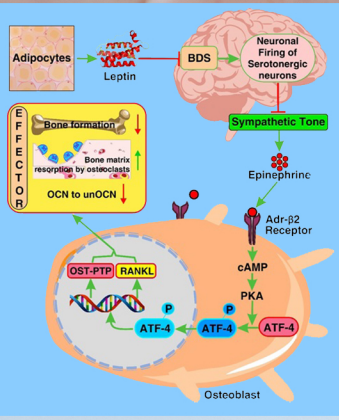

PHARMACOLOGICAL AND MOLECULAR PERSPECTIVES ON DIABETES

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Madhukar Saxena

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PREFACE

Type 2 diabetes mellitus (T2DM) is one of the most challenging public health issues of the 21st century. T2DM, a complex polygenic metabolic disorder, is characterized both by hyperglycemia and hyperinsulinemia resulting from the interplay of genetic/epigenetic along with environmental factors. Epigenetic alterations present in T2DM patients and not in normal healthy individuals may give an insight into how environmental factors might contribute to T2DM. Epigenetic mechanisms involve DNA methylation, histone modification, and gene expression alterations *via* micro RNAs (miRNA). These changes lead to glucose intolerance, insulin resistance, β-cell dysfunction, and ultimately T2DM. Extensive studies based on alterations in gene expression associated with DNA methylation/histone modifications are required to elucidate the relationship between vital environmental factors and T2DM progression. Candidate genes responsible for inter-individual differences in antidiabetic responses may also undergo epigenetic alterations. Identification and characterization of such epigenetic biomarkers may help in the prediction of T2DM risk as well as response to antidiabetic treatment and form an essential part of personalized medicine. The results of many clinical studies support the view that chromium can improve both insulin and glucose metabolism in patients with T2DM, especially in the form of dietary supplements (chromium picolinate). However, insufficient data are available to create a conclusive hypothesis that nutritional supplements of chromium could be useful for the treatment of T2DM, and thus there is no need to endorse a general prescription for the management of diabetes using these supplements. Chromium supplements have minimal usefulness based on the lower impact of established evidence, and there is no reason for promoting their use for glycemic control in patients with existing T2DM. Well-designed, high-quality, broad, and long-term trials are required to improve the current data and ensure the protection and efficacy of drugs. Osteocalcin, a well-known bone formation marker, is secreted from osteoblasts and exists in fully carboxylated, partially carboxylated, and completely uncarboxylated forms. The endocrine involvement of uncarboxylated osteocalcin in glucose homeostasis has recently been confirmed. It has been demonstrated that double recessive osteocalcin mutant mice are hyperglycemic and hypoinsulinemic, have reduced β cell numbers, and are insulin resistant. In contrast, leptin (an adipocyte-derived hormone) indirectly regulates the secretion of insulin in part through the inhibition of osteocalcin conversion to uncarboxylated form *via* β2 adrenergic receptor signaling in osteoblasts. Diabetes exerts widely known noxious effects on the kidney and blood vessels. Besides these effects, it also causes damages to the nerve cells and glial cells in the brain that result in impaired memory. The altered memory formation in patients with diabetes might be due to Alzheimer's, stroke, and high sugar levels in the blood. Among all of the above parameters, damage to blood vessels is most common. Although both diabetes and Alzheimer's patients share common symptoms so it can be concluded that diabetes might cause an increased risk of development of AD. However, pioneer studies have found that coronavirus disease 2019 (COVID-19) has shown severity in patients with diabetes mellitus. COVID-19 may potentially cause hyperglycemia in patients who have been exposed to it. Along with other risk factors, high blood glucose may also affect immune and inflammatory responses, thus inclining patients to severe COVID-19 with a much higher mortality rate. Angiotensin-converting enzyme 2 (ACE2) receptors are the common entry point for SARS-CoV-2. Recent findings suggest dipeptidyl peptidase 4 (DPP4) can also act as a binding and entry target. Glucose-lowering agents and anti-viral treatments can alter the risk, but there exist limitations to their use, and its possible interactions with COVID-19 treatments should be carefully assessed. Most of these conclusions are preliminary, and further investigation of the optimal management in patients with diabetes mellitus is warranted. Evidence from the literature shows that in T2D, alterations in the level of cytokine inflammatory gene (IL-1, IL-6, TNF-a)

expression increased while anti-inflammatory gene (IL-1Ra, IL-4, IL-10, and IL-13) expression decreased. Various physical activities like weight loss and exercise are beneficial for patients with T2D. Many anti-diabetic drugs are effective against type 2 diabetes in which liraglutide, sulfonylureas, and salsalate drugs exert an anti-inflammatory action in obese patients with type 2 diabetes. They all have a potent anti-inflammatory effect due to the inhibition of the NF-kB pathway, the upregulation of SIRT1 expression, and down-regulation of pro-inflammatory factors, including cytokines (TNF-α, IL-1β, and IL-6. Current insulin therapies more closely mimic the normal physiologic insulin secretion by the pancreas, which gives a better-glycosylated hemoglobin level in patients suffering from diabetes. This chapter includes the many types of insulins and their regimens, the classification of insulin types, which insulin is best for different age groups, the diet to follow, the principles of dose adjustment, and an overview of insulin pump therapy. Thus, it seems the need of the hour to focus on chronopathology and chronomedicine as alternative treatment strategies to manage and prevent T2DM, which can further contribute to the reduction of the risks of metabolic co-morbidities in the human population.

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INTRODUCTION

Pharmacological and Molecular Perspectives on Diabetes is a book devoted to publishing the latest and the most important advances in anti-diabetic drugs and their associated complications. Eminent researchers and scientists have contributed chapters focused on all areas of rational pharmacological and molecular perspectives associated with diabetes mellitus. This book should prove to be of interest to all pharmaceutical and molecular scientists who are involved in research in drug design and discovery especially associated with diabetes and who wish to keep abreast of rapid and important developments in the field.

Topics included in this book are:

- Epigenetic alterations and type 2 diabetes mellitus.
- Responses to nutritional chromium supplements for type 2 diabetes mellitus.
- Endocrine role of osteocalcin in homeostatic regulation of glucose metabolism.
- Effect of diabetes on memory.
- Osteoarthritis in relation to type 2 diabetes mellitus: prevalence, etiology, symptoms and molecular mechanism.
- Infection of novel coronavirus in patients with diabetes mellitus.
- Role of an anti-Inflammatory agent in the management of type 2 diabetes mellitus.
- Role of antidiabetic agents which help regulate TCF7L2 variations in type 2 diabetes mellitus.
- Relationship between type 2 diabetes mellitus, PCOD and neurological disorders: Role of antidiabetic drugs.
- Comparision of different types of insulin available for type 1 diabetes treatment.
- Circadian rhythm disruption: special reference to type 2 diabetes mellitus.
- Type 2 diabetes mellitus and its complications: Pharmacogenetics based correlations and circulating microRNA as biomarkers.

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CHAPTER 1

Epigenetic Alterations and Type 2 Diabetes Mellitus

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Abstract: Type 2 diabetes mellitus (T2DM) is one of the most challenging public health issues of the 21st century. T2DM, a complex polygenic metabolic disorder, is characterized by hyperglycemia and hyperinsulinemia resulting from the interplay of genetic/epigenetic and environmental factors. Epigenetic alterations present in T2DM patients and not in normal healthy individuals may give an insight into how environmental factors contribute to T2DM. Epigenetic mechanisms involve DNA methylation, histone modification, and gene expression alterations *via* micro RNAs (miRNA). These changes lead to glucose intolerance, insulin resistance, β-cell dysfunction, and ultimately T2DM. Extensive studies based on alterations in gene expression associated with DNA methylation/histone modifications are required to elucidate the relationship between vital environmental factors and T2DM progression. Candidate genes responsible for inter-individual differences in antidiabetic responses may also undergo epigenetic alterations. Identification and characterization of such epigenetic biomarkers may help in the prediction of T2DM risk as well as response to antidiabetic treatment and form an essential part of personalized medicine.

Keywords: T2DM, Epigenetic biomarkers, DNA methylation, Histone modification, Personalized medicine.

INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is an incurable, progressive polygenic metabolic disorder characterized by both hyperglycemia as well as hyperinsulinemia. It is a major source of morbidity and mortality worldwide [1] and has increased dramatically over the past decades [2]. The global burden of

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diabetes is presently 351.7 million affected people of working age (20-64 years), which is expected to rise to 486.1 million in 2045 [3]. A total of 77 million Indians were diagnosed as diabetics in the age group 20-79 years in 2019, and this figure is estimated to rise to 134.2 million in 2045 (IDF, 2019). It has been reported that subjects having T2DM-affected siblings are at two-to-three folds higher risk of developing T2DM compared to the general population [4]. Having one or both parents with diabetes increases the risk of developing T2DM by 30-40 and 70%, respectively [5].

T2DM develops due to impaired insulin signaling, predominantly in genetically predisposed subjects exposed to lifestyle risk factors like obesity, physical inactivity, and aging [6]. Environmental factors *viz*. diet and sedentary lifestyle play crucial roles in the progression of T2DM and seem to alter the epigenome. The connecting link between environment and disease is epigenetics which influences gene transcription followed by organ functions [7]. However, all individuals do not respond to environmental conditions in an equal manner. Alterations in the epigenome are more frequent than mutations in DNA and may occur in response to environmental, psychological, and pathological stimuli [8].

Epigenetic alterations consist of DNA methylation, histone modifications, and miRNA dysregulation. Such changes can be passed from one generation to the next (mitotic inheritance) or between generations, *i.e.*, meiotic inheritance. Several candidate genes are associated with glucose and lipid metabolism *viz*. insulin gene [9], peroxisome proliferator-activated receptor γ coactivator 1-α (*PGC-1α*) [10 - 12], *etc.* have been reported to be epigenetically misregulated. Epigenetic alterations may predispose the future development of disease or might increase in number once a disease has developed. Large numbers of human models are subsequently required to dissect the key role of epigenetics in the pathogenesis/onset of T2DM. These models may consist of case-control cohorts, cultures of human cells exposed to environmental risk factors, prospective cohorts, and intervention studies [13].

Identification of individuals having the risk of developing T2DM in the future could facilitate early intervention strategies to delay/prevent disease progression, therefore resulting in minimization of disease burden. Epigenetic alterations can be reversed; hence can be used as potential therapeutic targets. Epigenetic therapy has been strongly suggested as a forthcoming possibility for T2DM treatment on an individual basis.

