [5].

Though the common manifestation is hyperglycemia, the etio-pathogenesis, natural history and management differs hence classification of the disease is crucial. In a latest progress, Scandinavian researchers have identified five different cohorts by which diabetic patients can be classified, based on clinical and genetic parameters. In an article featured in the Lancet Diabetes & Endocrinology, diabetic patient was clustered according to the following baseline parameters:

- Age at diagnosis, BMI
- Glutamate decarboxylase antibodies (GADA)
- Glycosylated hemoglobin A1c (HbA1c) levels
- Homeostatic model assessment 2 to estimate beta-cell function (HOMA2-B) and insulin resistance (HOMA2-IR) using C-peptide concentrations [6].

Based on these, diabetics have been classified into the following cohorts:

- Severe autoimmune diabetes (formerly type 1 diabetes): characteristics include early-onset disease, relatively low BMI, and GADA-positive
- Severe insulin-deficient diabetes: GADA-negative but similar to cluster 1; lowest HOMA2-B scores
- Severe insulin-resistant diabetes: higher HOMA2-IR scores
- Mild obesity-related diabetes: obese, but not insulin resistant
- Mild age-related diabetes: older than other clusters, but largely similar to cluster 4 [6].

Metabolic syndrome is closely related to the etiopathogenesis or manifestation of type 2 diabetes mellitus. American Heart Association (AHA) estimates about 23% of adults globally to be affected by metabolic syndrome and is at greater risk of cardiovascular disease, diabetes, stroke and diseases owing it to vascular abnormalities, primarily. Age, sedentary lifestyle, genetic predisposition and obesity have been attributed strongly as risks of developing metabolic syndrome [7]. Three or more of the following criteria confirms the presence of metabolic syndrome (American Heart Association):

- Abdominal obesity (Waist circumference of greater than 40 inches in men, and greater than 35 inches in women);
- Triglyceride level of 150 milligrams per decilitre of blood (mg/dL) or greater;
- HDL cholesterol of less than 40 mg/dL in men or less than 50 mg/dL in women;
- Systolic blood pressure (top number) of 130 millimeters of mercury (mm Hg) or greater, or diastolic blood pressure (bottom number) of 85 mm Hg or greater;
- Fasting glucose of 100 mg/dL or greater [7].

Most patients with beginning type 2 diabetes are around middle age. Many of them have gone through major stress situations in life and many are still in them. Their adrenal cortex is forced to produce vast amounts of cortisol during the stressful years and is gradually burning out. Adrenal fatigue is amplified by the syndrome of "pregnenolone steal" At the same time, the sex hormones are no longer secreted at the same levels as when the patients were younger. In an attempt to produce more sex hormones and cortisol, the body makes more cholesterol. The years of stress and elevated cortisol production give patients the appearance of having Cushing's syndrome. Body fat is mostly around the mid-section; some even show fat accumulation in the area of the seventh cervical vertebra, the so-called "buffalo's neck" typical of Cushing's disease. Often, we see the "moon face" as well.

Weight reduction, healthy lifestyle and regular physical activity have been devised as weapons to fight against sugar. Carbohydrate exclusion or restriction sits at the tip of the sword. This strategy has been well documented to render a good glycemic control, reduce blood glucose leading to reduction in the doses of oral antidiabetic agents and in some cases, the total elimination of the said.

Role of AMPK in regulation of glucose and lipid metabolism

Adenosine monophosphate activated protein kinase or shortly, AMPK is the primary fuel sensing enzyme, a chief control which

regulates glucose and lipid metabolism, ensuring a balance between energy supply and demand by orchestrating the anabolic and catabolic cellular metabolisms, safeguarding the cellular energy supply. The AMPK is an energy gate, activated in conditions of high energy phosphate depletion, muscle contraction and myocardial ischemia. Activation of this enzyme facilitates glucose transport across cell membranes and fatty acid oxidation. AMPK is found in cell membranes with AMP/ATP gradients, mainly in skeletal muscle and liver [8].

