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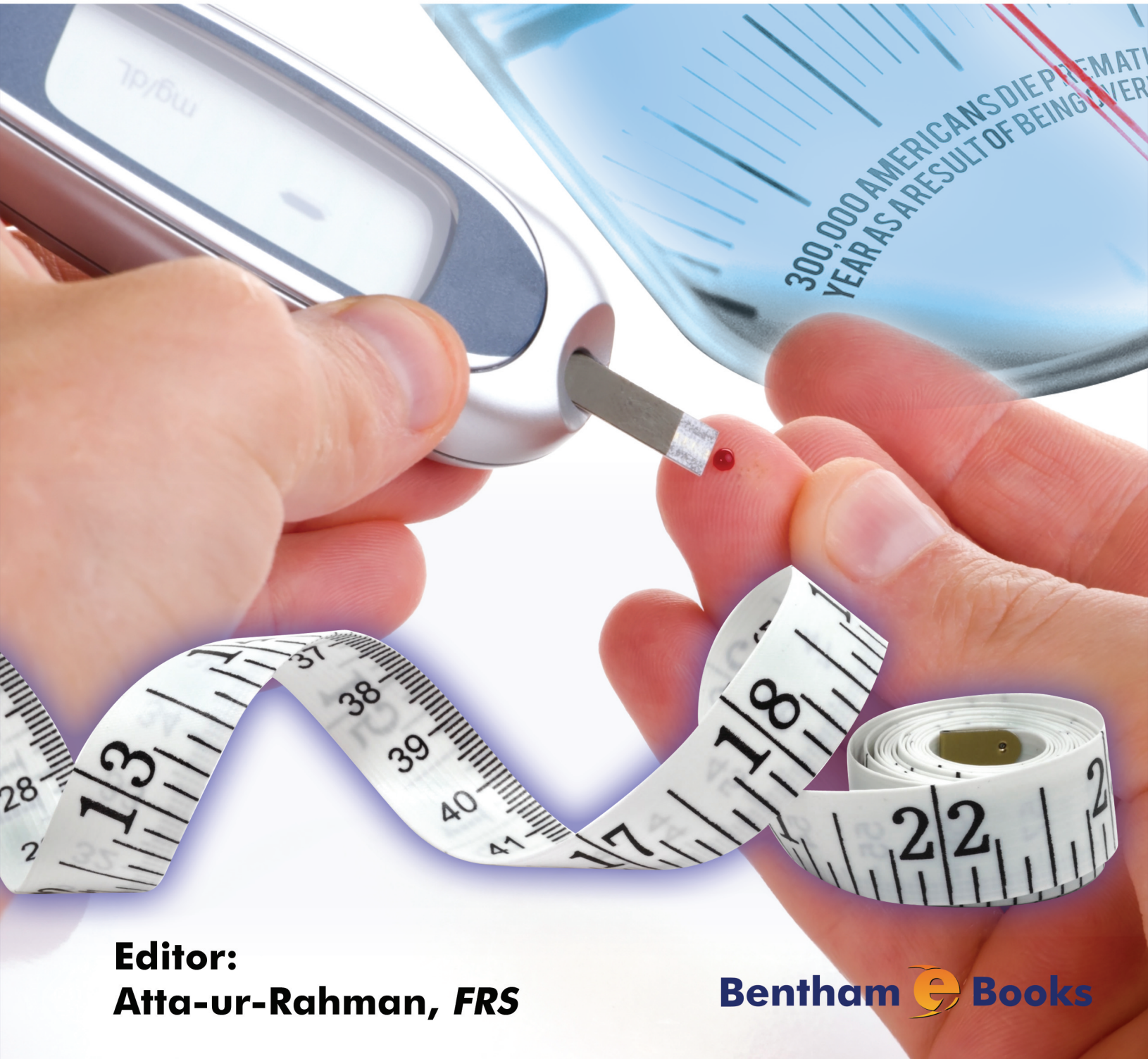
(Diabetes and Obesity)



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Frontiers in Clinical Drug Research – Diabetes and Obesity

(*Volume 5*)

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CONTENTS

PREFACE

The fifth volume of Frontiers in Clinical Drug Research – Diabetes and Obesity comprises five comprehensive chapters discussing novel approaches to combat diabetes and obesity.