EPIGENETIC ALTERATIONS RELATED TO T2DM

DNA Methylation

DNA methylation is a regular physiological process that is involved in gene expression and regulation, therefore, playing a crucial role in disease progression and development [14]. It occurs in many key physiological processes, including X-chromosome inactivation, imprinting, and silencing of germline-specific genes and repetitive elements. DNA methylation has been reported to alter the expression of genes involved in glucose intolerance, insulin resistance, and β-cell dysfunction, which ultimately leads to the onset of T2DM [15]. Several enzymes are responsible for the attachment/removal of methyl groups to the CpG sites and histone modifications in the human genome. DNA methyltransferases (DNMTs) catalyze the addition of methyl groups from S-adenosyl-L-methionine (SAM) to the 5^{th} position of so-called CpG sites in DNA moieties. Methylated cytosine at CpG sites represses transcription by inhibiting the binding of transcription factors or increases the binding of some transcriptional repressors, including histone deacetylases (HDACs).

In mammals, five types of DNMTs have been reported, *viz*. DNMT1, DNMT2, DNMT3A, DNMT3B (2methyl transferases), and DNMTL. Out of these DNMT1, DNMT2, and DNMT3B play a pivotal role in DNA methylation [16]. DNMT1 is responsible for the maintenance of methyltransferase and the pattern of DNA methylation during cell replication. DNMT3A/DNMT3B encodes *de novo* methyltransferases and hence is responsible for the transfer of methyl groups required to establish and conserve genomic methylation [17, 18]. It is the location of methylation which decides whether it will repress or activate gene expression. Usually, methylation at the transcription start site or enhancer region leads to suppression of gene expression.

DNA methylation can be categorized into two subgroups, *i.e*., hypermethylation and hypomethylation. DNA methylation in the enhancer region may change transcription levels (hyper/hypo) of distal promoters *via* binding of chromatin modulating proteins and transcription factors [19], leading to abnormal gene expression responsible for several diseases. In the peripheral blood mononuclear cells (PBMCs), hypomethylation in the promoter region of monocyte chemoattractant protein-1 (MCP-1) was found to be significantly associated with serum MCP-1 levels, fasting blood glucose and HbA1c in T2DM patients [20]. Hyperinsulinemia, one of the characteristics of T2DM, is directly regulated by pancreatic β cells.

CHAPTER 2

Responses to Nutritional Chromium Supplements for Type 2 Diabetes Mellitus

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Abstract: Based on research, several scientific publications proposed dietary trivalent chromium as an attractive alternative for the prevention of hyperglycemia in people at high risk of type 2 diabetes mellitus (T2DM). The objective of the study is to determine the influence of chromium on the reaction of glucose and insulin in individuals with type 2 diabetes and healthy subjects. The study was based on several clinical reports of randomized clinical trials (RCTs). Available RCTs that were issued before December 2020 were routinely looked for in PubMed/Medline, Scopus, Web of Sciences, Google Scholar, and Cochrane Library. Keywords, such as "chromium" OR "chromium supplements" OR "chromium picolinate" in combination with "type 2 diabetes" were also checked in English. The results of these clinical studies support the view that chromium can improve both insulin and glucose metabolism in patients with T2DM, especially in the form of dietary supplements (chromium picolinate). However, insufficient data are available to create a conclusive hypothesis that nutritional supplements of chromium could be useful for the treatment of T2DM, and thus there is no need to endorse a general prescription for the management of diabetes using these supplements. Chromium supplements have minimal usefulness based on the lower impact of established evidence, and there is no reason for promoting their use for glycemic control in patients with existing T2DM. Well-designed, high-quality, broad, and long-term trials are required to improve the current data and ensure the protection and efficacy of drugs.

Keywords: Chromium supplements, Chromium picolinate, Hyperglycemia, Type 2 diabetes mellitus, Insulin metabolism.

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Madhukar Saxena (Ed.)

INTRODUCTION

Chromium (Cr) is an essential trace element of the human body. It is found in two stable forms: Cr (VI) and Cr (III). Cr (VI) is recognized as a toxic element to the human body because it is permeable to the cell membrane system, whereas Cr (III) is less toxic and impermeable to the cell membrane barrier. However, it is readily absorbed along with other organic ligands such as picolinic acid by the cell membrane barrier [1]. Cr (III) is used as a dietary supplement because it is present in most food such as egg yolks, grains, cereals, coffee, nuts, green beans, broccoli, meat, and brewer's yeast [2]. Cr usually occurs in Cr (III) form in nature, while Cr (VI) in the environment is derived from anthropogenic activity [3]. Cr (III) with Picolinate, Histidine, and Nicotinate show effective signs of diabetes regulation by improving insulin sensitivity. Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of Cr for children above 7 years and adult is 50-200 μg/day, as recommended by the U.S. National Academy of Sciences. It seems, however, that Americans typically eat 50-60% of the recommended indicated daily consumption of 50 μg [2].

Several clinical trials have demonstrated that Cr shows positive effects on people with impaired glucose tolerance and T2DM. Impaired glucose tolerance is a critical feature of Cr deficiency [2, 4, 5]. Several studies suggested that chromium deficiency or lower circulating chromium levels occur in subjects with diabetes and aggravates the severity of diabetes, including decreased insulin receptors, receptor binding, and intracellular signalling [6]. Diabetic patients have altered the metabolism of chromium, while non-diabetic individuals have higher absorption of chromium but greater excretion as well [7]. The hair and tissue chromium levels of diabetic patients are lower than those of non-diabetic subjects [8]. Diabetic patients appear to lose the capacity to transform chromium to a useable form, depending on the level of diabetes [9]. A human study revealed a high chromium dose (200-1000 ug/d) supplement could boost T2DM metabolic regulation [10]. T2DM turns out to be a worldwide health concern, with T2DM's worldwide cases estimated at 350 million by 2030 and growing from 350 million to 592 million today by 2035 [11, 12]. Recent studies have shown that diabetes mellitus has increased in prevalence from 451 million people in 2017 to a projected 693 million by 2045. T2DM is diagnosed in most patients (more than 90%) with elevated blood glucose levels [13]. In 2015, CDC estimated that 13% adult population of Americans and 30% elderly population of Germany were living with diabetes in 2015, and 1.7 million new cases of diabetes were diagnosed in the USA [14]. Diabetes is the major cause of blindness in the United States, moreover, it raises the risk of cardiovascular disease and neuropathy. CDC, 2017, reports that diabetes in the United States was the seventh leading cause of death [15]. An important cause of the increased prevalence of T2DM is

the result of a modern way of life associated with the high-fat diet and lack of physical activity inducing problems of overweight and obesity issues [16]. T2DM is characterised by irregular secretion of insulin that causes carbohydrate and lipid metabolism defects, leading to hyperglycaemia [17].

In preventing prediabetes from progressing to overt diabetes, dietary strategies play a central role. In the landmark Diabetes Prevention Program (DPP), the importance of such measures in controlling the progression of prediabetic states to T2DM was underlined. The DPP continued to develop lifestyle changes as the 'gold standard' for the prevention of T2DM, such as dietary reform, physical activity, and weight loss. Dietary strategies lead to weight loss by allowing healthy foods to derive calories which tend to be the main triggers for reducing diabetes risk. Several methods, ranging from nutritional regimens to pharmacological therapies, physical activity, and psychological interventions, have been suggested for the treatment of excess weight and its negative effects. Most of them are healthy, although some are deeply worried. A dietary supplement that increases the insulin response and promotes therapy will also be useful in controlling weight gain and obesity. Several studies suggest that Cr supplement improves insulin resistance in patients with T2DM [18]. However, because of contradictions in published data, the utility of Cr treatment for T2DM has been questioned. The US Food and Drug Administration assessed the benefit of chromium picolinate supplementation in lowering the incidence of insulin resistance and T2DM as extremely questionable as early as 2005 [19]. Many researches have looked into the link between Cr supplements and T2DM in the past few years. However, the results are conflicting [20, 21]. There is insufficient evidence to support the effect of Cr on T2DM. Therefore, this review is focused on the influence of Cr supplement on the reaction of glucose and insulin in individuals with type 2 diabetes and healthy subjects.

METHODS

The present study focuses on the previous pieces of literature published in Elsevier, Scopus, Medline/Pubmed, Cochrane library, Google Scholar and Web of science by searching keyword “chromium” OR “chromium supplements” OR “chromium picolinate” in combination with “type 2 diabetes” were also checked in English. In the first stage, a computer-based search was carried out to identify all appropriate published works and their references were reviewed until December 2020.

In the second stage, studies satisfying the following requirements were included: a comprehensive review, case-control studies, randomized clinical trials (RCTs), meta-analyses and reports on chromium dietary supplements, hyperglycemia and

CHAPTER 3

Endocrine Role of Osteocalcin in Homeostatic Regulation of Glucose Metabolism

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Abstract: Osteocalcin, a well-known bone formation marker, is secreted from osteoblasts and exists in fully carboxylated, partially carboxylated, and completely uncarboxylated forms. The endocrine involvement of uncarboxylated osteocalcin in glucose homeostasis has recently been confirmed. It has been demonstrated that double recessive osteocalcin mutant mice are hyperglycemic, hypoinsulinemic, and have reduced β cell numbers and insulin resistance. In contrast, leptin (an adipocyte-derived hormone) indirectly regulates the secretion of insulin in part through inhibition of osteocalcin conversion to uncarboxylated form *via* β2 adrenergic receptor signaling in osteoblasts. Because uncarboxylated osteocalcin is a secretagogue of insulin, which in turn positively regulates the bone formation, osteocalcin lies at the centre of the complex mechanism of glucose homeostasis and bone remodeling network.

Keywords: β2 adrenergic receptor, Bone Gla Protein, Bone remodeling, GPRC6A, Glucose homeostasis, Hyperglycaemic, Insulin, Receptor tyrosine kinase, Leptin, Sympathetic tone, Uncarboxylated osteocalcin.

INTRODUCTION

The prevalence of obesity, metabolic syndrome, and diabetes is increasing globally; they are the outcomes of impaired glucose homeostasis. Minute to minute adjustments in the blood glucose level involves an intricate balance between external glucose uptake from the intestine, endogenous glucose production by the liver, and cellular glucose oxidation and energy expenditure. This fine-tuning is achieved primarily by the timely and antagonistic actions of two hormones: glucagon and insulin, resulting in normoglycaemia [1, 2].

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A novel endocrine player regulating glucose homeostasis is osteocalcin (OCN), which comes from the bone. Bone performs versatile functions including locomotion, skeletal support to soft tissues, storage of vital ions (calcium), providing niche to multipotent stem cells, site of immune interaction, secretion of OCN and other molecules involved in energy balance, glucose homeostasis, *etc.* [3]. Bone is a dynamic tissue requiring energy for its various metabolic processes, particularly bone remodeling, where bone gets continually renewed. The bone-forming osteoblasts lay down the collagen and other non-collagenous proteins into the matrix, whereas bone-resorbing multinucleated osteoclasts resorb mineralized bone matrix in an acidic environment [3].

