A REVIEW OF DIABETES MELLITUS AND AVAILABLE TREATMENTS

By

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Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study comprises no human or animal trial.

Abstract/ Executive Summary

The Present Condition Has shown us that diabetes mellitus is a major health problem which has impacts on all ages of people from children to aged persons. Once a person gets himself into diabetes mellitus disease, he can’t come out from that. A person can face other health issues due to diabetes mellitus. So people should try to prevent it before happening. People can follow some steps like dietary or nutritional approaches or some medications to prevent this disease. One can’t fully cure diabetes mellitus but can control it or reverse it. Some available treatments for type diabetes mellitus are: stem cell therapy, gene therapy, immunotherapy, Proper diet plan and exercises etc.

Keywords: Diabetes Mellitus, Insulin, Stem Cell therapy, Immunotherapy, Gene therapy.

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DM	Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
IRS	Insulin Receptor Substrate
IR	Insulin Rasistant
HLA	Human Leukocyte Antigen
M.Value	Morbus Value
FFA	Free Fatty Acids
JDRF	Juvenile Diabetes Research Fund

List of Acronyms

TEDDY	The Environmental Determinants of Diabetes in the Younf
PTMs	Post-translational Modifications
CGM	Continuous Glucose Monitoring
OGTT	Oral Glucose Tolerance Test
ATG	Anti-thymocyte Globulin
PCR	Partial Clinical Remission
NOD	Non-obese Diabetic
MAFA	MAF BZIP Transcription Factor A
AAV	Adeno-associated Virus
DPP4	Di-peptidyl Peptidase 4

Chapter 1: Introduction:

Diabetes is a significant pandemic of our century, with prevalence rising by 50% in the past ten years. Diabetes is a lipid, protein, and carbohydrate metabolic disorder that affects a sizable portion of the global population. Numerous organs' ability to function normally is hampered by hyperglycemia and the related lipid, protein, and carbohydrate metabolic disease (Patel et al. 416). Its origin is complicated, its progression is gradual, and it manifests in a wide range of symptoms, such as hyperglycemia, inflammation, discomfort, and weight loss, among others. The hallmarks of hyperglycemia include chronic and diverse metabolic dysfunctions of protein, lipid, and carbohydrate metabolism. Hyperglycemia is due to abnormalities in the production of insulin, action of insulin or both (Sameer et al. 174).

Diabetes' rising global prevalence has been identified as one of the most important and challenging health issues now affecting the population of the entire planet. The life expectancy of diabetics is lowered by around 10 and 20 years for type I and type II diabetes and they have a 15% higher risk of dying early. With 1.6 million deaths directly attributed to the condition, The world's fifth-leading cause of death is still diabetes. Due to diabetes and its effects, over 4.2 million adults aged 20 to 99 died in 2019. Diabetes-related healthcare costs reached at least 760 billion USD in 2019. One in every six women had diabetes while pregnant, which is estimated to have caused harm to more than 20 million live births. Roughly 32 000 Germans under the age of 20 have type 1 diabetes, according to registry data from 2010 (Ziegler and Neu).

On the Other hand, Prediabetes is a condition of elevated plasma glucose that can lead to the development of type 2 diabetes and cardiovascular diseases but has not yet crossed the threshold for diabetes. It is considered to be a condition that carries a high risk of developing into diabetes (Ziegler and Neu).

Table 1

A comparison between normal, pre-diabetes and diabetes based on three diagnosis methods.

	FPG	PG in OGTT	A1C
Normal	<100 mg/dL or 5.5 mmol/L	<140 mg/dL or 7.8 mmol/L	<5.7% or 39 mmol/mol
Pre-Diabetes	≥100 mg/dL or 5.5 mmol/L	≥140 mg/dL or 7.8 mmol/L	≥5.7% or 39 mmol/mol
Diabetes	≥126 mg/dL or 7.0 mmol/L	≥200 mg/dL or 11.1 mmol/L	≥6.5% or 48 mmol/mol

Table 1: Using three different diagnosis methods, normal, pre-diabetes, and diabetes are compared.

1.1 Aim:

This project is a study of diabetes mellitus, it's types, prevention and treatments. So, this project aims to suggest the knowledge of diabetes, way of prevention and what treatment should people get according to their type of diabetes and this study will be upgraded if more scientific and medical evidences become accessible.

1.2 Objectives:

- To study diabetes mellitus
- To discuss the causes of different types of diabetes
- To know the prevention method
- To know the common treatments available for various types of diabetes.

1.3 Types of Diabetes Mellitus:

We can classify Diabetes Mellitus into two major types. These are:

I. Type 1 Diabetes Mellitus
II. Type 2 Diabetes Mellitus (Forbes and Cooper 140).

Some other types of Diabetes Mellitus that can happen are, "gestational Diabetes Mellitus, monogenic defects of ß cells, neonatal Diabetes Mellitus, maturity onset diabetes of the young, genetic defects in insulin action, Diseases of the exocrine pancreas, endocrinopathies (Gilor et al. 935).

1.3.1: Type 1 Diabetes Mellitus:

The most prevalent kind of diabetes is T1DM and is typically identified as insulin insufficiency at a young age (Li et al. 33). It is caused by autoimmune-mediated death of pancreatic -cell islets which results in complete insulin insufficiency (Patel et al. 414). The pancreatic ß cell is destroyed because in type 1 diabetes, hyperglycemia is caused by an intricate process of illness in which genes from previous generation and environmental factors trigger immune-mediated feedback which is still unknown (Forbes and Cooper 140). The biology underlying the autoimmune processes linked to T1D is discovered months to years before symptoms appear. The initial autoantibody type depends on genetic and environmental causes. Depending on whether there is hyperglycemia or not and symptoms such polyuria and thirst, pathogenesis can be separated into three stages. T1DM patients require lifetime insulin injections, however new treatments are being developed, including as insulin pumps, continuous glucose monitoring, and hybrid closed-loop devices. To improve the quality of life and diagnosis of people affected, significant research efforts are required to achieve an early diagnosis, avoid cell loss, and create better treatment choices (Katsarou et al.).