The skeletal muscle exhibits high energy turn over and fluctuating power demands hence it is important to maintain a well-balanced interior milieu of tissue perfusion, oxygenation and energy store. In acute energy depletion, the AMP/ATP and ADP/ATP ratio increases intracellularly, signalling the activation of AMPK towards a cascade of events leading to energy production [9]. These include the upregulation of cellular mitochondrial biogenesis, the cellular power house, via a complex signalling pathway involving the activation of PGC-1α and nuclear respiratory factor 1. Activation of AMPK also leads to increased glucose transportation and fatty acid oxidation, the energy substrates, while suppressing the energy-conserving glycogen synthase and protein synthesis [10]. Researchers have found that pharmacological activation of AMPK in animal models along with 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) leads to reduction in plasma glucose, cholesterol and triglyceride levels, making AMPK a promising target for treating type 2 diabetes and other metabolic disorders [11].

Mitochondrial metabolism and diabetes

The power house of cells, the mitochondrial biogenesis has been observed to be upregulated in energy depleted state. The energy production of eukaryotics cells are primarily by the mitochondria, in the form of adenosine triphosphate (ATP) via metabolism of nutrients and oxidative respiration. The production of ATP requires two pivotal steps namely the oxidation of NADH (or $FADH_2$) and phosphorylation of ADP to form ATP (oxidative phosphorylation). NADH or $FADH_2$ are generated during glucose metabolism via glycolysis and the tricarboxylic acid cycle or β-oxidation of fatty acids. Mitochondrial metabolism ultimately leads to three main outcomes:

1. The generation of ATP: The electron transport chain generates electrochemical gradient through the proton accumulation in the intermembranous space. This in turn provides the driving force in ATP synthesis.
2. The generation of reactive oxygen species (ROS): Ineffective electron transport or leakage of electrons leads to the generation of ROS.
3. Energy depleted state or lethal amount of ROS leads to programmed self-destruction of the cell, apoptosis, mediated by proteins such as caspases or cytochrome C [12].

The pathophysiology of diabetes mellitus seems to have taken scientists through a labyrinth. As medical science advances, new discoveries perplex the scientific fraternity. Mitochondrial dysfunction in diabetics was not discovered earlier. Researchers have postulated few factors contributing to mitochondrial dysfunction in patients suffering from type 2 diabetes mellitus and age-related insulin resistance [13,14].

Mitochondrial biogenesis, including the number of mitochondria produced in a cell and the capacity of the mitochondria is highly affected and seen to be reduced in the diabetics. Nuclear respiratory factor (NRF)-1 and PPAR-γ and –α are found to be vital mediators that control the expression of genes involved in mitochondrial biogenesis, mainly the OXPHOS gene and mitochondrion transcription factor. Peroxisome proliferator-activated receptor (PPAR) coactivator (PGC)-1, specifically PGC-1α has been identified as a cofactor that activates the formers. The Expression of PGC-1 is age dependent and has been found to be declining with age. It has also been found to be decreased in insulin-resistant and diabetics, as well as the NFR. The expression of PGC-1α is seen to be increased in energy depleted states such as physical activity, fasting and exposure to cold environment. Activation of AMPK physiologically or pharmacologically upregulates mitochondrial biogenesis [15].

Mitochondria have been found to be the main site of Reactive oxygen species (ROS) production in the cell, during the electron transportation, mostly at the complex I and III. ROS is produced when the mitochondrial respiratory chain is supplied with excessive electron and coupled to oxygen without energy production, this being augmented in high proton gradient. Resulting superoxide is usually converted to hydrogen peroxide, either spontaneously or catalysed by superoxide dismutase. The milieu interior is well armed with glutathione, superoxide dismutase and catalase to buffer the ROS. Excessive ROS causes damage to DNA, protein and lipids and in turn results in mitochondrial dysfunction [12].

DNA damage, shortening of telomeres and oxidative stress been direct associated to aging. Mitochondrial biogenesis, structure and capacity are among the factors proven to be defective as age advances, including the reduced expression of PGC-1 and activation of AMPK. In general population, aging is generally related to reduced physical activities, increased visceral fat and impaired energy expenditure, leading to reduced oxidative capacity of the skeletal and cardiamyocytes. The net outcomes of these are the mitochondrial dysfunction and impaired insulin sensitivity [12-14].