OCN, also known as Bone γ-carboxyglutamic acid (Gla) protein or BGLAP, is one of the most abundant non-collagenous bone matrix proteins secreted by mature osteoblasts. OCN is a 49 amino acids (50 amino acids long in rat) long polypeptide [4]. Post translationally, it is γ-carboxylated at three glutamate residues in a vitamin K dependent reaction. Its fully carboxylated form has high binding affinity with hydroxyapatite crystals and gets embedded in bone matrix during mineralisation [4]. During resorption, due to the acidic environment of the resorption pit, OCN is released in partially and completely uncarboxylated form into the circulation [5]. *Ocn*$^{-/-}$ mice model is largely utilized for exploring the role of bioactive OCN in mechanistic understanding of glucose metabolism, fat metabolism and energy homeostasis. Through a trail of experiments, it is found that undercarboxylated forms of OCN (unOCN) or bioactive OCN modulates glucose metabolism mainly through its action on insulin secretion [5 - 9]. Moreover, and interestingly, the role of insulin as an anabolic agent favouring bone formation and in turn, OCN secretion is confirmed [5]. So there exists a bone-pancreas feedback loop which, in an integrated manner, regulates glucose homeostasis and bone remodeling.

The aim of this chapter is to provide an insight into the regulation of glucose homeostasis *via* OCN signaling.

ENDOCRINE BONE AND GLUCOSE HOMEOSTASIS

Glucose Homeostasis

Implications of impaired glucose homeostasis manifest in the form of obesity (BMI ≥25kg/m^2), metabolic syndrome and diabetes [10].

When the blood glucose level falls below normal (hypoglycaemia; during exercise, sleep or in fasting), glucagon is secreted by the pancreatic α cells. Glucagon signaling promotes glycogenolysis and inhibits glycolysis in liver;

promotes gluconeogenesis in kidneys and liver, thus maintaining blood glucose levels to normal. Just after a meal, when the postprandial glucose concentration reaches ≥ 7.8 mM, insulin is released by the β cells of pancreas into the circulation. This favours glucose uptake, enhanced glycolysis, glycogenesis, adipogenesis, lipogenesis and protein synthesis in insulin responsive tissues. These processes that maintain the steady state glucose concentration are both insulin dependent and insulin independent. Uptake of glucose by brain and kidneys is an insulin independent process, whereas adipose tissue, skeleton, skeletal muscle and liver rely on insulin signaling dependent glucose utilisation [1, 11 - 14] (Fig. **1**).

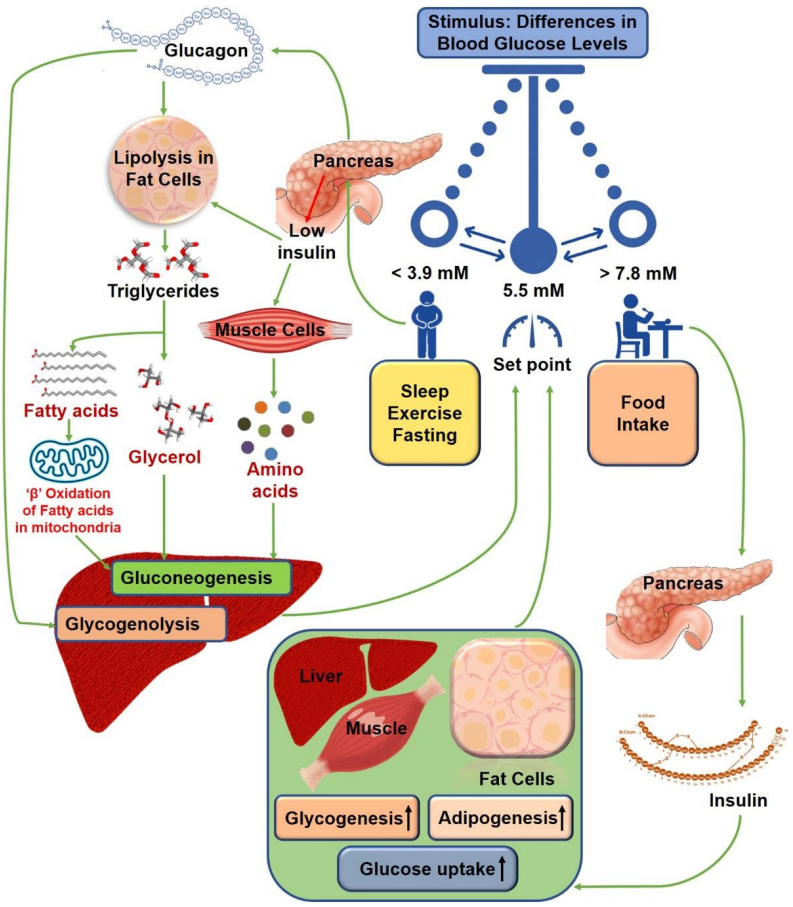

Fig. (1). An abstract diagram of Glucose homeostasis. Glucose homeostasis corrects deviations from a set point for blood glucose by the balanced and timely corrective actions of glucagon and insulin. This efficient homeostatic system minimises the size of the oscillations (deviations from set point).

CHAPTER 4

Effect of Diabetes on Memory

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Abstract: Diabetes is a condition that occurs due to a chronic increase in the blood sugar level either by no insulin production by beta cells of Langerhans of the pancreas or no response from body cells against insulin hormone. Although diabetes has serious complications on health among different kinds of diabetes. Type 2 diabetes mellitus has a more prominent role in the loss of memory and cognitive impairment. Diabetes exerts widely known noxious effects on the kidney and blood vessels. Besides these effects, it also causes damage to the nerve cells and glial cells in the brain that result in impaired memory. The altered memory formation in patients with diabetes might be due to Alzheimer's, stroke, and high blood sugar levels. Among all of the above parameters, damage to blood vessels is the most common. Although both diabetes and Alzheimer's patients share common symptoms, it can be concluded that diabetes might cause an increased risk in the development of Alzheimer's Disease. Indeed, our brain has receptors for insulin that recognize the insulin hormone and thus can regulate the glucose metabolism and insulin signaling. Any imbalance in the blood sugar level, either by low or no secretion of insulin hormone or no response to insulin by body cells, results in the chance of development of memory and cognitive impairment. By managing the normal blood sugar level, memory loss can be prevented.

Keywords: Diabetes, Memory, Alzheimer's disease (AD), Insulin, Ageing, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus.

INTRODUCTION

Diabetes is a disease characterized by high levels of blood glucose. This is known as hyperglycemia. A person with hyperglycemia cannot produce or respond to insulin. Blood sugar levels tend to be high because insulin production is reduced or the hormone is resistant to the body. In both animal models and humans with T1DM and T2DM, diabetes predisposes to cognitive decline, leading to dementia [1 - 3]. The data shows that dementia is more associated with T2DM than T1DM.

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Specifically, T2DM is associated with a 50% increase in the risk for dementia [2], in addition to impaired attention, processing speed, executive functions, and verbal memory [1, 4, 5]. Hyperglycemia is the component of metabolic syndrome most strongly associated with cognitive impairment [6]. Due to the increase in the prevalence of T2DM and the longer life expectancy, diabetes-related cognitive dysfunction is likely to pose a serious challenge to future health resource demands (Fig. **1**).

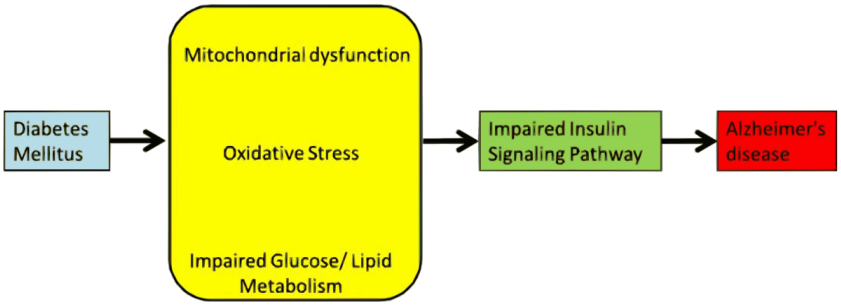

Fig. (1). Representation of the impairment in the mitochondrial dysfunction, oxidative stress, and glucose/lipid metabolism resulting from diabetes, which causes the impaired insulin signaling pathway that leads to the development of Alzheimer's disease.

PROGNOSIS

Diabetes can be checked by measuring blood sugar levels. Doctors use several methods for the detection of sugar levels in the blood.

1. Fasting blood sugar test (sugar level checked without food at least for 8 hours)
2. Random glucose test (sugar level checked at any time)
3. Oral glucose tolerance test (measured sugar level after fasting overnight and then again 2 hours following a sugar drink)
4. A1C blood test (it provides an idea of average glucose level for the past 2 - 3 months)

EPIDEMIOLOGY

Dementia is a common problem, and there are approximately 40 million people living with it worldwide; this number doubles every 20 years and is estimated to be over 110 million by 2050 [7]. In mid-aged people, there is a 19% greater cognitive decline over 20 years for people with diabetes than for those without diabetes [8 - 10]. Chronic diabetes occurs when the pancreas does not produce enough insulin or when the body cannot utilize the insulin produced by the pancreas. Insulin is a hormone responsible for regulating blood sugar. Diabetes

leads to hyperglycemia, or elevated blood sugar, which can lead to nerve and blood vessel damage and other serious consequences over time. Diabetes affected 8.5% of adults aged 18 and older in 2014. Diabetes contributed directly to 1.5 million deaths in 2019, and 48% of all diabetes-related deaths occurred before the age of 70 [11]. Diabetes mellitus poses a significant risk for both vascular-based dementia and Alzheimer's disease. Major risk factors include T2DM, smoking, obesity [12]. All types of diabetes lead to multisystem complications of microvascular endpoints, including retinopathy, nephropathy, neuropathy, and macrovascular endpoints, including ischaemic heart disease, stroke, and peripheral vascular disease [13]. The premature morbidity, mortality, reduced life expectancy, and financial costs due to diabetes make it a critical public health condition.

MEMORY

Memory is the process that is used to acquire, store and retrieve information. There are three processes that are involved in memory, encoding, storage, and retrieval. Memory is a form of a diary that we all carry around with us and use to guide our behaviour in the future. Several types of memory are described by scientists, which include episodic memory, semantic memory, procedural memory, working memory, sensory memory, *etc* [14]. Each kind of memory has distinct uses. According to the cognition theory of memory, it is assumed that a specific task measures a single cognitive process, and each process is mediated by a specific brain region. Many of these articles discuss subjects that have sparked decades of investigation, such as synaptic plasticity, adult neurogenesis, neuromodulation, and sleep in learning and memory [15]. There are various types of memory, as shown in Fig. (**2**).