In the first chapter, Mandrioli *et al*, present the three most important classical neuroleptics (chlorpromazine, haloperidol and loxapine). The most important antipsychotics are individually analyzed in relation to their propensity to cause metabolic syndrome. In chapter 2 of the book, Sobrevia *et al* summarise some examples of the wide variety of protocols for insulin therapy and the potential consequences of this protocol on the foetoplacental unit and the neonate from women with Gestational diabetes mellitus (GDM).

Growing evidence suggests that hyperglycemia results in increased reactive oxygen species (ROS) production, leading to oxidative stress which affects and damages various tissues and organs. Oxidative stress results from an imbalance between ROS and antioxidants. Houreld and Rajendran highlight the understanding of oxidative stress-related mechanisms underlying the development of diabetes. Their review also elaborates on antioxidant therapy strategies to diminish oxidative stress and to treat diabetic associated complications.

Diabetes mellitus (DM) is a metabolic disorder which is the most alarming disease of the modern era. It occurs as a result of lack of insulin secretion or reduced insulin secretion or peripheral insulin resistance. In chapter 4, Anreddy *et al*. describe the issues concerned with the oral delivery of insulin and also discuss possible routes for the administration and use of Nanoparticles (NPs) for the best delivery of insulin.

In the last chapter of the book, Sharma *et al*. give comprehensive details about the merits and demerits of a class of drugs called Sodium-glucose co-transporter-2 (SGLT-2) inhibitors.

I owe special thanks to all the contributors for their valuable contributions in bringing together the fifth volume of this book series. I also thank the editorial staff of Bentham Science Publishers for their help and support.

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CHAPTER 1

Metabolic Syndrome in Schizophrenia: Focus on the Role of Antipsychotic Medications and Indications for Therapeutic Drug Monitoring (TDM) Methods

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Abstract: Metabolic syndrome is a complex pathology characterized by imbalances in lipid and glucose metabolism and weight gain, and consequently by an increase in the incidence of type II diabetes and cardiovascular disease. Metabolic syndrome is rapidly becoming one of the most important side effects of treatment with modern "atypical" antipsychotic agents, probably due to their specific mechanisms of action. Although the most recent members of this class (aripiprazole, asenapine, ziprasidone) seem to produce a reduce incidence of metabolic syndrome, the problem is far from being resolved. In this chapter, the three most important classical neuroleptics (chlorpromazine, haloperidol and loxapine) and the most important atypical antipsychotics will be individually analyzed in relation to their propensity to cause metabolic syndrome. The most reliable, current data will be presented, also in the perspective of possible interventions to mitigate metabolic imbalances, comparative studies, switching studies and augmentation strategies. An important strategy for metabolic syndrome prevention could also be the performing of an accurate therapeutic drug monitoring (TDM). Thus, an up-to-date overview will also be presented of recent and significant analytical methods for the determination of the drugs of interest and their main metabolites in human biological fluids.

Keywords: Antipsychotic drugs, Diabetes, Hypercholesterolemia, Hypertriglyceridemia, Metabolic syndrome (MetSyn), Obesity, Pharmacotherapy, Polypharmacy, Therapeutic Drug Monitoring (TDM).

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INTRODUCTION

Psychiatric disorders are currently one of the main causes of disability and years lost to illness all over the world: According to recent World Health Organization (WHO) statistics, almost 30% of people have experienced a common mental disorder at some time during their lifetimes [1]. Psychiatric disorders often take a heavy toll on patients' well-being also from a purely physical point of view. Since they often cannot take care of themselves optimally, comorbidity is very frequent, and naturally it increases with age. On top of all of this, one must remember that pharmacological therapy, albeit one of the most effective forms of treatment, is also in itself a potential source of iatrogenic effects. According to some studies, it is estimated that up to 74% of patients discontinue the medication before 18 months [2], and between 10 and 20% are forced to interrupt the pharmacologic treatment due to side or toxic effects [2, 3]. Two major factors contribute to exacerbate this situation: polypharmacy and lifelong chronic therapy. Psychiatric patients are often subjected to polypharmacy due to the inherent difficulty in controlling the disorder's multifaceted symptoms, and also due to the relatively low rate of success of the therapy. It is estimated that between 20 and 60% of schizophrenic patients are currently treated with two or more drugs for their illness [4]. Since schizophrenia is a very complex, articulated syndrome, different drugs are usually able to control just a part, or some aspects of the overall symptoms; hence the need for polypharmacy. Of course, this situation becomes even more complicated and worrying for elderly patients, who are usually subjected to pharmacological therapies for other severe illnesses as well as for the psychiatric disorder. Regarding the therapy duration, psychiatric disorders are eminently chronic. What is worse, current treatments are not resolutive of the underlying problem, nor an etiologic agent is currently known. As a consequence, lifelong treatment with one or more drugs is relatively frequent [5]; periods of remission, followed by one or more relapses, are quite common as well [6]. Minimum therapy duration is measured in months or years, not in weeks.