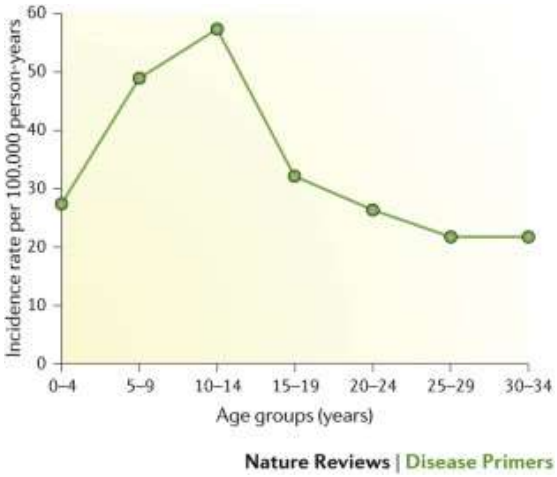

Figure 1: Age-specific incidence rates of T1DM (Katsarou et al.).

1.3.2: Type 2 Diabetes Mellitus:

A widespread and deadly chronic condition known as type 2 diabetes mellitus is caused by a complicated interaction between genetics, environment, and additional risk factors like obesity and inactivity. Type 2 diabetes mellitus also develops more quickly as a result of the loss of the initial phase of releasing insulin, an atypical impulse of basic insulin excretion, and an increase in glucagon secretion. Analysis of current statistical data shows that it has some new epidemiological features. First, diabetes is increasing in developed countries such as the United States and Japan. And it's worth noting that the prevalence of type 2 diabetes mellitus is increasing at an alarming rate in developing countries. This will continue to increase over the next 20 years, with more than 70% of patients expected to occur in developing countries, most of whom are estimated to be 45 to 64 years old. Second, while aging is a risk factor for type 2 diabetes, an increased incidence of childhood obesity leads to an increased prevalence of type 2 diabetes in children, teens and adolescents, leading to a serious epidemic. Shows the emergence and scope of serious new public health problems (Wu et al. 1194).

1.3.3: Gestational Diabetes Mellitus:

When pregnant women who have never had diabetes acquire chronic hyperglycemia, it can lead to gestational diabetes mellitus, a serious pregnancy disease. Reduced glucose tolerance, which is brought on by pancreatic beta-cell loss in the context of chronic insulin resistance, is the main contributing cause (Plows et al. 3342). The likelihood of women with GDM getting type 2 diabetes mellitus in the years that follow is widely acknowledged. This gestational

diabetes may result in long-term consequences for both the mother and the child. As obesity rates have increased in women of childbearing age increases, GDM rates will continue to increase. The biggest concern is maintaining a diabetic cycle between mother and child (Szmuilowicz et al. 480).

1.4 Causes of Diabetes Mellitus:

Main types of diabetes mellitus are, T1DM and T2DM where T1DM occurs because of insulin deficiency caused by β-cells damages and the type 2 diabetes is because of insulin resistance (Wolosowicz et al. 8651).

1.4.1: Causes or Risk-factors of T1DM:

Some risk-factors can trigger insulin resistant of type 1 diabetes mellitus which is shown in the figure below:

