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EC MICROBIOLOGY
Review Article

Overview of Diabetes Mellitus and New Modalities of Treatment

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Received: December 21, 2022; **Published:** December 26, 2022

Abstract

Introduction: Diabetes mellitus is a group of metabolic diseases where insulin is either deficient in quantity, or its action is resisted by target organs. Broadly, it is classified as type 1, type 2, gestational diabetes, and other less common ones like monogenic diabetes. It affects millions of people around the world of all age groups and is a major cause of mortality among humans. This review briefly discusses the epidemiology, pathogenesis, and conventional treatment, while focusing more on emerging modalities of management.

Aim of Work: The aim of this study is to review the fundamentals of diabetes mellitus and novel methods of treatment.

Materials and Methods: Comprehensive research of diabetes mellitus and novel methods of treatment. PUBMED search engine was the mainly used database for the search process, articles collected from the year 2000 to 2022 relating to diabetes mellitus treatment. The term used in the search were: Diabetes mellitus, gestational diabetes, insulin, beta cells, gene therapy, transdifferentiation, stem cells, iPSC.

Conclusion: Diabetes mellitus is a group of metabolic disorders that disrupt the homeostasis of insulin and glucose in the blood. It affects up to a tenth of the adult human population and is responsible for millions of death worldwide each year. Broadly, it is classified as type 1, type 2 and gestational diabetes, with each one having different etiopathogenesis from the other. Conventional treatments with insulin injections and oral hypoglycemic drugs have been in use for a while, but newer research into genetic engineering, transdifferentiation, and stem cell therapy is offering novel methods of managing this disease.

Keywords: *Diabetes Mellitus; Gestational Diabetes; Insulin; Beta Cells; Gene Therapy; Transdifferentiation; Stem Cells; iPSC*

Introduction

Diabetes is myriad of several metabolic disorders where the function of insulin is diminished either by deficiency, action, or both resulting in chronic hyperglycemia. Diabetes has traditionally been classified into three broad categories: type 1 diabetes, type 2 diabetes, and gestational diabetes. Type 1 diabetes usually occurs at a younger age and is characterized by the autoimmune destruction of insulin-producing beta cells of the pancreas. Type 2 diabetes comprises the majority of cases and usually occurs later in life. It is usually characterized by insulin resistance, followed by decreased insulin production as well. Hyperglycaemia seen during pregnancy is termed gestational diabetes. Other infrequent categories of diabetes include monogenic diabetes and diabetes secondary to other diseases, such as pancreatitis. This short overview will discuss diabetes mellitus in brief and its recent advances in its management [1].

Epidemiology

Diabetes in 2014 was reported to have affected at least 8.5 % of all adults, and it caused the death of 1.5 million people worldwide in 2019 [2]. Type 2 diabetes comprises up to 90% of all diabetes mellitus cases, whereas type 1 and gestational diabetes account for most of the remaining cases [1].

Pathophysiology

Type 1 diabetes mellitus is an insulin-dependent type of diabetes as there is a subsequent shortage of insulin secretion due to the autoimmune destruction of beta cells of the pancreas. Histopathological examination of pancreatic tissue has revealed infiltration of macrophages, dendritic cells, and lymphocytes (B and T). It is usually in early life but can also manifest in later years [3].

Type 2 diabetes mellitus is a non-insulin dependant type of diabetes, and it occurs in adult life. Two major anomalies characterize this disease: insulin resistance and dysfunction of pancreatic beta cells. In insulin resistance, cells of various tissues, such as muscle, liver, and adipose, become insensitive to insulin action. Initially, beta cells respond with a greater secretion of insulin, but over time, beta cells start to become dysfunctional, and hyperglycemia sets in. Type 2 diabetes is very slow in progression and may remain undiagnosed for several years [4].

Gestational diabetes is a type of diabetes diagnosed during pregnancy and is usually resolved after childbirth or pregnancy termination. It is often seen in 2nd or 3rd trimester, in older and obese women, and in certain racial groups (Indian, Aboriginal Australians, and Middle Easterners). The risk of developing type 2 diabetes remains high among these women. These women are recommended to undergo regular screening for early diagnosis of type 2 diabetes [5].