Many side effects of antipsychotic drugs are well known and readily taken care of during the treatment (*e.g.*, extrapyramidal symptoms); however, a few are still kept in the background and not completely acknowledged or understood. Perhaps the most important of these latter effects is metabolic syndrome (MetSyn). MetSyn is a chronic multifactorial disease related to several conditions that have the common trait of increasing the probability of a cardiovascular event. The most important conditions involved in MetSyn are diabetes, central or visceral obesity, hypercholesterolemia, hypertriglyceridemia and hypertension. The red line that connects these conditions is a metabolism imbalance associated with an insulin resistance state and an activation of the sympathetic nervous system [7, 8]. Since cardiovascular events are the leading cause of death and disability in the world's

population, it is easily understood how MetSyn could well be one of the most important diseases to attract the attention of clinicians and researchers alike. Criteria for the differential diagnosis of MetSyn, both epidemiologically and in clinical practice, have been laid out in 1999 by the WHO [9], in 2001 by the American Medical Association (in the National Cholesterol Education Program – NCEP – III definitions) [10] and in 2006 by the International Diabetes Federation [11].

A 2004 study based on prospective European cohort studies (more than 11,000 subjects) found a MetSyn prevalence of 15.7% for men and 14.2% for women [12]; since this study excluded diabetic patients, its results are probably underestimating the prevalence. Other papers underline that, due to the multiplicity of symptoms and measurement methods, it is very difficult to obtain reliable prevalence data and to compare different populations [13]. For example, in 2003 a discrepancy of 13% (13.6% *vs.* 26.6%) between the WHO and NCEP-III criteria was reported for the prevalence of MetSyn in Mexican subjects; even excluding diabetic patients, this discrepancy was largely maintained (9.2% *vs.* 21.4%, respectively). However, most studies agree that MetSyn prevalence increases with age: In the year 2000 in the USA, MetSyn prevalence ranged from 6.7% for patients aged 20-29 years to 42% for those aged more than 70 years. The age-adjusted prevalence was 23.7% [14].

Metabolic Syndrome in Psychotic Patients

Obviously, most patients suffering from schizophrenia are treated with some form of pharmacotherapy. As a consequence, it is difficult to separate the direct effect of the disorder on patients' health from that of the medications. Anyway, recent studies on the prevalence of MetSyn in schizophrenic patients are really alarming. About 55% of 252 Dutch patients were found to meet IDF criteria for MetSyn [15]; in a 10-year retrospective study on 174 Malaysian patients, 36% developed metabolic syndrome, 23% were hypertensive and 28% were diabetic, but 100% of them had significantly increased weight, body mass index (BMI), fasting blood sugar and blood pressure [16]. These prevalence data are higher than those of the general population, and should be an important source of alarm for clinicians during the therapy. Nowadays, it is widely acknowledged that antipsychotic therapy can have important, negative effects on the onset of MetSyn.

The Role of Therapeutic Drug Monitoring in Metabolic Syndrome Prevention and Treatment

The frequency and severity of MetSyn can often be correlated with chemical-clinical parameters, in particular with the plasma levels of the antipsychotic medication or some of its metabolites. This positive correlation between plasma

CHAPTER 2

Insulin Therapy and Foetoplacental Endothelial Dysfunction in Gestational Diabetes Mellitus

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Abstract: Gestational diabetes mellitus (GDM) is a condition characterised by glucose intolerance first diagnosed in pregnancy. The first line of treatment for women diagnosed with GDM is diet control (GDMd). However, some of these women even after diet persist continue showing hyperglycaemia. The second line of treatment is insulin therapy (GDMi). The latter protocol is reported to be effective in restoring glycaemia of the mother and the baby at birth. However, it is difficult to reach a consensus between the variety of protocols for insulin therapy since it depends on several factors including the population studied, ethnicity, among others. GDM*d* associates with deleterious effects on the foetoplacental vascular function, mainly due to endothelial dysfunction. These alterations regard with alterations in the L-arginine/nitric oxide signalling pathway, as well as in the expression of insulin receptors A and B, and insulin response. More recent studies suggest that c-Jun N-terminal kinase 1–mediated insulin resistance may result from increased endoplasmic reticulum stress in this type of cells from the human placenta. Interestingly, the insulin therapy is a protocol that does not restore the dysfunctional endothelium as seen in GDM*d*. Indeed, insulin therapy may associate with additional deleterious effects on the mother, the placenta and foetus, and the newborn in GDM. In this chapter, we summarised some examples of the wide variety of protocols for insulin therapy and the