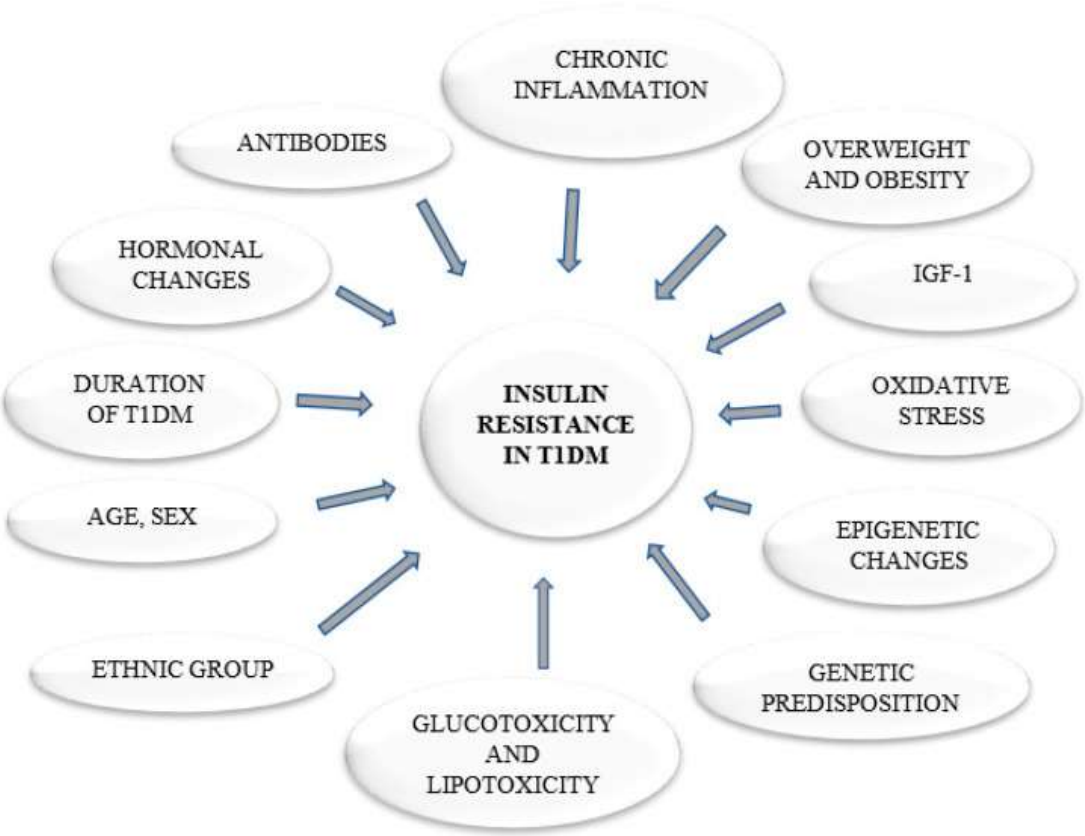

Figure 02: Factors causing resistance of insulin in T1DM (Wolosowicz et al. 8651).

Some factors are explained below:

Active oxygen species (ROS) can reduce GLUT4 gene transcription, serine/threonine phosphorylation of the insulin receptor substrate, decreased translocation of insulin signaling components in cells, and altered mitochondrial activity. As a result, oxidative stress disrupts the insulin signaling process. In type 1 diabetes mellitus, oxidative stress linked to hyperglycemia and lipotoxicity are two mechanisms that contribute to the development of IR (Wolosowicz et al. 8651).

In type 1 diabetes mellitus, chronic inflammation can potentially contribute to insulin resistance. Inflammatory substances like Il-6 and inhibitor of plasminogen activator are produced when adipocytes swell, causing a pro-inflammatory condition, thereby contributing to β-cell death which eventually decreases insulin secretion (Wolosowicz et al. 8651).

Type 1 diabetes mellitus, a frequent type of diabetes in young individuals, has age as one of its risk factors. The incidence rate grows from birth until puberty, which occurs between the ages of 10 and 14. After puberty, the rate starts to decline and stabilizes between the ages of 15 and 29. But sometimes adults can also develop the type 1 diabetes mellitus but the beta cell destruction is slower in adults than those who are at their puberty (Maahs et al. 488).

The existence of autoantibodies, such as antibodies against insulin receptors or endogenous insulin, may be the source of the rise in IR. Antibodies against exogenous insulin are created in some people receiving insulin therapy. This syndrome raises the likelihood of allergic reactions, abrupt blood sugar spikes, and an enhanced requirement for insulin (Wolosowicz et al. 8651).

It is believed that the complex interactions between a person's lifestyle and genetic predisposition have a considerable impact on when insulin resistance develops in type 1 diabetes mellitus. The human leukocyte antigen is primarily responsible for the aforementioned inherited susceptibility to insulin resistance in type 1 diabetes mellitus (HLA). A Todd et al. investigation discovered a strong correlation between type 1 diabetes mellitus and insulin resistance and the single amino acid on the DQB3 chain located at position 57 (Wolosowicz et al. 8651).

According to Millstein et al., T1DM affects women's adipose and skeletal muscle insulin sensitivity more than men's does. Participants in the control groups showed greater Morbus values (M-values) than those with DM, regardless of gender. When utilizing sexual intercourse, those with T1DM did not differ in M-values from those without T1DM, but women from the relevant manipulation organizations did (Wolosowicz et al. 8651).

1.4.2: Causes or Risk factors of T2DM:

T2DM is characterized by two primary pathophysiological mechanisms: decreased pancreatic production of insulin and insulin resistance, especially in skeletal muscle and the liver. Complex interplay between genes and the environment lead to T2DM, a condition. There is mounting evidence that hereditary variables have a significant impact on the chance of acquiring T2DM (Laakso).

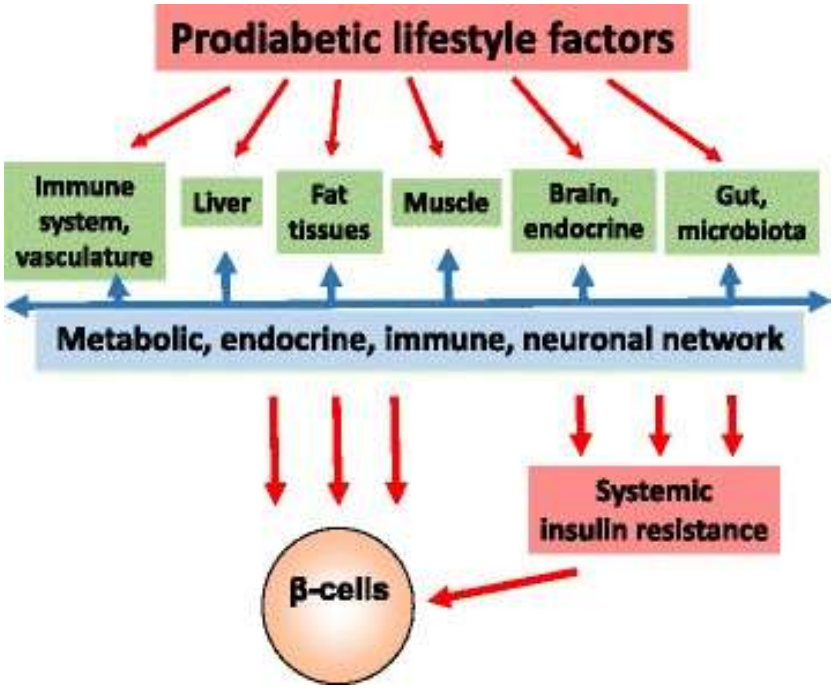

Figure 3: Pro diabetic lifestyle factors affecting beta cell (Kolb and Martin)

Few environmental and lifestyle factors that affect type 2 diabetes mellitus are explained below:

Diet: The relevance of diabetes is uncertain, meat is believed to be less protective than plant foods, low energy density foods are thought to be more protective than high energy density diets, and fermented milk products are believed to be superior to non-fermented ones. In addition, it seems that sugar-sweetened beverages and refined grains can cause obesity and diabetes (Kolb and Martin).