Diagnostic criteria

According to American Diabetes Association, fasting hyperglycemia (plasma glucose ≥ 126 mg/dL (7.0 mmol/L) after at least 8h of no food, hemoglobin A1c (HbA1c) ≥ 6.5% (48 mmol/mol), or a random plasma glucose > 200 mg/dL (11.1 mmol/L) with associated symptoms of hyperglycemia, or a plasma glucose > 200 mg/dL after a 75g glucose load on an oral glucose tolerance test [6].

Classical management

Insulin

Regular injection of insulin remains the mainstream treatment for controlling hyperglycemia. The frequent injection creates fear of needles among patients and thus results in poor compliance with treatment for many. Subcutaneous insulin pumps are available in the market, but they do carry certain risks, such as skin infections. Advanced pharmaceutical delivery systems, such as nanotechnology, could use oral routes for insulin delivery [7].

Oral hypoglycemic drugs

Biguanides, such as metformin, are the commonest antidiabetic drug and are the choice of drug as monotherapy. Metformin has multiple functions, such as improving insulin sensitivity, increasing the uptake of glucose, and downregulating gluconeogenesis. Thiazolidinediones (TZDs) are another group of drugs that improve insulin sensitivity. Sulfonylureases are known as secretagogues, where they act

on beta cells to trigger endogenous insulin secretions. A combination of drugs is used for faster and more effective responses in maintaining blood glucose levels [8].

Recent advances

Gene therapy

It is an advanced therapy that uses various modalities of introducing an insulin-producing gene into several types of cells, such as muscle, pancreas, intestines, etc. Various techniques for insulin gene introductions include viral vectors, liposomes (manmade cells), and plasmids. To genetically induce non-beta cells for insulin production is not an easy task as insulin production is a complex task within a cell. A T Cheung., *et al*. 2000 genetically engineered intestinal cells of mice to produce insulin with the promotion of gastric inhibitory polypeptide. They destroyed native beta cells using streptozotocin, and yet the mice showed normal glucose levels in the blood [9]. Another study by Nelson K F., *et al*. in 2008 was based on the introduction of insulin expression plasmid in surgically resected liver wedges of 10 pigs. The genetically modified tissue was reimplanted into the livers of streptozotocin-induced diabetic pigs. These pigs showed improvement regarding hyperglycemia, glucose intolerance, and metabolic abnormalities for more than 47 weeks [10].

Transdifferentiation

This idea involves stimulating non-beta cells to transform into insulin-producing beta cells of the pancreas. Pancreatic cells, duodenal cells, and hepatocytes originate from the endodermal cells of the foregut. A thorough understanding of various transcription factors that differentiate endodermal cells of the foregut into pancreatic cells can help us transdifferentiate other cells of similar origin [11].

Sarah Ferber., *et al*. in 2000, used recombinant adenovirus to transfer gene PDX-1, which regulates insulin gene function, into the liver tissue of mice. This induced expression of otherwise silent insulin 1 and 2 genes as well as prohormone convertases. There was a substantial increase in plasma insulin levels which controlled the hyperglycemia-induced in those study mice with streptozotocin [12].