EFFECT OF DIABETES ON MEMORY

Along with the age-dependent decrement in memory, there are certain other complications associated with loss of memory and cognitive functions. The brain's structure and cognitive function are altered in people with diabetes mellitus. Analyzing cognitive functions of patients with diabetes type 1 and type 2 compared to controls, it has been found that those with diabetes have mild to moderate impairments. In type 2 DM risk of dementia increases by nearly 50% [16].

CHAPTER 5

Osteoarthritis in Relation to Type 2 Diabetes Mellitus: Prevalence, Etiology, Symptoms, and Molecular Mechanism

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Abstract: Type II diabetes mellitus (T2DM) and osteoarthritis (OA) are chronic diseases that exhibit a strong relationship with age and obesity, and their co-existence tends to be accompanied by more altered disease conditions. With the increase in precision medicine, understanding the effect of common co-morbidities, such as diabetes, should result in improved management of OA. A higher prevalence of OA has been reported among patients with metabolic syndrome and diabetes mellitus (DM) and is considered an independent predictor for OA. The review of the literature suggests that DM may accelerate the symptoms, severity, and risk associated with joint replacement. Also, clinical and laboratory studies have suggested that there is an involvement of biochemical and biomechanical changes in articular cartilage in DM. Thus, the molecular mechanism that is activated in a diabetes-like environment that may contribute to OA could be characterized. Diabetes-influenced mechanism may provide knowledge on disease etiopathology and an improved understanding of the biological underpinning of disease for more specific therapeutic OA outcomes.

Keywords: Articular cartilage, Osteoarthritis, Type II diabetes mellitus.

INTRODUCTION

Osteoarthritis (OA) is a musculoskeletal disease common among the elderly population leading to joint pain, morning stiffness, and disability. Initially, it was considered a cartilage disease that is caused as an effect of ageing and mechanical stress. Recent studies have suggested that it is a whole joint disease. It is characterized by the loss of cartilage, synovial inflammation, bone sclerosis, and hypertrophy [1]. Bone remodelling and degeneration of cartilage are hallmarks of

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OA, and recently, bone has been the major focus of research. The main risk factors for the development and progression of OA are aging, excessive mechanical stress or injury, genetic pre-disposition, and obesity [2, 3]. Present evidence and epidemiologic studies have suggested a positive correlation between OA and conditions like glucose metabolism, metabolic dysfunction, and diabetes mellitus (DM) [4 - 7]. The association between DM and OA has been suggested in a study that showed a higher incidence of radiographic OA was present in diabetic patients with an earlier onset and more severe manifestations of the disease [8]. The incidence of both OA and T2DM increases with age and raises the possibility that these two conditions coexist by chance [9]. Therefore, it is suggested that the metabolic and systemic disturbances due to hyperglycemia or altered insulin plasma levels that are characteristic of T2DM may have consequences in joint tissues. Several mechanisms may contribute to the worsening of OA and promote its progression in T2DM patients [10]. Involvement of other metabolic factors like type II diabetes mellitus (T2DM) and dyslipidemia have been included in the metabolic syndrome, thus, generating another phenotype called metabolic OA. It has been associated with obesity and metabolic syndrome through systemic mechanisms [11, 12]. The different pathophysiologic mechanisms are involved in understanding the problem associated with OA.

The articular cartilage is an avascular tissue, and therefore, glucose reaches chondrocytes through diffusion from the synovial fluid [2]. Articular chondrocytes are glycolytic and require a steady supply of glucose to obtain energy for maintaining the cell homeostasis for anabolic functions like the synthesis of cartilage matrix [13]. The articular chondrocytes are sensitive to changes in the synovial fluid concentration of glucose on hypoglycemia or hyperglycemia conditions. Chondrocytes respond to change in concentrations of glucose by changing the various isoforms of glucose transporter (GLUT) receptors, among which GLUT-1 is positively regulated by both anabolic and catabolic stimuli while GLUT-3 are constitutively expressed and shown to remain unaffected by those stimuli [14 - 18]. The high and low glucose concentrations in the articular chondrocyte matrix have shown anincrease in matrix metalloproteinase-2 (MMP-2, an enzyme that digests the cartilage matrix in late OA) expression and induction in insulin-like growth factor-1 (IGF-1) resistance with decreased proteoglycan and collagen type-II synthesis [2, 14, 19, 20]. The increased production of reactive oxygen species (ROS) has been found to be a key mediator of the damage effects caused due to hyperglycemia [21]. Moreover, ROS pathogenesis during OA has been shown to induce catabolic cytokines like IL-1β in chondrocytes and alter the regulation of NF-κB that is involved in cartilage degradation [2, 22, 23].

In this chapter, through a critical review of literature, we seek to explore how T2DM is associated with OA pathophysiology. Aging, obesity, and T2DM are common risk factors that promote low-grade inflammation, oxidative stress, and dysregulation of cell function, resulting in cell toxicity and OA-related cartilage and bone abnormalities. Hyperglycemia and insulin resistance are associated with cartilage health and play important roles in the molecular pathophysiologic mechanism through the activation of various pro-inflammatory and catabolic cytokines.

PREVALENCE OF OA

T2DM and OA are among the common diseases that are expected to increase in prevalence and, therefore, represent a major public health challenge [24, 25]. Both age and obesity have long been identified as risk factors for OA and T2DM [26 - 29]. T2DM and OA National diabetes statistics report of the year 2020 shows the crude estimation from US population, where 34.2 million people (10.5%) of all ages had diabetes. T2DM affects 4.6 million people in the United States between the ages of 18 and 44, rising to 14.3 million people between the ages of 45 and 64 [29]. The International Diabetes Federation, 2016, had estimated that the global population with diabetes between the ages of 20-79 was 285 million (6.4%) that would rise to 439 million (7.7%) by 2030 [24]. Similarly, the prevalence of symptomatic knee OA was 4.9% among adults aging ≥26 years and 6.7% among adults aging ≥45 years [30]. Overall, 46.4 million people in the United States have arthritis, with that number expected to rise to 67 million by 2030 [25, 31].

The co-existence of type II diabetes mellitus (T2DM) and osteoarthritis (OA) is due to their shared risk factors like age and obesity, and high prevalence [28, 32 - 35]. There is a number of studies that relate increasing incidences of OA with T2DM. Approximately, half (47.3%) of the patients with T2DM have some kind of arthritis [36]. A recent study suggested a 52% prevalence of arthritis in adults (18–64 years) with T2DM as compared to 27% in those without T2DM [37].

A recent study has suggested that adults between 18–64 years showed a 52% prevalence of arthritis in those with T2DM compared to 27% in those without T2DM [37]. The exact reason for the high incidence of arthritis in those with T2DM is still not clear. OA has been associated with systemic metabolic disturbances generally seen in T2DM. Therefore, it suggests that diabetes itself influences the pathophysiology of OA independently of obesity or aging. These metabolic disturbances have been linked to the development of OA and T2DM.

CHAPTER 6

Infection of Novel Coronavirus in Patients with DiabetesMellitus

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Abstract: According to the preliminary research, coronavirus disease 2019 (COVID-19) has been found to be more severe in patients with diabetes mellitus. Furthermore, COVID-19 might also lead to hyperglycaemia. Along with other risk factors, high blood glucose may also affect immune and inflammatory responses, thus inclining patients to severe COVID-19 witha much higher mortality rate. Angiotensin-converting enzyme 2 (ACE2) receptors are the common entry point for SARS-CoV-2. Recent findings suggest that dipeptidyl peptidase 4 (DPP4) can also act as a binding and entry target. Glucose-lowering agents and anti-viral treatments can alter the risk, but there exist limitations to their use, and its possible interactions with COVID-19 treatments should be carefully assessed. TMPRSS2 and Neuropilin-1, the key components that facilitate SARS-CoV-2 infection, are also the potential targets forthe treatment of COVID-19. Finally, severe acute respiratory syndrome coronavirus 2 infections might represent a worsening factor for people with diabetes, as it can precipitate acute metabolic complications through direct negative effects on cell function. Thus, this chapter deals with the treatment options of diabetes and COVID-19. Most of these conclusions are preliminary, and further investigation of the optimal management in patients with diabetes mellitus is warranted.

Keywords: Diabetes, COVID-19, Angiotensin-converting enzyme 2 (ACE-2), Treatment options of Diabetes, Interrelation of COVID-19 and diabetes.

INTRODUCTION

Diabetes mellitus (DM) has become an international health threat, and in recent years, it has increased to several folds. According to the recent global estimate

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provided by the International Diabetes Federation, the total number of affected patients in 2019is 463 million. Current estimations predict that by 2045, it may furtherrise to 700 million [1, 2]. Diabetes leads to earlier mortality due to co-morbidities associated with it; like end-stage renal disease,glaucoma, loss of memory, COPD, and heart failure [3]. Diabetic ramifications cause more impairment and at the extreme, life-threatening disorders [4].

Because the entire world is dealing with a pandemic, it becomes necessary to understand its effects on the patient's already suffering fromcomplications. In that line, diabetes is one such complication. In India, the first case of COVID-19 was observed on 30th January 2020 in Kerala. The pathogen has been identified as a novel enveloped RNA beta-coronavirus [5]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonia spread so fast that it became a newly recognized illness that spread rapidly throughout the world from Wuhan (Hubei province) to other provinces in China [6]. The World Health Organization (WHO) pronounced the official name of SARS-CoV-2-induced disease as the coronavirus disease 2019 (COVID-19). The common symptom includes fever, dry cough, dyspnea, fatigue, and lymphopenia [7, 8]. The vulnerable people for earlier and lethal infection from COVID-19 are people of older age, diabetic patients, patients of lung disease, and cardiac patients [9 - 11]. Among all the other complications and COVID-19 exposure, patients with chronic diabetes should be taken proper care as discussed earlier that diabetes in most cases is associated with co-morbidities. The presentchapter discusses diabetes, COVID-19 infection, and its effect on patients with chronic diabetes.

DIABETES MELLITUS

The "Diabetes" is a Greek word meaning "siphon". Aretus a Greek physician during the second century A.D., named the condition *diabainein* as, the patients suffering from this disease show symptoms of polyuria. Later in 1675, Thomas Willis called it as Diabetes mellitus by diagnosing excess glucose in the blood and urine of a patient. Thus, together it means "siphoning off sweet water". It is a manifold disorder characterized mainly by the absence or presence of insulin. Insulin is produced by the pancreas after meal to supply the glucose present in our blood into the cells, as soon as glucose enters the cells, thus leading to a drop in blood-glucose levels. In diabetic patients, the absence or ineffective presence of insulin cannot transport glucose and leads to hyperglycemia associated with long-term complications and hence affecting the eyes, kidneys, cardiovascular system and nervous system [12]. The continued chronic hyperglycemia generates free radicals and reactive oxygen species (ROS), which causes oxidative stress. Thus, diabetes is grouped as a metabolic disorder.