Living & lifestyle: Observational studies concur that there is a link between increased exposure to airborne fine particles, noise, and residential traffic and a higher chance of developing type 2 diabetes within five to twelve years. People who have lived near busy highways, have been exposed to more fine particles than 10 g/m3 during a 10-year period, or have been subjected to noise levels of at least 10 dB higher are at an increased risk of 20 to 40 percent (Kolb and Martin)

Coffee, tea, alcohol and smoking: Comparatively to non-smokers, passive and active exposure to secondhand smoke is linked to a higher incidence of type 2 diabetes. On the other hand, it seems like drinking alcohol has dose-dependent health risks. Consistent epidemiological data suggests that moderate alcohol use can reduce the incidence of type 2 diabetes by up to 20%, albeit this effect is probably only seen in females and does not apply to those of Asian ancestry. Also Epidemiological studies demonstrate a marginal 10-15% reduction in the risk of T2D in individuals who consume more than 3 cups daily (Kolb and Martin)

Impact of socioeconomic status: Low socioeconomic determinants are connected with 40-60% higher relative risk than high-scoring subgroups. In a UK aging longitudinal study, those with the lowest socioeconomic position had a greater than doubled risk of developing diabetes over the course of their lives (Kolb and Martin).

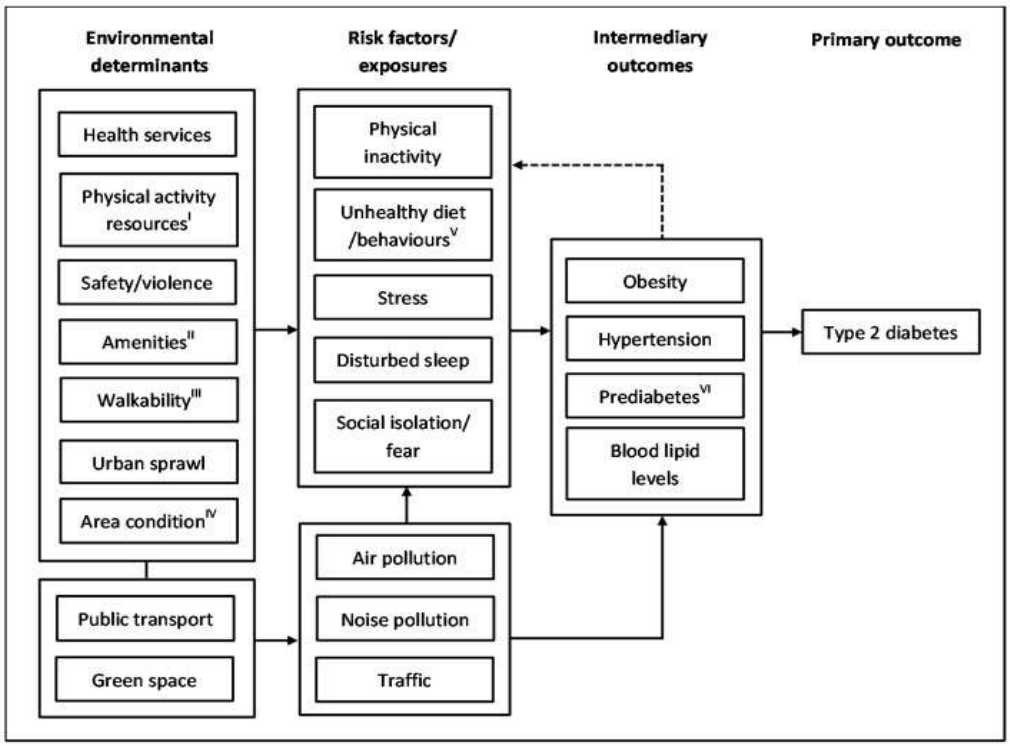

Figure 4: Diagrammatic representation of potential mechanisms through which the environment affects the incidence of type 2 diabetes mellitus (Dendup et al. 78).

Chapter 2: Prevention:

2.1: Prevention of T1DM: We can divide prevention into three stages which are given below:

Primary prevention: Primary prevention aimed at preventing autoimmunity against islet autoantigens on those who have high risk of developing T1DM. A randomized, placebo-controlled primary prevention trial that was begun by the investigator, was carried out in clinical research facilities in various countries. In order to determine whether daily oral insulin administration to young children with a high chance of developing T1DM from the age of 4 to 7 months to 36 months reduces the incidence of T1DM, this study set out to test this hypothesis. Diabetes and autoantibodies against beta cells do not. The study's justification is that antigens can be used to induce immunological tolerance (Primavera et al.).

Neoepitopes are significant because they may serve as a different antigenic target for acceptable T1DM vaccines. A vaccine that develops beta-cell antigen-tolerant immunity as

well as a vaccine against viruses are both in development. Research in this field is being funded by the JDRF and may provide interesting opportunities in the near future (Primavera et al.).

