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Review Article

Current Treatment Approaches for Type-II Diabetes Mellitus

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Abstract

Diabetes is one of chronic metabolic disorder. Increase in the concentration of glucose level in the blood due to impaired insulin secretion in the body state of hyperglycemia occurs which can be termed as Diabetes Mellitus. As proper treatment of the disorder is still undiscovered various management therapies either external insulin supplement or various other oral hypoglycemic agents are in use. Those available drugs are used only for the management of the disorder without any significant treatment. Such medicaments need to be taken daily throughput the lifetime. Since many decades the treatment approaches are made which still does not have any proper significance. Here in this review few recent treatment approaches for Type-II Diabetes Mellitus are discussed which may be helpful in the treatment of disorder.

Keywords: Metabolic Disorder; Insulin; Hyperglycemia; Glucose Level

Introduction

One of a best way to solve a problem is to think backwards. It is Previously defined and proved by Sir Isaac Newton by the identification of calculus and solving the mathematical problem backwards and showing it in conventional mathematics. The same mechanism can also be used to cure an uncurable disease if the complete pathogenesis of the disease is known [1]. Diabetes Mellitus is one of metabolic disorder due to the impaired functioning of pancreatic - cells so that the hormone, insulin cannot be secreted in sufficient amount or no secretion of insulin at all, which leads to presence of excess glucose in blood also called as hyperglycemia. As of now cure for DM is not available, the disorder can only be managed by some oral hypoglycemic agents and use insulin injection, in case of no secretion of Insulin [2]. Reverse diabetes is process involving the regeneration, replacement and protection of the pancreatic - cells for sufficient secretion of insulin needed for the body. Although this approach may be useful in the treatment of disease but due to lack of scientific evidences it is not used commercially till date [3].

Pancreas is a major organ performing both exocrine and endocrine metabolic functions in the body. Insulin and glucagon hormones are secreted from the endocrine portion of the pancreas and dysregulation of the organ leads to changes in the metabolic functions in the body causing fluctuations of the blood glucose level and other complications [4]. In case of diabetes, lack or no secretion of insulin the blood glucose level elevates and leads to the state of Diabetes. As this may be due to dysfunction or destruction of the - cells of islets of pancreas which cannot be recovered by the body so that impaired insulin secretion occurs. In the following review various approaches and methods for the regeneration of - cells are illustrated which may be useful in the permanent treatment of the diabetes mellitus rather than its management [5].

Current approaches

-Cells Regeneration

-cells of pancreas are responsible for the secretion of insulin in human body. Dysfunction or damage to those cells leads to im-

paired insulin secretion due to which the state of hyperglycaemia takes place by the presence of excess unmetabolized glucose in blood [6]. Regeneration of those cells may help in the cure of the disease. -cells regeneration process can be carried out by followed mechanism:

-cells proliferation

In human, -cells begins to grow during the neonatal period, however the development of the cells seizes as the person becomes mature. During pregnancy and obesity-induced insulin-resistant state the growth of the cells continues [7]. Therefore, external means can be implied so as to increase the endogenous -cells using *in-vivo* and *ex-vivo* methods in diabetic people for the treatment of diabetes [8]. In the past 3 decades, several -cell lines have been used in rodents and numerous attempts to generate -cells in human however the amount of insulin secretion was found very less or insufficient. In the last decade, transducing human foetal pancreases was established in human for insulin production using lentiviral vector which expressed SV40LT and human telomerase reverse transcriptase named as EndoC-H1 and the process was able to secrete insulin in response to the amount of glucose present in blood. Development of new generation of EndoC-H1to EndoC-H3 which contains an integrated tamoxifen inducible form of CRE recombinase and floxed immortalizing transgenes which were found to massively multiply capable of producing non-proliferating and proper functioning human β-cells. These can be used for the treatment of diabetes however further studies is needed for safety [9].

Trans-differentiation into -cells

Trans-differentiation is a process in which one type of cell is made to function other cells. Islets of pancreas consists of different types of cells such as cells. Out of which only β cells are responsible for secretion of insulin. In recent study it was found that the α cells has the capability to function as β cells and secrete insulin [10]. Collombat and colleagues carried out a research which shoes ectopic expression of Pax4 could possibly help in conversion of α cells into β cells and function as β cells. It is shown that pancreatic α cells phenotype can drive into β cells phenotype by GABA and antimalarial drugs i.e. artemether following GABAergic Pathways [11,12]. Thorel and his colleagues reported the use of diphtheria toxin mediated β-cell ablation model which could function similarly and secrete insulin in the body. So this trans-differentiation mechanism can be included in the treatment approaches for diabetes mellitus [13].

Pancreas transplantation

Pancreas transplantation for the treatment of Type-I diabetes mellitus has already shown significance by proper secretion of insulin in the recipients for longer period of time. Around 90% of the allograft transplantation in type-I diabetes mellitus has shown excellent results for a long period of time [14]. But in case of Type-II diabetes mellitus lesser surgery has been performed so only of around 9% success rate is observed. The reason might be weak cardiovascular system in Type-II diabetic people as for transplantation strong cardiovascular system is necessary [15].