- Types of Diabetes:
  1. Diabetes mellitus: It is a group of diseases that affect the utilization of blood sugar (glucose). Glucose is vital for health as it is an important source of energy for muscles and other tissues. It is caused by a combination of genetic susceptibility and environmental factors.
  2. Diabetes insipidus: In this type of diabetes, cells become resistant to the action of insulin, andthe pancreas are unable to make enough insulin to overcome this resistance. Instead of moving into your cells where it is needed for energy, sugar builds up in your bloodstream.
  3. Gestational diabetes: It is a condition in which blood sugar levels become high during pregnancy and affects up to 10% of women. They are of two classes:
     - Class A1 controlled by diet and exercise.
     - Class A2 needs insulin.

EPIDEMIOLOGY

The current trends of detected cases may vary with time and places. The epidemiological research focus on defining the prevalence of type 2 diabetes and is defined by oral glucose tolerance test (OGTT). As per the recommendation of WHO, diabetesis defined by fasting glucoseof 7.0 mmol/L or more and/or 2-hour post-challenge glucoseof 11.1 mmol/L or more. According to the International Diabetes Federation estimates, nearly 415 million people had DM in 2015 and the rise in number would be 642 million by 2040 [13]. India is found to be the home to 70 million diabetic people. The prevalence of DM ranges from 5–17%, with increasing incidence in the southern part of the country and urban areas [14 - 20]. The major source of infection includes: ageing, urbanization, changes in feeding habits, continual busy schedule and now work for physical activity.

ETIOLOGY

Diabetes is a multifactorial disease and has its occurrence due to multiple factors, which include lifestyle, environmental changes, and genetics and hormonal changes, either its action or resistance. Diabetes affects many organs of the body like nervous system, eyes, foot, liver, pancreas *etc*. Factors affecting diabetes can be depicted in Fig. (**1**).

CHAPTER 7

Role of an Anti-Inflammatory Agent in the Management of Type 2 Diabetes Mellitus

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Abstract: Metabolic syndrome is a group of diseases, which include high elevated blood pressure, increased glucose level, abdominal obesity, and low high-density lipoprotein cholesterol levels. Clinical implications of metabolic syndrome indicate the risk of insulin resistance. Convincing data in the literature demonstrate alterations in the expression of cytokine inflammatory gene (IL-1, IL-6, TNF-a) expression highly increased and reduced the expression of the anti-inflammatory gene (IL-1Ra, IL-4, IL-10, and IL-13) in Type 2 diabetes (T2D). Various physical activities, like weight loss and exercise, are beneficial for patients with T2D. Many anti-diabetic drugs are effective against T2D in which liraglutide, sulfonylureas, and salsalate drugs exert an anti-inflammatory action in obese patients with T2D. They all have a potent anti-inflammatory effect due to inhibition of the NF-kB pathway, upregulation of SIRT1 expression, and down-regulation of pro-inflammatory factors, including cytokines (TNF-α, IL-1β, and IL-6). They mediate a long-lasting effect by epigenetic regulation of the NF -kB pathway by SIRT1. These 3 drugs, namely liraglutide, sulfonylureas, and salsalate, are used for glycemic control by T2D patients. Moreover, with the help of different mechanisms, these three regulate the level of glucose by the inhibition of the NF-κB pathway.

Keywords: Type 2 diabetes, Anti-inflammatory cytokines, Liraglutide, Salsalate, Sulphonyl urea, NF-κB pathway.

INTRODUCTION

Inflammation is a process that is caused by many severe metabolic disorders, resulting in T2D, which involves hyperglycemia, dyslipidemia, oxidative stress, and endoplasmic reticulum stress [1]. T2D is characterized by defects in insulin secretion yet as peripheral insulin resistance in muscle, fatty tissue, and liver. The progression from obesity-related insulin resistance to T2D occurs when the.

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Inflammation pancreatic β-cells fail to Inflammation complete insulin resistance results in β cell dysfunction [2]. The idea of previous literature the amount of proinflammatory cytokine (IL-1, IL-6, TNF-α, and TGF-β) increased and reduced the number of anti-inflammatory cytokines (IL-1Ra, IL-4, IL-10, and IL-13) [3]. Metabolic dysregulation and chronic inflammation are found to be associated with increased cardiovascular morbidity and mortality in T2D patients.

IL-1-beta thus increasing inflammation including accumulation of macrophages and increase expression of IL-1β are documented in T2DM patient. Additionally, the depletion of resident islet macrophage in high fat-fed transgenic mice with islet amyloid formation was found to reduce IL-1β expression, improve β cell insulin secretion, and restore glucose tolerance. The therapeutic inhibition of IL-1β ameliorates β cell dysfunction and glucose homeostasis in an individual with T2D. When IL-1β appears to be a direct reason for β cell dysfunction, evidence exists that the proinflammatory cytokines TNF-α could be a key molecule in insulin resistance. In a healthy human, TNF-α was shown to inhibit whole-body insulin-mediated glucose uptake and signal transduction by inhibiting peripheral insulin-stimulated glucose uptake *via* impaired phosphorylation of Akt substrate 160, a key step within the canonical insulin signaling cascade regulating GLUT4 translocation and uptake [2]. IL-6 was originally identified as a β-cell differentiation factor, and many cells were reported to produce IL-6, like endothelial cells, skeletal cells, smooth somatic cells, thyroid cells, fibroblast, mesangial cells, and certain tumor cells. Obesity, particularly excess visceral adiposity, could lead to the event of chronic low-grade inflammation. This low-grade inflammation indicates the elevation of IL-6 in T2D patients [4].

IL-1Ra inhibits the results of IL-1β by competitive binding to the IL-1 receptor I (IL-1RI) without inducing a cellular response. IL-1β is a crucial cytokine in T2D because it is associated with insulin resistance and β-cell dysfunction. IL-1β interferes with insulin signaling in adipocytes and hepatocytes, suppresses insulin-induced glucose uptake, inhibits lipogenesis, and reduces the discharge of adiponectin [5, 6].

Physical activity is a first-line treatment for hyperglycemic conditions. Additionally, exercise is understood to modulate inflammation acutely and chronically [7]. Various physical activities included exercise without weight loss reduce chronic inflammation, the anti-inflammatory art is mediated by secretory peptides, so-called myokines, produced by working striated muscle. Striated muscle can communicate with other organs by secreting these myokines, and this muscle secretome consists of several hundred peptides that are the conceptual basis for a replacement paradigm of muscle communication with tissues, including fatty tissue, liver, pancreas, and brain. Myokines include various

muscle-secreted cytokines, like IL-6, IL-7, and leukemia inhibitory factor, and other peptides, like brain-derived neurotrophic factor, insulin-like protein 1, fibroblast protein 2, follistatin-related protein 1 (FSTL-1), and irisin [8, 9]. The available treatments for T2D act through diverse mechanisms which reinforce glycemia. Many of thesetreatments also exert anti-inflammatory effects, which canbe mediated *via* their metabolic effects on hyperglycemia and hyperlipidemia or by directly modulating the system. A neighborhoodof the findings on the results of various medications on systematic and tissue specific inflammation was obtained in animal model [10 - 13].

Due to the influence of upper glycemic level, islet macrophages start to supply inflammatory cytokines IL-1β, which involve in the impairment of pancreatic secretory function by increasing the β cell apoptosis rate .so one in every of the recombinant human IL-1 receptor, Anakinra is employed to inhibit the function of IL-1 in T2D and reported beneficial in both hyperglycemic and secretory function of insulin-related to the reduced level of C reactive proteins [14].

DRUGS

LIRAGLUTIDE

They have two brand first one is Victoza and the other is Saxenda. The Victoza brand of liraglutide is combined with diet and exercise to improve blood sugar control in adults and children at least 10 years old who have T2D. It is also used to help reduce the risk of a serious heart problem such as heart attack or stroke in adults with T2D and heart disease.Victozoa is not for treating Type 1 Diabetes (T1D), the Saxenda brand of liraglutide is used to together with diet and exercise to help lose weight when they have certain health conditions. Saxenda is for use in adults with a Body mass index (BMI) of 30 or higher and for children at least 12 years old who weigh more than 132 pounds [15].

Dosage

Do not use Saxenda and Victoza together. It is injected under the skin at any time of the day, with or without a meal. The bioavailability of liraglutide after subcutaneous injection is approximately 55% and maximum concentrations are reached after 11.7 hours.

CHAPTER 8

Role of Antidiabetic Agents which Help Regulate TCF7L2 Variations in Type 2 Diabetes Mellitus

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Abstract: Type 2 Diabetes Mellitus (T2DM) is the most challenging health issue of the 21st century; it results from a complex interaction between multiple gene and environmental factors. TCF7L2 encodes a transcription factor that is involved in the Wnt signaling pathway that regulates gene expression of pro-glucagon. Effective treatment is needed to properly manage T2DM patients. Currently, 5 major classes of oral pharmacological agents are available for the treatment of T2DM, like metformin, sulfonylureas, meglitinides, thiazolidinedione, and alpha-glucosidase inhibitors.

Keywords: TCF7L2, Wnt signaling, Pharmacological agent, Type 2 diabetes mellitus.

INTRODUCTION

T2DM is the most challenging health issue of the 21st century. It results from a complex interaction between multiple gene and environmental factors. The pathological process that lead to the development of T2DM are still unclear, however, impairment in insulin secretion and activities is clearly understood. T2DM is a complex disease interplay between genetic, epigenetic and environmental factors. T2DM is a heritable condition. Today, almost 60% of subjects report at least one parent, full siblings or half siblings with diabetes, and almost 90% have an affected grandparent with T2DM. Currently, the preferred therapies for T2DM treatment include the use of anti-diabetic drugs, healthy nutrition and daily physical activity, and monitoring of arterial pressure and lipid profile. Effective treatments are needed to properly manage diabetic patients. Common genetic variations of Wnt signaling gene are related to metabolic

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syndrome and diabetes. Current studies show the interplay between WNT and insulin signaling pathways and its potential role in the development of insulin resistance and T2DM. TCF7L2 encodes a transcription factor involved in the Wnt signaling pathway that regulates gene expression of pro-glucagon. Synthesis of GLP-1 hormone in the intestine stimulates insulin secretion. Currently, five major classes of oral pharmacological agents are available for the treatment of T2DM, like metformin, sulfonylureas, meglitinides, thiazolidinedione, and α-glucosidase inhibitors [1].