Some SCFA compounds, such as butyrate, support anti-inflammatory responses, control T-cell activity, and maintain intestinal epithelial integrity. Understanding the function of the microbiome can help with the creation of risk-free methods for modifying the immune system in young children and newborns. (Primavera et al.).

Secondary Prevention: This is relevant to people who have numerous islet autoantibodies, which are intended to decrease autoimmune processes and maybe delay the onset of clinical diabetes. Most people with T1DM or children who are prediabetic showed a unique autoantibody potential, according to Strollo et al. They found that the positive of oxPTM-INS-Ab and IA2A dictated the best sensitivity and specificity of humoral biomarkers, in contrast to GADA and IAA, which showed lower sensitivity and specificity. Particularly, the specificities of oxPTMINSAb, IA2C, GADA, and IAA were 91, 91, 66, and 68 percent, respectively, whereas the sensitivities were roughly 74, 71, 65, and 50%, respectively. However, much research is still needed to confirm the CGM's predictive price. Additionally, a small amount of fasting or following a glucose load increases the risk of T1DM. In contrast to T1DM, CGM anticipates the response to a synthetic sugar load. There have been reports of several immunological treatments delaying the loss in beta cell activity. One of the promising treatments is teplizumab, an anti-CD3 monoclonal antibody that does not interact to the Fc receptor is investigated in patients in phase 2 research who had abnormal OGTT results and at least two autoantibodies at the time of the investigation. Anti-CD3 monoclonal antibodies need an active autoimmune response, according to preclinical research (Primavera et al.).

Tertiary Prevention: When the condition manifests clinically, tertiary prevention of T1DM concentrates on the disease's consequences and aims to reduce or ameliorate them.

Another method to delay the disease's progression is vitamin D supplementation. In this context, a randomized placebo study is still being conducted to determine whether vitamin D works to lengthen the duration of the partial clinical remission (Primavera et al.).

2.2: Prevention of T2DM:

Dietary and Nutritional approaches for preventing T2DM:

Weight Management: Having insulin resistance and being overweight or obese are frequently linked to type 2 diabetes mellitus. As a result, maintaining a healthy weight and losing weight are essential components of therapeutic care (Forouhi et al.).

Balancing Energy: Most suggested practices encourage weight loss in overweight or obese individuals by lowering energy. Control section is a technique to control the quantity of energy using a healthy supply model focused on an energy supply that includes complete or unprocessed food in conjunction with active and supporting activities taking place (Forouhi et al.).

Dietary patterns: This evidence is high in dairy products such as vegetables, fruits, fruits, cereals, legumes, nuts, yogurt, and some attention is paid to promote food intake patterns. First, due to their high starch or sugar content, several diet approaches advise avoiding fruits, meat, and leguminous vegetables. Scientists and doctors are separated in the field of fruit supply, particularly in the area of diabetes. However, fructose intake from fruits is recommended from fruitose intake from fruit, and fructose intake from fruit is preferred, and additional micro nutrients, phytochemical and fiber content of fruits are preferred. However, nuts can be useful to resist the formation of type 2 diabetes (Forouhi et al.).

The recommended daily fiber consumption for those with type 2 diabetes should be at least as high as that of the general population, and whole grains and fiber are preferable to refined grains. A high glycemic index and high load diet are linked to an elevated risk. There is some proof that consuming white rice and potatoes may make you more likely to develop type 2 diabetes (Forouhi et al.).

Medication: At 10 years, metformin showed a significant reduction in type 2 diabetes incidence (18% increase over placebo), but it was less effective than lifestyle interventions. According to this information, metformin may be helpful for diabetics who are still in the early stages of the condition even after the course of therapy. The prevalence of latest T2DM had been reduced by 25% with the help of a wide range of different pharmaceutical treatments. (Shubrook et al. 734). There are other medications as well that helps to prevent T2DM.

Chapter 3: Treatment:

3.1: Treatment for Type 1 Diabetes Mellitus: Some treatments for type 1 diabetes mellitus, are discussed below:

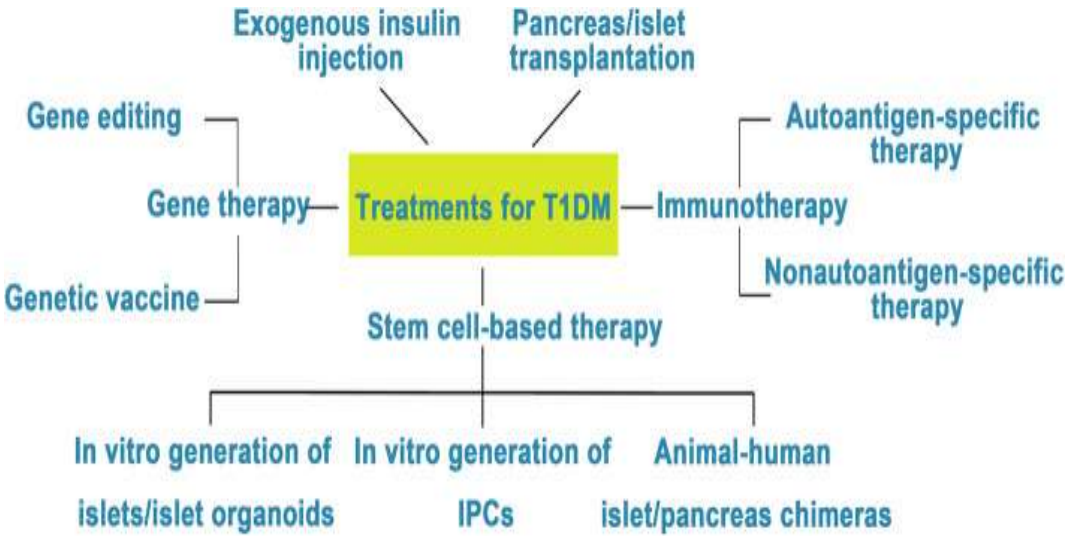

Figure 5: treatments for type 1 diabetes mellitus (Chen et al.).