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potential consequences of this protocol on the foetoplacental unit and the neonate from women with GDM.

Keywords: Diabetes, Diet, Endothelium, Endoplasmic reticulum stress, Gestational diabetes, Human, Insulin, Insulin therapy, Placenta.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance first recognised during pregnancy that is not overt diabetes [1]. The worldwide prevalence of this condition ranges from 6–20% of pregnant women [2, 3]. GDM shows with endothelial dysfunction and altered insulin signalling in the foetoplacental vasculature [4 - 10]. GDM is a disease of pregnancy that not only alters maternal metabolic parameters [11, 12] but also results in adverse foetal and newborn outcome. Worryingly, newborns to GDM pregnancies are prone to developing obesity and type 2 diabetes mellitus (T2DM) in adulthood [13 - 16].

Pregnant women diagnosed with GDM are first enrolled in a protocol including a controlled diet with regular glucose checking and physical activity (hereafter referred to as GDM*d*) [17]. The percentage of women with GDM that achieve suggested glycaemia values (*i.e.* fasting: ≤95 mg/dL (5.3 mmol/L), 1 h postprandial: ≤140 mg/dL (7.8 mmol/L), 2 h postprandial: ≤120 mg/dL (6.7 mmol/L)) [18] by changing their lifestyle is ~75% [1, 5, 14, 17, 19]. Women following a controlled diet but do not reach the recommended glycaemia values are referred to insulin therapy (*i.e.* GDM*i*) [1, 5, 20, 21]. Interestingly, insulin therapy in pregnant women with GDM seems to be equally efficient as diet [21]. It is reported that even when insulin therapy normalises maternal and newborn glycaemia the harmful effect of GDM on the placenta function and the neonate metabolic state persist [5, 22, 23]. Thus, other factors than plasma D-glucose may be involved in the effects of GDM on vascular function in the mother, the foetus, and the newborn [23]. One of the general proposed mechanisms that could explain this phenomenon include a metabolic memory as a phenomenon triggered by a short-term foetal exposure to high D-glucose or oscillating D-glucose level before and during GDM treatment [24].

Several metabolic alterations are seen in the foetoplacental vasculature in GDM, including abnormal metabolism of the endogenous nucleoside adenosine or the cationic amino acid L-arginine, and altered synthesis of nitric oxide (NO). These alterations are crucial in the regulation of the vascular function since these molecules are active vasodilators acting in concert in the placental vasculature in this disease of pregnancy [8 - 10]. Additionally, GDM associates with imbalanced

unfolded protein response (UPR) leading to a state of endoplasmic reticulum (ER) stress. In ER stress, various factors are involved in the modulation of key phenomena that regulate the endothelial function. One of these altered signalling mechanisms is an increase in the expression of c-Jun N-terminal kinase 1 (JNK1), which associated with inhibition of insulin signalling [25]. Whether defective insulin actions in the foetoplacental vasculature in GDM are due to alterations in these mechanisms is unclear. In this review we summarised the current evidence about the treatment with insulin (*i.e.* insulin therapy) in pregnant women with GDM and the potential involvement of insulin signalling on the foetoplacental tissue.