DISEASES ASSOCIATED WITH GENE POLYMORPHISM

TCF7L2, a member of the T cell factor/lymphoid enhancer factor family, generally forms a complex with β-catenin to regulate the downstream target genes as an effector of the canonical Wnt signaling pathway. In islets, TCF7L2 not only affects the insulin secretion of the β-cells, but also has an impact on other cells [2]. The TCF7L2 gene encodes a TF involved in the canocial β-catenin dependent Wnt pathway and expressed in the mature and developing β-pancreatic cells [3]. Two gene polymorphisms of TCF7L2 that are in complete LD, rs7903146 (C>T) and rs12255372 (G>T), are highly associated with the incidence of T2DM in different populations, like European, Asian and African, as shown in genome-wide association studies and global meta-analyses; however, Pima Indians, rs12255372 polymorphism was found to be associated with BMI only. In all tested human populations, an association between TCF7L2 polymorphism and T2DM was observed. The effect of TCF7L2 rs7903146 polymorphism is similar. The TCF7L2 rs7903146 T allele confers increased risk of developing T2DM. The association of TCF7L2 rs7903146 T allele with T2DM is derived from different quantitative glycaemic traits, such as fasting plasma glucose level and HbA1C, with consistent results. The TCF7L2 gene encodes a TF involved in the canocial β-catenin dependent Wnt pathway and expressed in the mature and developing β-pancreatic cells. Although the exact role of TCF7L2 rs7903146 gene polymorphism in T2DM is still unknown, it is directly or indirectly related to β-cell function and possibly stimulates β-cell proliferation. The pharmacogenetic effect of the TCF7L2 variant on therapeutic response to hypoglycemic agents has been explored in only a few studies. The T allele was associated with an increased risk of sulfonylurea treatment failure, whereas it showed no effect on the therapeutic response in metformin-treated patients. However, a recent study suggests that TCF7L2 could be implicated in both sulfonylurea and metformin response (Fig. **1**) [4].

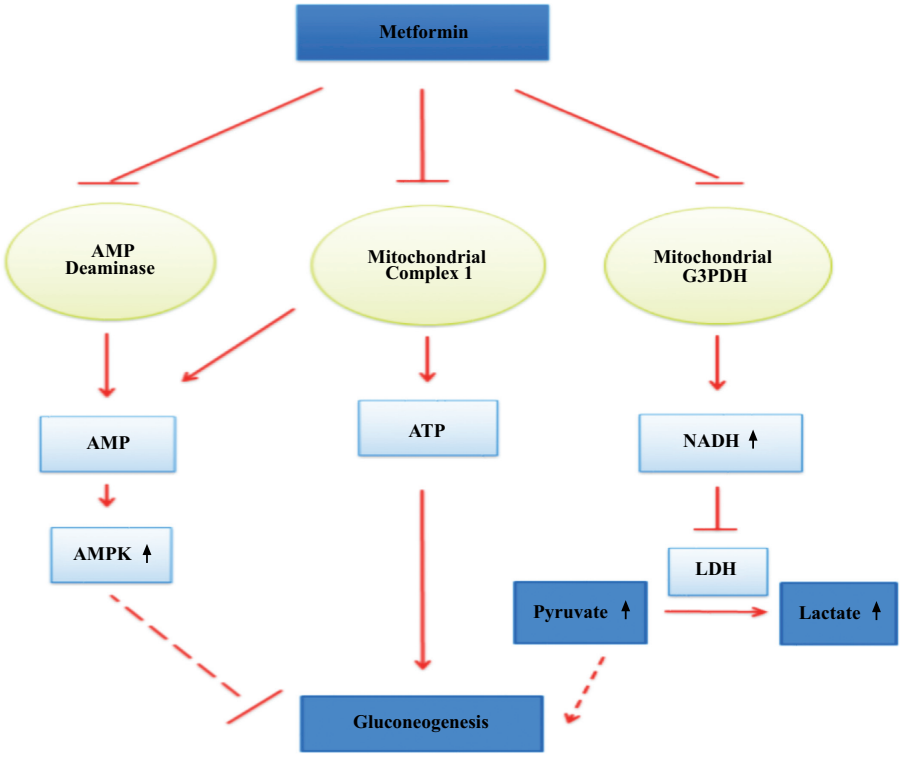

Fig. (1). Mechanism of action of metformin. AMP- Adenosine monophosphate, AMPK- AMP-activated protein kinase, ATP- Adenosine triphosphate, NADH-Nicotinamide adenine dinucleotide, LDH- Lactate dehydrogenase.

MAJOR CLASSES OF ORAL PHARMACOLOGICAL ANTI-DIABETIC AGENTS

There are currently five major classes of oral pharmacological agents available for the treatment of T2DM.

Metformin

It is the first line pharmacological drug for the treatment of type 2 diabetes mellitus; however, mechanisms underlying the plasma glucose level lowering effects of metformin still remain incompletely understood. The study shows the effects of the TCF7L2 rs7903146 genotype metformin response in T2DM. Mitochondrial respiratory chain complex 1 is targeted by metformin, and its inhibition is involved in AMP-activated protein kinase-independent regulation of hepatic gluconeogenesis cellular energy charge and redox state. Its action is to

CHAPTER 9

Relationship between Type 2 Diabetes Mellitus, PCOD, and Neurological Disorders: Role of Antidiabetic Drugs

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Abstract: Polycystic ovarian disease (PCOD), Alzheimer's disease (AD), and type 2 diabetes mellitus (T2DM) have strong co-relation with each other, according to the accumulated evidence. However, many pieces of evidence have suggested that diabetes is the major risk cause behind PCOD and AD. We have focused on shedding light on the close association between PCOD, AD, and anti-diabetic drugs. When the family history of diabetes is studied extensively, it is illustrated that there are known associations between insulin resistance and development of the PCOD.Studies have been performed on different individuals with PCOD, both oligomenorrheic and eumenorrheic women. Irrespective of the criteria of obese and non-obese women, there is a high prevalence of type 2 diabetes history in their family, hence proving the family inheritance of the ovarian disorder. While studying the pathophysiology of diabetes, it is observed that many characteristics of AD are similar to that of T2DM such as elevated oxidative stress, amyloid-beta (Aβ) production at a high level, cerebrovascular complication, and dysfunctional insulin signaling. Among the anti-diabetic drugs, metformin is most commonly used, and it has many useful functions, such as controlling serum lipid profiles, having positive control over the hemostasis process, and serving an anti-inflammatory role.

Keywords: Alzheimer’s disease, Diabetes, Eumenorrheic, Insulin signaling, Metformin, Neurodegeneration, Oxidative stress, Oligomenorrheic, PCOD.

INTRODUCTION

Many cases of PCOD have been observed in families as genetic clusters, and various research groups have observed that the disorder occurs on a genetic basis. PCOD comprises a characteristic of inherited congenital adrenal hyperplasias that

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is because of a 21-hydroxylase deficiency. Such disorders are considered rare and result in very few cases of PCOD. Both type 2 diabetes and PCOD have comprised a common property that is insulin resistance. Studies have confirmed that type 2 diabetes is a result of genetic inheritance, and PCOD is considered to arise as a result of insulin resistance. According to the analysis of such observations, PCOD suspected women might have a risk factor of developing type 2 diabetes in the future [1]. AD is a disorder that is ruinous and originates over a long span of time, which results in memory loss and cognitive disability that involves neural death over many regions of the brain, such as in the hippocampus, basal area of the forebrain, and in the entorhinal cortex. Studies have revealed that about 12-13% of people aged above 65 are more prone to be affected by AD. Nowadays, life span has increased than earlier, due to which the chances of people getting affected by AD have increased. Categories in which the AD has been divided are sporadic Alzheimer's disease (SAD) and familial Alzheimer's disease (FAD).

RELATION BETWEEN T2DM AND AD

SAD is accompanied by many other risk factors, such as cancer, stroke, and dysfunctional glucose tolerance. The initial stage of AD causes an increased level of oxidative stress, and scientists have analyzed that oxidative stress is the major causative agent behind the AD-derived impaired insulin signaling that affects AD patients' brains in a ruinous manner. Oxidative stress-induced cellular level damage is very dangerous as this causes a halt in the lipid and protein synthesis process. Along with that, enzyme activity is also reduced, and that ultimately leads to the inactivation of enzymes and a drastic change in receptor function. Damages that occur during AD include the following: impaired function of mitochondria, the dysfunctional process of neurogenesis, and decreased level of nerve growth. Moreover, the neurotrophic factor is also involved in AD (Fig. **1**).

AD = Alzheimer's Disease

As this disorder progresses, it encompasses hyper depression, anger, language disabilities, and irritation, diagnosed by means of brain scanning and behavior-based tests. A representative kind of relief will be provided to patients with the help of a balanced and healthy diet as well as different pharmacological treatments given to the brain. As time passes, instead of all the protective measures taken, the disorder may progress and become severe. The onset of AD begins by the formation of the amyloid-beta (Aβ), which contains the neuritic plaques that are obtained as a result of the excess production of peptides of the Aβ that are generated by the amyloid precursor protein (APP), and its generation also involves the phosphor tau-positive neurofibrillary tangles formation that arises

from the paired helical filaments (PHFs). Important genetic mutations involved in the AD onset are presenilin 1 (PSEN1), APP, and followed by presenilin 2 (PSEN2) [2]. The major risk of neuropathy nowadays is crucially in those countries where there is a prevalent increase in the rate of obesity [2, 3]. It is well known that type 2 diabetes is a complex metabolic disease that possesses characteristic features such as an increased level of blood glucose and insulin resistance. Reputed journals have prominently published that diabetic patients are much more susceptible to AD. Diabetes affects almost all vital organs, such as the brain. In fact, diabetes is known to become a major cause of dementia and cognitive impairment. For the treatment of diabetes, various kinds of drugs are used, including meglitinides, thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogs, sulfonylureas, inhibitors of α-glucosidase, dipeptidyl peptidase 4 inhibitors (gliptins), and biguanides. Recently, various diagnosed diabetic patients have been treated by metformin therapy. Researchers have analyzed that metformin controls or, more precisely, reduces the interleukin 1 β (IL-1β) stimulated proinflammatory phosphokinases activation such as Akt (protein kinase B) and ultimately, aids in controlling inflammation.