Gene Therapy: Delivering or modifying genetic material into cells as a therapeutic strategy to cure a disease is known as gene therapy. The goal is to effectively prevent the start of the disease or stop the progression of such a condition by correcting the defective gene that causes its onset. The three major intervention techniques in gene therapy include:

By a) adding new genes to the body,

b) swapping out dysfunctional genes with functioning ones, and

c) inhibiting the disease-causing gene's abnormality.

Type 1 diabetes and obesity are two conditions that are increasingly being treated with gene therapy, however their safety in people has not yet been demonstrated. In this investigation, we used non-obese diabetic (NOD) mice and a lentiviral vector carrying the regenerated islet-derived gene (Reg3g). It caused signal converters and activators like Janus kinase (JAK) 2 to produce more hepatic -antitrypsin 1 (AAT1) as a result. AAT1 seems to possess anti-apoptotic

and anti-inflammatory qualities that shield pancreatic beta-cells from autoimmune destruction and encourage beta cell regeneration, resulting in suboptimal or optimal insulin levels.

We considered the potential for reprogramming extra native pancreatic cells into cells that make insulin in the study of Matsuoka et al. They discovered that mafA, which is present in large amounts in islet cells, can enhance Pdx1's capacity to change Ngn3-positive cells into insulin-positive cells (Srinivasan et al.).

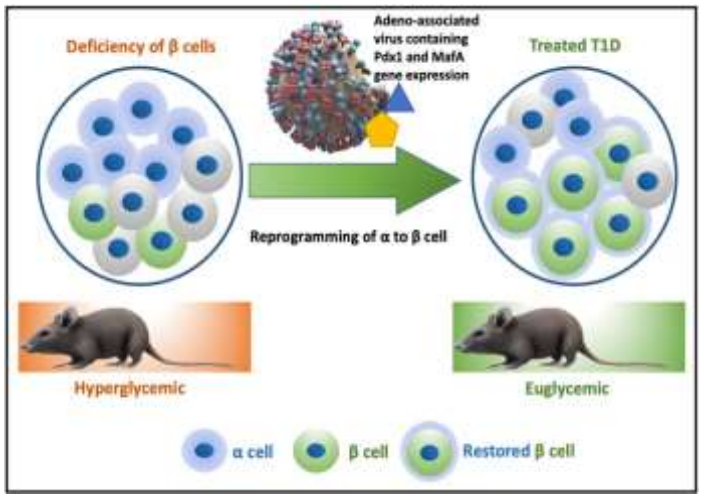

Figure 6: using gene therapy to reprogramme α cells to become β cells (Srinivasan et al.).

According to studies by Mallol et al., local synthesis of the growth factor insulin-like growth factor 1 protects NOD mice from spontaneous immune-mediated -cell loss. discovered to obstruct gene transfer and episodes of hyperglycemia. Last but not least, gene therapy that precisely causes the pancreas to overexpress IGF1 shows that T1DM disease development is controlled (Srinivasan et al.).

T1D is reversed by administering anti-T cell receptor antibodies and the neurogenin-3 betacellulin gene, which also targets and destroys diabetes-induced T cells. In NOD mice, a five-day course of therapy with 50 mg of anti-TCR-mAb recovered more than 80% of T1d recurrence. Additionally demonstrated to prevent collagen-induced arthritis and experimental autoimmune encephalomyelitis (Srinivasan et al.).

Yeh et al. looked into using lentiviral transgenic TCR to find autoantigens linked to type 1 diabetes. Both a high-affinity copy of the reactive glutamic acid decarboxylase TCR 555-567 and a lower affinity clone 4.13 specific for the same peptide were generated by cultured human T-regulatory cells. Treg avatars can reduce -cell autoimmunity and reveal fresh perspectives

on how to create certain phenotypes and features into cells to control Treg activity (Srinivasan et al.).

Yeh et al. looked into using lentiviral transgenic TCR to find autoantigens linked to type 1 diabetes. Human T-regulatory cells in vitro produced a high affinity copy of the reactive glutamic acid decarboxylase TCR 555-567 and a lower-affinity clone 4.13 specific for the same peptide. In vitro, bystander reactions and Tresp growth were successfully suppressed by Tregs.

We may conclude from the discussion above that these are some of the gene therapy techniques that have showed considerable promise in recent years. Animals or preclinical trials have been used frequently in contemporary studies (Srinivasan et al.)..

DPP-4 Inhibitors as Treatments for Type 1 Diabetes Mellitus:

Inhibitors of dipeptidyl peptidase 4 (DPP4) have been used to treat type 1 diabetes in numerous clinical investigations (T1DM). DPP4 inhibitors improved the genesis of T1DM in preclinical studies. The purpose of future study should be to use and report full-scale adverse effects.

Stem Cell therapy for type 1 diabetes Mellitus:

For T1DM patients with poor glycemic control, clinical pancreatic or islet transplantation has been researched as a viable treatment. As of 2015, pancreas transplants had been performed on more than 50,000 people globally (more than 29,000 in the US) (Chen et al.).