Pancreas transplantation includes the intraperitoneal placement of transplanted pancreas in a heterotopic location of body. The process is complex as the donor receives blood supply from iliac veins of recipient or systemic venous drainage. The chances of success in pancreas transplantation is around 90 - 95% [16]. The proper transplantation of organ leads to immediate insulin independence and further requirements of insulin and any other medication is not compulsory. This may be helpful in preventing further diabetic nephropathy due to decrease in glucose concentration in blood veins and nerves. Thus, the transplantation therapy may be very useful in the treatment of type-II diabetes mellitus [17].

Transplantation of islet organoid cells

Hormone expressing endocrine cells (ECs) are present in pancreatic islets along with -cells which are responsible for secretion of glucagon, -cells which secretes insulin, cells which produces ghrelin as well as cells secreting somatostatin and PP cells producing pancreatic peptide [18,19]. The ECs present in islets helps in regulation of glucose level in blood [20]. The similar structure of islets provides physiologically regulating of the synthesis of insulin [21]. There are few techniques to grow organoids which are the group of primary cells, can be grown *in-vitro* and these can function similar to organ and has self-replication properties [22]. In several studies [23], generation of hESC derived islets cells like clusters are done along with organoids similar to islets of pancreas [24]. Such cells were derived in 3D culture which formed into pancreatic islets similar to human cells of 50-150 in diameter [25]. Such organoids has all the cells as similar cells of islets of pancreas except - cells but they are analogues to human pancreatic cells as these have same size and has similar composition [26]. The level of beta cells are found more compared in endocrine cell clusters compared to endocrine cells [27-29]. Influx of intracellular Ca2+ too was higher in ECCs for glucose stimulation which helps in concluding the

transplantation of such organoids from hPSCs [30], thus this can be an alternative therapeutic treatment and cure of diabetes [31]. Those generated beta cells cannot co-express PP [32], somatostatin and glucagon so the mature beta cell markers whose genes were expressed has insulin secretory properties and secretes insulin in higher concentrations [33,34].

Bariatric surgery

This is generally performed for the obese people done generally to reduce body weight. As obesity is one of the primary cause of diabetes in people so the bariatric surgery can be helpful in the treatment of obese diabetic people. The process of bariatric surgery is allowed to be performed on the adult people with BMI body mass index less than 40 or people who have body density of 35 kg/m2 and is for obese people [35]. Various sleeve gastrectomy or robotic-Y gastric bypass and laparoscopic bariatric surgeries are performed till date, most of them are used in United States [36]. Intestinal malabsorption of food along with diet restriction are the major principle upon which the surgeries are performed. The results obtained from the surgery were found satisfactory in 75- 80% people reversing the diabetes in a very period of time [37]. Increase in insulin sensitivity and proper regular response to blood glucose level were found in the post-operative people [38]. Along with this regulation of release of GI hormone, peptide-tyrosine-tyrosine, ghrelin and leptin are shown [39]. Although all these impacts may be for the short period of time as the long term durability still remains uncertain [40]. The weight loss, along with improvements in triglyceride level and high density lipo-protein are seen. The mortality rate during the surgery is always high up around 13-21% and 0.28-0.29% in post-operative state [41]. Various other complications including haemorrhage, requirement of re-operation, dumping syndrome, micronutrient deficiencies, hypoglycaemia after operation and marginal ulceration may occur. It is highly certain that the post-operative weight loss which may be a significant signal for return to euglycemia [42].

The cost of the bariatric surgery may cost around 14,000-15,000 US dollars [43]. This cost significantly higher but according to pre study before surgery by *Pories* and his colleagues, people spend around $10,000 per year for the medications of diabetes. So, the rise in amount may be useful as one time investment for surgery may be helpful for longer period of time compared to daily medication [44]. The surgery is also helpful for the treatment of obesity so the process in cost-effective for both the category people. The improvement in metabolic syndrome, comorbidities improvements after the surgery was found common [45].

Bariatric surgery may be useful in improvement of reduction in de-novo production of glucose, increase in sensitivity of hepatic insulin and proper clearance of fasting hepatic insulin [46]. Improvement of -cells sensitivity towards glucose, improvement in GLP-1 secretion from gut and regular sensitivity of insulin in fatty cells and muscle during the period of 3 months to 1 year after the surgery [47]. So, this bariatric surgery may be a leap towards the process of treatment of diabetes [48].

Conclusion

The following approaches are being followed since many decades but these have not become so common for the treatment of the disorder. However, those approaches are helpful for cure for certain period of time for certain people who can use the treatment approaches correctly in time. These needs further research and proper scientific evaluation so that these can be made convenient means of permanent cure.

Conflict of Interest

Authors do not any competing interest.

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