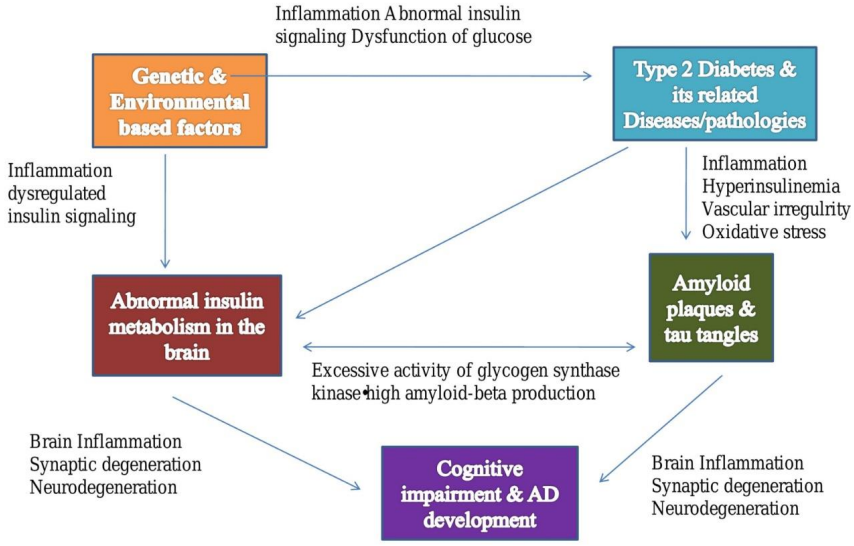

Fig. (1). The major association between AD and diabetes.

CHAPTER 10

Comparison of Different Types of Insulin Available for Type 1 Diabetes Mellitus Treatment

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Abstract: A handful of pharmaceutical companies manufacture different types of insulin which treat type I diabetes mellitus. Insulin brands are grouped by the onset of their action and how long their blood glucose-lowering effects last. Insulin analogs were introduced way back in 1996; since then, there has been a lot of advancement in their production as well as the mechanism of action. Current insulin therapies more closely mimic the normal physiologic insulin secretion by the pancreas, which gives a better-glycosylated haemoglobin level in patients suffering from diabetes. This chapter focuses on the types of available insulins and their regimens, classification of types of insulin that are best for different age groups, diet to be followed, principles of dose adjustment, and a glimpse of insulin pump therapy.

Keywords: Diabetes mellitus, Type I, Insulin.

INTRODUCTION

Classification of diabetes mellitus is important for treatment strategies, which sometimes is complicated as these patients do not easily fit into a single class, especially children below 18 years [1 - 4]. The classical classification of diabetes as proposed by the American Diabetes Association (ADA) in 1997 as type 1, type 2, other types, and gestational diabetes mellitus (GDM) is still the most accepted classification and adopted by ADA [1].

This chapter focuses only on people suffering from Type 1 diabetes mellitus who essentially take insulin which helps maintain the sugar levels [5, 6]. The market has various types of insulin that differ in terms of how quickly and how long they are effective and their chemical structure.

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Short-acting insulin or rapid-acting insulin work very quickly (0-2 hrs), while long-acting or basal insulin only start to work after a certain amount of time (12-24 hrs), and ultra-long acting can even work over a longer time period (48 hrs).

Some years back insulin was easily extracted from the pancreatic cells of pigs or cattle and purified for human use. Currently, most people use genetically engineered insulin for the treatment of diabetes. These recombinant insulins are now available in the market with the names of human insulin or insulin analogues. Human insulin differs from insulin analogues in chemical structure, but the effect is the same.

TYPE 1 DIABETES: TYPES OF INSULIN THERAPY

Maintaining the sugar level for a type 1 diabetic is the most important task because of the lack of insulin production in their body in order to prevent long-term complications. Diabetic patients all around the world follow either conventional or intensive or both of them to control their blood sugar levels.

Facts that regulate the blood glucose levels are the amount of insulin taken, diet, and the energy expended during physical activity. Other parameters that influence the blood glucose are the time of day when the injection is taken, inflammatory diseases, medications taken, and hormonal changes. Therefore, it becomes very important for a diabetic to know about one's body and eating habits which can correctly adjust the insulin therapy to be given [7].

Pharmaceutical industries manufacture different types of insulin [8 - 10], which differ only according to their time of action. The long-acting insulin works slowly and constantly over the whole day, and intermediate-acting insulin does the same for half a day. Short-acting insulin is generally taken just before the meals, whereas ultra-short acting insulins can be taken after the meals to maintain the sugar levels post-meal.

People with diabetes have the flexibility to choose between the types of insulin therapies, but most prefer following the intensive one in order to maintain their sugar levels as per their daily routine.

Conventional Insulin Therapy

Having a regular daily routine means that people inject their insulin at a fixed time every day, which is an older approach. Therapy involves injecting long-acting or intermediate-acting insulin as prescribed by the physician, and sometimes a short-acting shot is also preferred, which is effective in most people and helps maintain a sugar level in the blood. Most people use a standard mixture

of short-acting and longer-acting insulin, which can be taken before breakfast and before dinner to overcome the problem of injecting two times at the same time. The disadvantage of following this therapy is that these people have to eat calculated amounts of food regularly over the day. Those who go through many exercises can balance their blood sugar level by eating between meals.

Only those people living a strict life can take full advantage of conventional insulin therapy, but as the lifestyle has become more complicated and with the advent of fast food, the therapy can be much less effective at preventing diabetic complications.

Intensive Insulin Therapy

Since most type I diabetic people acquire IDDM between the ages 2 – 18 years and due to the modern lifestyle, intensive insulin therapy becomes the therapy of choice as an individual's blood sugar levels, diets, and physical fitness levels can be taken into account to adjust insulin doses flexibly and spontaneously. The treatment requires regular monitoring of blood sugar levels, and accordingly, an injection is administered multiple times each day, or an insulin pump is utilized. Long-acting insulin or basal insulin can be injected once or twice a day with a shot of short-acting insulin or bolus insulin before each meal to maintain sugar levels.

Insulin pumps deliver small amounts of insulin continuously to diabetics whenever they eat, so they only use short-acting insulin. This is the biggest advantage of intensive insulin therapy in keeping the blood sugar at nearly normal levels all day. That gives an individual the liberty to have some flexibility in daily routine, and neither the after-effects of taking too much or too little insulin comes into consideration.

Overall, intensive insulin therapy is healthier than conventional therapy, which lowers the risk of diabetes-related complications, affecting primarily our eyes, kidneys, and nervous system.

DIFFERENT TYPES OF INSULIN?

The following Table **1** shows the types of insulin products with their generic name and active substance along with the name of the company producing the drug [11].

CHAPTER 11

Circadian Rhythm Disruption: Special Reference to Type 2 Diabetes Mellitus

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Abstract: We live in a rhythmic world where both internal (in the body) and external (natural) processes are harmoniously synced to each other to function in a rhythmic pattern. Whenever this synchronization between the two is disturbed, it creates misalignment leading to rhythm disruption. In today's 24x7 society, the majority of health issues are due to lifestyle disorders that have their genesis in circadian rhythm disruption. One such lifestyle disorder that has reached the heights equivalent to the epidemic is Type 2 diabetes mellitus (T2DM). In the current chapter, the role of the endogenous biological clock (of organ and tissue) in regulating glucose metabolism is discussed by citing the basal and advanced research done in the related field. Our effort is to build up a connection between circadian misalignment and its probable effect with special reference to T2DM. We started with the description of circadian rhythm, over-viewing the daily glucose metabolism. We then discussed the pathophysiology of type 2 diabetes mellitus in light of circadian rhythm disruption. Every organ in the human body has its clock and rhythm, thus it is a complex mechanism involving dysfunction of pancreatic b-cells, deposition of fat near visceral organs and insulin resistance, *etc*. Workstress and schedules have increased the risks of obesity and diabetes. Thus, it seems the need of the hour to focus on chronopathology and chronomedicine as alternative treatment strategies to manage and prevent T2DM, which can further, contribute to the reduction of the risks of metabolic co-morbidities in the human population.

Keywords: Circadian rhythms, Clock disruption, Diurnal pattern, Glucose metabolism, Lifestyle disorders, T2DM.

INTRODUCTION

8th edition of 'Diabetes Atlas' 2017 issued by the International Diabetes Federation reported a rise in diabetic cases around the globe. According to the report, one person dies every seven seconds as a result of diabetes or its complications.

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Out of this, 50 percent of deaths occur in people under the age of 60 [1]. The global prevalence of diabetes has continued to expand from 151 million in the year 2000 to 285 million in 2009 and 382 million in 2013. This is against the backdrop of the world population with a global prevalence of diabetes which was 8.8% in 2017, standardized for the group of individuals in the age range of 20-79 years. By 2045, the prevalence is predicted to rise further to 9.9%. Overall this represents a population of 424.9 million people worldwide in 2017 with an estimated rise of 48%, which will constitute 628.6 million people by 2045. Disastrously, around 50% of all diabetics are not diagnosed, particularly in developing countries [1]. 95% of all diabetes cases are suffering fromT2DM [2]. In the current chapter, the focus is laid upon T2DM. The exponential increase in the cases of T2DM in the past decade can be explained by evaluating the lifestyle changes in society that include physical inactivity, smoking and poor diet. Along with these in recent decades, a new risk factor in the lifestyle of modern society has become common, *i.e*., circadian disruption. In particular, about 20% of people are working in shift-based duties [3], 33% are sleeping less than 6 hours [4] and 69% are dealing with social jetlag [5]. Studies have shown considerable linkage of increased risk of type 2 diabetes with lifestyle disturbance and circadian disruption *e.g*. individuals working in shift duties are 10-40% more prone to the risk of diabetes [6]. As per the potential correlation between circadian disorders and diabetes risk, the role of the circadian system and its disorders must be investigated about the regulation of glucose metabolism. The current review also offers a summary of the circadian regulation of glucose metabolism and the effect of clock disruption on glucose control.

DAILY RHYTHMS AND THEIR DISRUPTION

The circadian clock system has developed in a way to regulate the daily functioning of physiological and biological processes (endogenous rhythms) rhythmically. These rhythms are aligned with the 24 hours of environmental rhythms (exogenous rhythms) that are generated by the rotation of the Earth. The rhythmicity in our physiology is a result of proper synchrony between the internal body clock and socio-environmental cues in everyday life [7, 8]. The internal multi-oscillating body clock mechanism is made up of a central clock *i.e*., Suprachiasmatic Nucleus (SCN) present in the hypothalamic region of the brain, along with the peripheral clocks (organ clocks) ticking in every tissue and cell of the body [8]. Molecular clocks work on feedback loop mechanisms (*e.g*. transcription-translation negative feedback loop) including core clock genes such as CLOCK, BMAL1 (or ARNTL), PER and CRY [8]. The SCN is mainly entrained by light cues through the retinohypothalamic tract. In turn, the hormonal/neural/thermal pathways transmit time signals to other brain areas and

body organs, such as the liver, GI tract, pineal and adrenal glands, muscle, pancreas and adipose tissues (Fig. **1**). SCN not just affects the organ system *via*. 'classical' neuroendocrine controlling [7] but also by synchronizing organ functions with the molecular clocks present in the peripheral organs [8]. These molecular clocks can affect the clock-controlled genes hence altering the organ functions. Peripheral clocks can also be entrained strongly by non-photic cues such as temperature, food, workout [9]. Out of these, food is one of the powerful zeitgebers to organs involved in metabolism, such as the liver [7].