IPCs, or islet organoids, have been produced in vitro through extensive study while human pluripotent stem cells have been waiting for use in regenerative medicine. The resulting IPC represents the final differentiation state and is a typical pancreatic cell. Additionally, these in vitro created IPC respond to changes in blood glucose levels, produce enough insulin, and finally reverse hyperglycemia after being transplanted into DM patients or immunodeficient diabetic mice (Chen et al.). Stem cell-based therapies are thought to be effective prospective treatments for diabetes, particularly type 1 diabetes. But the main issues relate to this method are:

(1) A technique for developing hPSC into more developed and useful -like cells in a lab setting.

(2) How to increase the effectiveness of IPC and hPSC differentiation.

(3) How to stave off autoimmune reactions on the transplanted IPC.

(4) A technique for producing enough of the desired cell types to be used in clinical transplants.

(5) How to completely eliminate your need for insulin.

Despite these issues, the most cutting-edge method of treating type 1 diabetes is the use of stem cell-based therapies (Chen et al.).

Immunotherapy for type 1 diabetes mellitus

Most preventative research focuses on people with a greater than 50% likelihood of developing type 1 diabetes in the next five years. This risk is often influenced by a combination of genetic factors, HLA, islet autoantibodies, and glucose tolerance. Several medications have proven to be effective at preventing T1D in preclinical studies using the NOD mouse model (Warshauer et al. 47).

Teplizumab has been used in the sole successful human clinical trial for T1D prevention to date. Despite prior research demonstrating that teplazumab did not improve normoglycemia in people with previously discovered diagnoses (Hagopian et al., 2013). An immunological biomarker was used in the first effective preventative trial to pinpoint individuals who would benefit from therapies focused on genetics, metabolism, and disease prevention. In a preventive study by Herold et al., patients who had HLADR4 present, HLADR3 absent, antiZnT8 AAb absent, or either a low C-peptide response were found to respond to teplizumab most favorably. Abatacept selectively targets naive T cells, hence there is a solid mechanism of action for the positive outcomes in T1D prophylaxis (Warshauer et al. 47).

Insulins:

Exogenous insulin therapy (EIT) is essential for the management of T1D patients and is often administered through subcutaneous insulin infusion (CSII) or several daily injections (Warshauer et al. 47).

Non insulins:

A huge amount of glucose inconsistency of blood glucoma in self-managers with T1D with T1D for INSULIN single therapy and low blood glucose risk are insulin requirements and treatment of non-Is Island that helps reduce these related risks We brought a search for law. Targeting insulin-independent pathways proved successful in lowering hyperglycemia in T1D patients. It is an approach that reduces glucone formation or increased glucose excretion (Warshauer et al. 47).

3.2: Treatment for Type 2 Diabetes Mellitus:

Although it is difficult to manage patients with type 2 diabetes because there are no currently available treatments, blood glucose can be controlled by pharmacological treatment (Artasensi et al. 1987).

However, type 2 diabetes mellitus can be managed by:

- Possible diabetes medication or insulin therapy
- Exercising regularly
- By eating healthy
- By losing weight etc.

Numerous anti-diabetic medications work in different ways to produce clinical benefits.

a) Biguanides, which include the drug metformin, lower hepatic gluconeogenes.

b) Insulin secretagogues, which include medications like sulfonylureas, stimulate the pancreas to release insulin.

c) Thialzolidinediones are insulin sensitizers that increase the sensitivity of peripheral tissues to insulin.

d) Exogenous insulin is provided by insulin or its analogues in the form of recombinant insulin (Artasensi et al. 1987).

The first-line therapy for T2DM is metformin. It not only lowers blood sugar levels but also has diverse impacts on tissues such the liver, skeletal muscle, endothelium, adipose tissue, and ovaries that are insulin-sensing. A second medication should only be added if the HbA1c level is above 7.0 percent after three months. Unfortunately, metformin has a multitude of adverse effects that cause poor adherence, making it the oral diabetes medication with the lowest adherence rate (Artasensi et al. 1987).

Incretin-Based Therapies:

Augmenting the effects of incretin is an important approach to the successful treatment of diabetes and the management of overweightness. Therapies based on incretins take advantage of glucagon-like peptide 1 (GLP-1) and the hormone glucose-dependent polypeptide (GIP) activity (GLP1). In reaction to carbs, the gut releases these incretin hormones. Visceral and serve as crucial postprandial glycemic control regulators. They are specifically linked to a number of positive pancreatic effects, including as increased insulin secretion and insulin gene expression, support for -cell survival, enhanced -cell glucose sensitivity, and decreased glucagon secretion. Additionally, the incretin hormones have numerous extra-pancreatic activities that have a good impact on slowing gastric emptying, reducing food intake, and reducing stomach emptying, as well as weight loss (Artasensi et al. 1987).

In the disturbed state, subjects with T2D exhibit no incretin-mediated hypoglycemic response. Decreased postprandial circulating levels of GLP1 and decreased GIP receptor activation or desensitization are the causes of this. However, it is possible to restore the effectiveness of GIP in patients with type 2 diabetes: preclinical and clinical studies have shown this to be achievable when amelioration of hyperglycaemia is achieved. medication or lose weight. Patients who received GLP1 for six weeks had enhanced insulin sensitivity and decreased levels of glycated hemoglobin HbA1c in relation to glucose-dependent endocrine hormones (Artasensi et al. 1987).

Although the biological half-lives of these peptides are incredibly brief due to the effective breakdown of the enzyme Dipeptidyl Peptidase (DPP) 4 and subsequent renal filtration, incretin hormone does have a lot of potential for treating diabetes. That severely restricts the treatment's applicability (Artasensi et al. 1987).