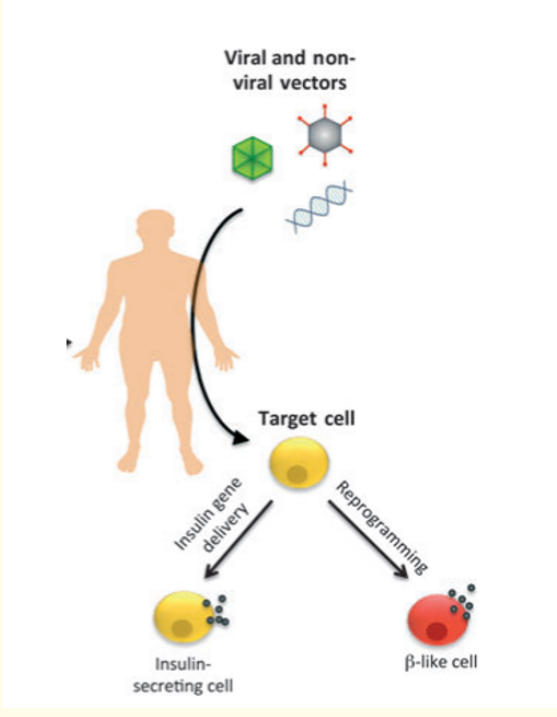

Figure 1: *Showing gene therapy (left) and transdifferentiation (right) [13].*

Stem cells

Stem cells are non-specialized cells capable of reproducing themselves as well as differentiating into specialized cells. Embryonic stem cells (ESC) are the most undifferentiated category of cells but are available at the embryonic stage of life, and harvesting them raises many ethical questions. To overcome this hurdle, the somatic cells of an individual can be reprogrammed to produce induced pluripotent stem cells (iPSC). iPSC can be autogenously harvested, thereby escaping immune response, and they also have similar properties to ESC. The reprogramming of adult cells is done by introducing transcriptional factors (Oct4, Sox2, c-Myc, and Klf4) via a retrovirus vector [14].

The iPSCs have to be provided with proliferative and differentiation signals to make endocrine beta cells. Cytokines and signaling modulators such as activin, BMP, FGF, hedgehog, and retinoids are used. The 1st step of the differentiation protocol involves creating embryoid bodies that spontaneously differentiate into 3 germ layers. Endoderm from the 3 germ layer is further differentiated into pancreatic progenitors, pancreatic endocrine cells, and finally, mature beta endocrine cells. There is further complexity because normal beta cell populations are not all the same, and the kinetics of insulin release are complex, which iPSCs must achieve [14].

Conclusion

Diabetes mellitus is a group of metabolic disorders that disrupt the homeostasis of insulin and glucose in the blood. It affects up to a tenth of the adult human population and is responsible for millions of death worldwide each year. Broadly, it is classified as type1, type 2 and gestational diabetes, with each one having different etiopathogenesis from the other. Conventional treatments with insulin injections and oral hypoglycemic drugs have been in use for a while, but newer research into genetic engineering, transdifferentiation, and stem cell therapy is offering novel methods of managing this disease.

Bibliography

1. Goyal R., *et al*. "Diabetes Mellitus Type 2 (Nursing)". In Stat Pearls. Stat Pearls Publishing (2021).
2. Roth GA. "Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018". *The Lancet* 392 (2018): 1736-1788.
3. Knip M and Siljander H. "Autoimmune mechanisms in type 1 diabetes". *Autoimmunity Reviews* 7.7 (2008): 550-557.
4. Leahy JL. "Pathogenesis of type 2 diabetes mellitus". *Archives of Medical Research* 36.3 (2005): 197-209.
5. Lawrence JM., *et al*. "Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005". *Diabetes Care* 31.5 (2008): 899-904.
6. International Expert Committee. "International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes". *Diabetes Care* 32.7 (2009): 1327-1334.
7. Gedawy A., *et al*. "Oral insulin delivery: existing barriers and current counter-strategies". *Journal of Pharmacy and Pharmacology* 70.2 (2018): 197-213.
8. Tan SY., *et al*. "Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention". *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* 13.1 (2019): 364-372.
9. Cheung AT., *et al*. "Glucose-dependent insulin release from genetically engineered K cells". *Science* 290.5498 (2000): 1959-1962.
10. Chen NK., *et al*. "Nonvirally modified autologous primary hepatocytes correct diabetes and prevent target organ injury in a large preclinical model". *PLoS One* 3.3 (2008): e1734.
11. Habener JF., *et al*. "Minireview: transcriptional regulation in pancreatic development". *Endocrinology* 146.3 (2005): 1025-1034.
12. Ferber S., *et al*. "Pancreatic and duodenal homeobox gene 1 induces expression of insulin genes in liver and ameliorates streptozotocin-induced hyperglycemia". *Nature Medicine* 6.5 (2000): 568-572.

13. Tudurí E., *et al*. "Restoring insulin production for type 1 diabetes". *Journal of Diabetes* 4.4 (2012): 319-331.

14. Silva IBB., *et al*. "Stem cells differentiation into insulin-producing cells (IPCs): recent advances and current challenges". *Stem Cell Research and Therapy* 13.1 (2022): 1-24.

Volume 18 Issue 12 December 2022