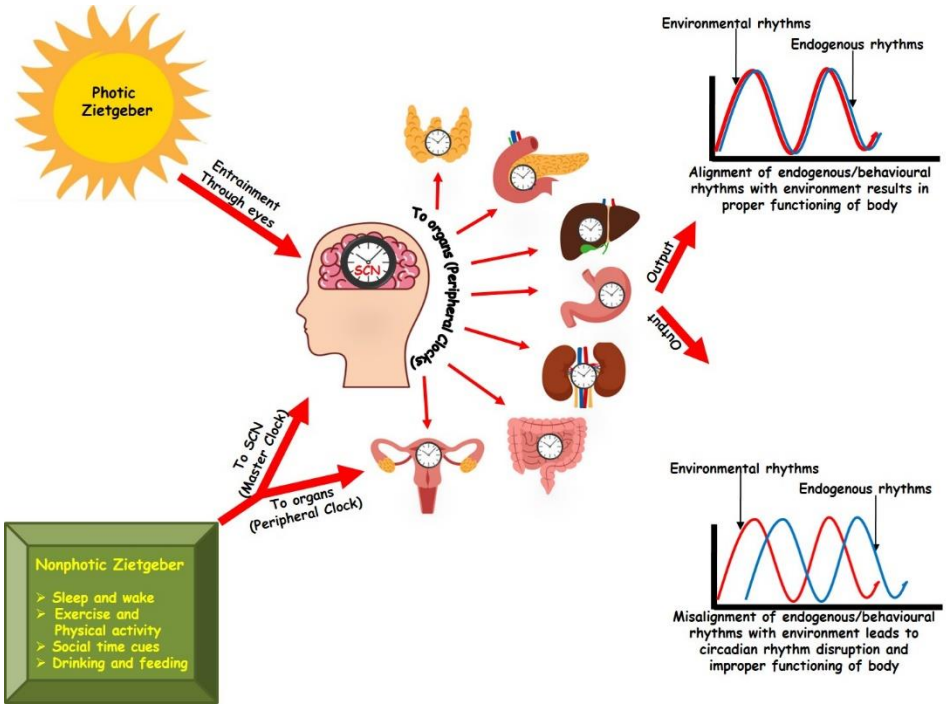

Fig. (1). Diagrammatic representation of entrainment of circadian timekeeping system. Entrainment of central/peripheral clocks is done by both photic (environmental) and non-photic (behavioural) cues. Synchronization of endogenous/behavioural rhythms with the environment leads to rhythm alignment whereas desynchronization between them leads to misalignment of rhythms.

As the timings of photic and non-photic cues play an important role in maintaining the physiological functioning of the body, misalignment or clock disruption can occur on various levels. Circadian misalignment between the body clock and the surrounding environment is called 'environmental misalignment' *e.g*. light-dark cyclicity. It is known as 'internal misalignment' when it occurs between the master and peripheral clock network in the body (Fig. **1**) and when the misalignment takes place between the central clock and daily behaviours it is

CHAPTER 12

Type 2 Diabetes Mellitus and its Complications: Pharmacogenetics Based Correlations and Circulating MicroRNA as Biomarkers

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Abstract: The field of pharmacogenetic is focused on find out the ways in which genetic variance in an individual affects the efficacy and potent action of drugs, moreover, in how many ways genetic variance affects the drugs toxicity has also been a major topic of discussion. Nowadays, pharmacogenomics is clearly focused on the establishing personalized medication and finding and developing new drugs. Many approaches have been identified that can play a major role in promoting the concept of personalized medicine and helping in identifying major genetic variance that can further work as a biomarker and provide major clinical insights. As it has been known, the patients of diabetes have been treated with more than one type of drugs that can be defined as oral antidiabetic drugs (OAD) that also plays major role in curing out the diabetes associated complications such as hypertension and dyslipidemia. If major steps should be taken to treat diabetes than only major changes can be made to control it's associated complications and if any kind of genetic testing will be created than it can work as an predictor tool for the disease. Role of, microRNA (miRNA), which is a class of non-coding RNA, is also known to play a major role incausing chronic inflammation if it gets dysregulated along with that also causing β-cell degeneration, followed by insulin resistance.

Keywords: MicroRNA (miRNA), Oral Antidiabetic Drugs (OAD), Personalized Medicine, Pharmacogenetic, T2DM.

INTRODUCTION

According to Diabetes Atlas 2021 by International Diabetes Federation (IDF) the estimated number of Diabetic individuals of adults (20–79 years) in 2021, 2030 and 2045 will be 536.6 million 642.7 million 783.2 million, respectively.

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Estimates according to diabetes atlas-2014 show that 382 million people have Type 2 Diabetes Mellitus (T2DM) throughout the world between the age group of 20-79 years [1]. 152.8 million (46%) people out of 382 million remain undiagnosed for the disease. South-East Asia has 72 million people diabetic, out of which 35.1 million are undiagnosed for T2DM [2]. India alone in South-East Asia has 65.1 million people with T2DM [3]. There is an urgent need to conduct a survey of Indian population using the simplified Indian Diabetes Risk Score (IDRS) because about 50% undiagnosed population [4]. IDRS is based on anthropometric, demographic and behavioral factors, for identifying diabetic subjects in India [5]. IDRS not only predicts diabetes, but also identifies individuals with higher cardiovascular risk *i.e.*, those with metabolic syndrome, even at a stage when they have normal glucose tolerance [6].

T2DM is a worldwide epidemic with considerable health and economic consequences [7]. T2DM patients are often treated with more than one drug, including OADs and drugs used to treat diabetic complications, such as dyslipidemia and hypertension [8]. Appropriate measures could be taken to treat T2DM more efficiently if genetic testing is employed to predict treatment outcomes [9]. A brief representation of the mechanism of action and adverse effects of drugs along with candidate genes involved in pharmacokinetics and pharmacodynamics has been shown below in Fig. (**1**) and (Table **1**).

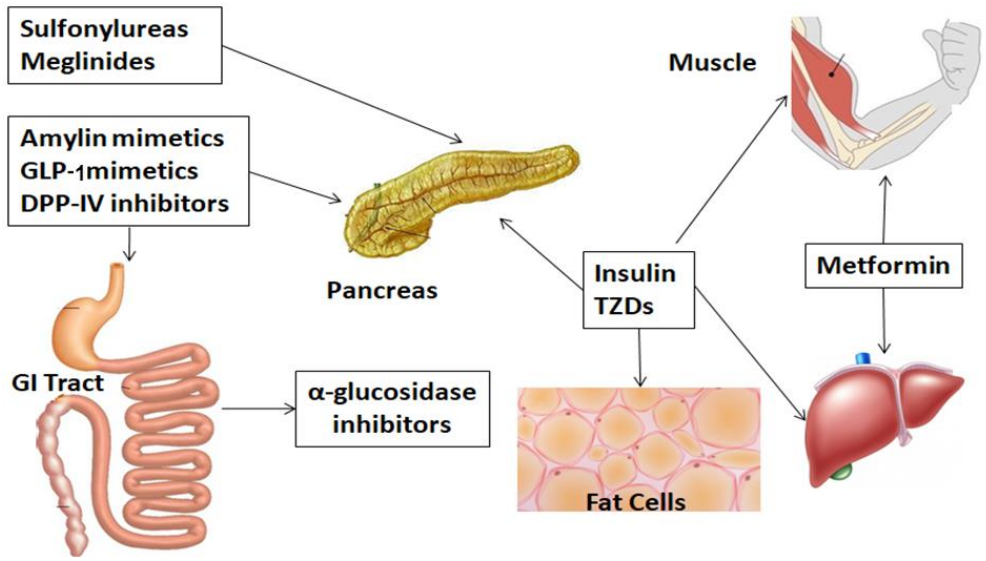

Fig. (1). Tissue targets of the major classes of OADs.

Table 1. Targets, clinical responses and candidate genes involved in drug response of OADs.

Drugs	Mechanism of Action	Main Effect(s)	Potential Adverse Events	Candidate Genes Putatively Affecting Response
Sulfonylureas	ATP-dependent K channel inhibition	Insulin secretion Glucagon Secretion	Hypoglycemia, Allergic reaction to sulfa drugs	*CYP2C9, ABCC8, KCNJ11, TCFL2*
Metformin	AMP-dependent kinase (AMPK) activation	Insulin Sensitivity Hepatic gluconeogenesis	Lactic Acidosis	*SLC22A1, SLC47A1, ATM*
Thiazolidinediones	Enhance PPARγ binding to DNA response element	Glucose uptake by Skeletal muscle Lipolysis Hepatic Glucose Output	Fluid overload, Congestive heart failure, Fractures, Hepatotoxicity	*ADIPOQ, CYP2C8*
Insulin	Insulin/IGF-1 receptor pathway	Tissue glucose uptake	Hypoglycemia	??
Meglitinides	ATP-dependent K channel inhibition	Insulin secretion Glucagon Secretion	Hypoglycemia	??
α-Glucosidase inhibitors	Inhibit pancreaticα-amylase and intestinal α-glucosidase	Glucose absorption by GI tract	Hypoglycemia	??
Amylin minetics	Amylin receptor pathway	Gastric emptying rate Insulin secretion Glucagon Secretion	Hypoglycemia	??
GP-1 mimetics	GLP-1 receptor pathway	Glucose-dependent insulin secretion Gastric emptiying rate Statiety Glucagon secretion	Nausea, vomiting, Hypoglycemia, Acute pancreatitis, angioedema, anaphylaxis.	??
DPP-IV inhibitors	GLP-1 receptor pathway	Glucose-dependent insulin secretion		??

OADs have multi-organ effects apart from primary tissue targets shown. The dotted line denotes putative mechanisms that remain to be fully demonstrated in humans. DPP-IV, dipeptidyl peptidase-IV; GI, gastrointestinal tract; GLP-1, glucagon-like peptide-1; TZDs, thiazolidinediones [4].

With a dramatic increase in the incidence of T2DM globally, diabetic complications have become the leading cause of renal failure globally, *i.e.*

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Madhukar Saxena

Dr. Madhukar Saxena, Senior Researcher in Department of Biotechnology, Babasaheb Bhimrao Ambedkar University, Lucknow, India. He has published many national and international publications in the field of molecular biology, biochemistry, clinical genetics, and stem cell biology of type 2 diabetes mellitus. He is also the author, editor, and co-editor of many publications of international repute. He received prestigious grants from the Department of Science and Technology, University Grant Commission and Indian Council of Medical Research, New Delhi. He has received the Best Young Scientist Award from the Zoological Society of India and the S.C. Pant Memorial Award from the Society of Professional Biotechnologists, India. Dr. Madhukar is working in the field of adipocyte biology in relation to diabetes mellitus.