By and large, the reduced insulin sensitivity is the result of high levels of free fatty acids, intracellularly. This could be due to excessive dietary lipid consumption, lipodystrophy or stress induced. This free fatty acid renders a low glycolytic efficiency while stimulating the oxidative enzymes, leading to reduced oxidative capacity of the mitochondria. This cascade ultimately ends in impaired insulin sensitivity. It is notable to mention, mitochondrial anomalies including faulty respiratory chain complexes, impaired mitochondrial β-oxidation, mtDNA depletion and ultra-structural lesions are found to be common in patients with non-alcoholic steatohepatitis or fatty liver disease [16].

The promising path

Despite the existing and up and coming chemotherapeutic agents, the final antidote for diabetes mellitus is still a hanging rope. The success directly implies on fixing the insulin resistance and in long run, replacing the functional insulin-producing pancreatic β cells, with pancreas or islet-cell transplants as age related atrophy and dysfunction is eventually inevitable.

Medical science continues to dedicatedly find a cure but it is pertinent to point out, it is within vicinity with Stem Cell therapy. Let's step into the future dimension of the cure for Diabetes Mellitus.

Unfortunately, difficulties in acquiring donor organs have prompted the search for alternative treatment modalities. Stem cell therapy and mito-organelles have shown promising results and been paving the path to what previously seemed impossible to the medical fraternity.

Stem cell therapy in treating diabetes mellitus

Literature gives an account of both embryonic stem cells and adult stem cells being used to generate substitute β cells or otherwise restore β-cell functioning with varying degree of results [17-19]. It is understood that stem cell therapy would benefit most to patients who are suffering from type 1 diabetes mellitus and to a certain extent, type 2 diabetes mellitus. It type 1 diabetes mellitus, it is pertinent to ensure the increase of beta cell production to destruction ratio. Researchers in University of Alberta in Edmonton came up with the famous Edmonton protocol which involves harvesting cadaveric beta cells and implanting to subjects via portal vein [20]. This effort showed numerous downfalls including aberrant production of insulin, the need of post therapy immunosuppression and the difficulties in obtaining the donor cells. That includes the number of donors needed for a single patient, stringent protocols and the cost involved.

This led to the use of precursor/progenitor stem cells. Unlike other treatment protocols, in treating diabetes mellitus, the progenitor stem cells are directly implanted and not injected into the blood stream. Injected cells take about 1 to 2 weeks to establish vascular network, exhibiting adult cell functions and exert the therapeutic properties among which includes activation of resident stem cells, arresting inflammation and apoptosis, increase cell division rate as well as buffer oxidative stress successfully [21,22]. Safety and long-term favourable outcomes have been documented and xenogenic transplantation has been proven to completely evade the hyperacute and acute graft vascular rejection [23-25]. Patients suffering from type 1 diabetes mellitus benefit the most, from stem cell therapy [26].

The various intrinsic etio-pathology of insulin resistance in type 2 diabetes mellitus, as discussed previously, has much been linked to metabolic syndrome and obesity. Researches have devised that curbing obesity and the linked metabolic syndrome would enhance insulin sensitivity, rendering optimal glycemic control, ultimately a hope for cure [27].

Mitochondrial peptides in treating diabetes mellitus

Down-sizing the whole therapeutic scale, researchers have found certain mitochondrial derived peptides are target effective in halting the etiologies involved in developing insulin resistance [28,29]. As discussed previously, the optimal function of mitochondria is vital in maintaining the insulin sensitivity [30-33]. Among the mitochondrial peptides that have been therapeutically utilised include small humanin like peptide (SHLP) – 1 to 6 with potent cytoprotective properties and SHLP 2 and 3 with anti-aging properties. These peptides are also known to be vital in insulin synthesis, expression of metabolic and inflammatory markers and halt age-related disease progression [30,33]. These peptides also regulate the production of leptin, thus improving insulin sensitivity by balancing the energy reserve and utility [28,29].

Holistic approach to the treatment of diabetes

Cell therapy is particularly well suited to helping prevent secondary complications of diabetes such as atherosclerosis, kidney damage and retinal damage. It can also help lower the required dosage of oral anti diabetic drugs and/or insulin.

As it was already mentioned the metabolic situation causes the insulin receptors in cell membranes to lose their affinity for insulin. Glucose has trouble entering the cells where it is needed and most patients have no energy, no drive and feel very fatigued. In an effort to push glucose into the cells, the body makes more and more insulin, thereby lowering the sensitivity of insulin receptors even more. The elevated insulin levels lead to more fat accumulation around the mid-section and the vicious circle continues [34,35].