PPARs-Based Therapies:

A family of nuclear receptor proteins known as PPARs is made up of three subtypes, each with a specific tissue distribution. These subtypes are PPAR, PPAR (also known as PPAR), and PPAR. Due to the fact that activating PPAR enhances lipid metabolism and consequently raises HDLC cholesterol levels, tissues with high levels of fatty acid oxidation, such as the liver, kidney, myocardium, and vascular endothelial cells, have high levels of PPAR expression (Artasensi et al. 1987).

After ligand activation and heterodimerization with the 9cis retinoic acid receptor, PPARs can control gene transcription by attaching to certain DNA response regions (RXR). Free fatty acids, eicosanoids, and vitamin B3 are some examples of endogenous ligands that can activate different subtypes. Other examples are the PPAR-mediated lipid-lowering class fibrates and the anti-diabetic medication thiazolidinedione. It is also an over-the-counter drug. Activates PPARγ. Dual PPARs agonist design is currently developing to create synergistic anti-diabetic patients (hyperglycemia and hyperlipidemia). The most promising efforts have been made in developing a dual PPARα/γ agonist that shows potent therapeutic effects on diabetes mellitus (Artasensi et al. 1987).

Application of herbal medicine

Phytocomplexes take advantage of the "herbal pistol effect," in which several components bind with various targets, just like multi-target ligands do. The "miracle" approach, which describes the results of a single substance operating on a single target, contrasts with the multitarget approach. There is evidence to support the synergistic and multifactorial benefits of many plant extracts against DM. Momordica Charantia, also known as bitter melon, Panax Ginseng, Trigonella Foenum-Graecum, Scutellariae Radix, Coptidis Rhizoma, and other herbal products are among the most effective ones. Additionally, gurmar , ivy gourd , cinnamon , psyllium , and garlic have beneficial benefits on type 2 diabetes mellitus (Artasensi et al. 1987).

Exercise in the management of type 2 diabetes:

Exercise is frequently one of the first management measures suggested. Some exercises are mentioned below:

Aerobic exercise: Workout which continually and rhythmically engages vast muscular groups includes cycling, jogging, and walking. Increased VO2max cardiac output from moderate to strenuous aerobic exercise training (65 to 90 percent of maximum heart rate) is linked to significantly lowered cardiovascular and total mortality risks in type 2 diabetics (Kirwan et al.).

Enough research has been done to conclude that aerobic exercise is a reliable exercise program for the management and prevention of type 2 diabetes. Additionally, studies looking at the advantages of aerobic exercise for people with type 2 diabetes have repeatedly shown that it enhanced glycemic control, insulin sensitivity, oxidative capacity, and other factors (Kirwan et al.).

Resistance training: Resistance education has received sizeable popularity as a feasible exercising education choice for kind 2 diabetes sufferers. Resistance exercising includes actions utilising unfastened weights, weight machines, frame weight exercises, or elastic resistance bands. In older adults, resistance training can offer extra fitness advantages in response to age-associated decline in muscle mass, called sarcopenia (Kirwan et al.). According to a study by Dunstan et al., type 2 diabetes patients aged 60 to 80 showed a three-fold decrease in HbA1c when compared to controls who did not exercise (Kirwan et al.).

High-intensity interval training: It is one of the fitness regimens that has grown most in popularity in recent years. In HIIT, 4 to 6 quick repeats of maximum effort are alternated with quick rest intervals or active recovery. In persons with well-controlled type 2 diabetes, it improved skeletal muscle oxygenation, glycemic management, and insulin sensitivity. In 50 trials, HIIT individuals showed 1.3 kg less weight loss and a 0.19 percent increase in HbA1c compared to the control group (Kirwan et al.).

HIIT appears as additional method that is successful in enhancing metabolic health. A time-saving option to ongoing aerobic exercise may be HIIT for type 2 diabetes individuals who can handle it. A 6-week CrossFit program was observed to lower the zscore of body fat, diastolic blood pressure, lipids, and metabolic syndrome in a proof-of-concept research (Kirwan et al.).

Reversing type 2 diabetes through diet:

Type 2 diabetes, often thought to be progressive, incurable after diagnosis, has recently generated interest due to the possibility of remission. The lack of dietary energy to achieve remission and the composition of key nutrients are still controversial (Forouhi et al.).

Remission achieved by eating a low-calorie, energy-dense diet: The quick return of glucose to normal. After tomography, fasting blood pressure indicates that deterioration is not inescapable. Researchers have used a low-calorie diet as a tool to investigate the root causes. A study showed that fasting blood sugar levels returned to normal after seven days of calorie restriction. Insulin secretion boosted by glucose gradually reverted to normal over the course of eight weeks (Forouhi et al.).

Chapter 4: Conclusion:

Diabetes Mellitus is major type of health issue which is increasing day by day worldwide and it occurs when the body absorbs sugar (glucose) into cells and cannot use it as energy. This leads to the accumulation of excess sugar in your bloodstream. Since diabetes mellitus is a chronic condition, people should learn about it and take steps to avoid it before it reaches the

pre-diabetes stage. Diabetes mellitus can cause other damages to our body. Such as, cardiovascular issues, kidney damage, nerve damage, skin infections, depression, dental problems etc. and this disease doesn't allow the infections and cuts to heal soon. But there are some available treatments for diabetes mellitus but it doesn't make the disease permanently go way but helps to control it and reduce the risk. Like for example, for type 1 diabetes mellitus, insulin injections, insulin pumps, carbohydrate counting etc. can work and for type 2 diabetes mellitus, diabetes medication, lifestyle changes, losing weight and monitoring blood sugar etc. can work. As this disease is increasing in an alarming rate, we should be aware of it and also spread the awareness among all so that we can prevent it before happening.

Chapter 5: References

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