The treatment cannot be to increase insulin as this will only amplify the vicious circle. Therapeutic protocols include the progenitor cells of adrenal cortex, heart, liver, and the gonads. Islet cells of the pancreas should be given especially in the later stages, as the pancreas burns out with time. The specific cell therapy tissue preparations that are meant to help with blood sugar regulation are pancreas, liver, and hypothalamus. Pancreas is given especially in more advanced stages as the chronically elevated blood sugar damages the β-cells in the pancreas. Cells of the retina, arteries and kidney are given to help with the prevention of secondary complications caused by diabetes, and adrenal cortex and placenta are given as supporting tissues for dealing with adrenal fatigue and for the growth factors and hormones of the placenta that stimulate cell regeneration and well-being [32,33].

Testicular cells for men and ovarian cells for women are also required to help regulate the expression of sex hormones. Especially in men, an increase in testosterone will help with muscle build-up, boosts metabolism and thus improves glucose utilization [32,36].

Cell therapy renders very promising results with regard to diabetic complications. In one of the recent studies comparing outcomes of the intramuscular and intraportal cell culture transplantation in patients with diabetic complications three months post-implantation 81.4% of patients experienced substantial reduction or disappearance of pain due to polyneuropathy; after six months

the same effect was present in 74.2%, and after 12 months in 50% of patients in the intramuscular route group. In the second group (intraportal route), at three months follow-up 87.8% of patients were pain-free, and after 12 months - 76.1% patients [37].

In the earlier study that assessed dynamics of peripheral angiopathy, 74% of patients had stabilization of peripheral artery disease, 18% improvement and 8% worsening. Stabilization of retinopathy was observed in 70% of patients, improvement in 25%, worsening in 5%. In 34% of the cases improvement of visual acuity occurred, in 60% stabilization, in 6% worsening [38].

According to the report from another Eastern European study, 85.7% of patients observed early post-transplantation improvements: decreased weakness, increased physical and mental capacity, reduction or complete disappearance of chronic pain and aches, better concentration, stabilization in sleep patterns, etc. All patients tolerated implantation well and no adverse reactions were observed.

Over the first week after cell implantation, in 42.9% of cases a transient increase of blood glucose levels by 15–25% was observed, and subsequently spontaneously reduced within two weeks. No evidence of severe hypoglycemic response was reported by the patients. Tendency to decreased fasting blood glucose levels was seen over 2–3 months of observation. The likelihood of decreased fasting glycaemia levels was also revealed over 5–7 months after treatment and remained low for the entire period of observation. The level of postprandial hyperglycaemia was decreased over 5–7 months in the study. In 64.3% of cases the 1.5–2-fold lowering in doses of hypoglycemic medicines over 4–6 months after islet precursor cells was reported. A gradual decrease in HbA1c levels was also observed in the majority of patients [39].

Improved insulin sensitivity and better glycaemic control are not the only benefits of the holistic approach applied to the design of the cell therapy protocols. The long term follow-up after cell therapy and continuous maintenance holistic treatment alleviated the parameters of the metabolic syndrome as well, including the status of lipids metabolism. The following positive changes were observed: 81% of patients had lowered levels of cholesterol, LDL levels reduced by 20–24% and HDL levels increased by 21–25%. BMI was reduced in 85.7% of cases over 12 months after fetal precursor stem cell therapy. Remarkably, fetal precursor stem cell treatment in diabetic patients results in 21% reduced mortality rates; acute myocardial infarction risks decrease in 15%; vascular complications are reduced by 37%, and there is a 47% reduction in mortality rate due to peripheral artery disease [31,32,39].

Conclusion

The medical science is facing an emerging era of non-communicable diseases, diabetes leading the list. The global disease burden is alarming and is expected to rise steadily if no effective, sustained intervention is established. Stem cell therapy and targeted peptide therapy with mitochondrial-derived cell extracts have successfully used to yield excellence in therapeutic outcome. These should be considered to be made one of the main stream treatment modality, of course with standardised treatment protocol and longitudinal surveillance.

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