Insulin Therapy in Gestational Diabetes Mellitus

The main goal of insulin therapy in GDM is to reduce the plasma glucose level to a normal range close to the glycaemia seen in pregnant women with a normal pregnancy. The final expected outcome is avoiding hyperglycaemia-associated maternal and foetal complications [5, 21, 26]. Several criteria are reported and used to decide the enrolment of pregnant women with GDM on a diet protocol or insulin therapy [5, 17, 21 - 23]. Individual studies suggest glycaemia values over which the insulin therapy should start. The values vary between 5.2–5.6 mmol/L (94–101 mg/dL) at fasting and between 6.6–7.9 mmol/L (119–142 mg/dL) after 2 h postprandial depending on the studied population [22, 27 - 29]. Efficiency of insulin therapy is expected to reach glycaemia values between 3.3–5 mmol/L (60–90 mg/dL) at fasting, 3.3–5.8 mmol/L (60–105 mg/dL) pre-prandial, 6.1–7.2 mmol/L (110–130 mg/dL) at 1 h post-prandial, 5.0–6.7 mmol/L (90–120 mg/dL) at 2 h post-prandial, and 3.3–6.7 mmol/L (60–120 mg/dL) at bedtime, with glycosylated haemoglobin A_{1c} (HbA_{1c}) within a normal range (≤6%) [30]. Unfortunately, one of the main conclusions recently reported for 7381 women with GDM proposed that there are not enough high-quality results to offer significant differences for health outcomes after using insulin in pregnant women with this condition [21, 23].

Protocols of Insulin Therapy

Insulin therapy in pregnant women with GDM refers to the use of neutral protamine Hagedorn (NPH) insulin. In general, a certain dosage of insulin should include 2 to 4 administrations daily. The rapid-acting insulin analogues lispro and aspart are continuously administered in patients that check their blood glucose level regularly and use glucose monitoring devices [31] including patients with type 1 diabetes mellitus (T1DM) [32]. Under this approach the insulin dosage is adjusted according to the variations of the glycaemia during the day. However, several different approaches showed that a proper decision for the administration

CHAPTER 3

Insights on Diabetes, Oxidative Stress and Antioxidant Therapeutic Strategies

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Abstract: Diabetes mellitus (DM) is a serious health concern that affects millions of people worldwide. Despite numerous studies on the topic, the exact mechanisms underlying diabetes progression and its complications is still unclear. Growing evidence suggests that hyperglycemia results in increased reactive oxygen species (ROS) production, leading to oxidative stress which affects and damages various tissues and organs. Oxidative stress results from an imbalance between ROS and antioxidants. During cellular metabolism free radicals such as ROS and reactive nitrogen species (RNS) are produced, and these free radicals have dual effects (both positive and negative) on nearby tissues and activate several oxidative stress-related signaling pathways. Oxidative stress has been identified as a major player in the pathogenesis of diabetes and its associated complications such as stroke, neuropathy, retinopathy, peripheral vascular disease, nephropathy and lower limb ulceration. Oxidative stress damages the surrounding tissue, and the effects continue for extended periods even after blood glucose concentrations return to normal. Prolonged oxidative stress results in insulin resistance, β-cell dysfunction, glucose intolerance and mitochondrial damage. Antioxidants are a group of enzymatic or non-enzymatic molecules that encounter and neutralize free radicals, thereby protecting the body from oxidative stress. Many exogenous molecules such as antioxidant supplements, vitamins (vitamin C and E) and metal ion chelators detoxify free radicals and maintain physiological levels. A better understanding of the involvement of oxidative stress in the pathogenesis of diabetes could have major therapeutic implications for treatment. An effective approach to treat oxidative stress is by using exogenous drugs that mimic antioxidants. Overall, this chapter highlights the understanding of oxidative stress-related mechanisms underlying the development of diabetes. It also elaborates on antioxidant therapy strategies to diminish oxidative stress and to treat diabetic associated complications.

Keywords: Antioxidants, Catalase, Diabetes, Free radicals, Glutathione, Hyperglycemia, Oxidative stress, Reactive oxygen species, Reactive nitrogen species, Superoxide dismutase.

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1. INTRODUCTION

Diabetes mellitus (DM) is a lifelong chronic, metabolic, non-communicable disease (NCD) characterized by prolonged hyperglycemia due to impaired insulin secretion/utilization and insulin metabolism, and is associated with defects in the metabolism of carbohydrates, lipids and proteins. Complications associated with DM vary from person to person and are determined by an individual's health and lifestyle [1, 2]. Worldwide, approximately 422 million people suffer from DM, and it is one of the most common non-epidemic causes of physical impairment and mortality [3, 4]. Hyperglycemia, as a result of DM, affects the vasculature of various organs such as the heart, kidneys, nerves and eyes. It induces myocardial infarction, diabetic nephropathy, neuropathy, retinopathy and atherosclerosis [5]. These complications lead to further secondary complications and are frequently associated with delayed wound healing and lower-limb ulceration, which commonly lead to amputation.

Hyperglycemia elevates the levels of unstable reactive molecules, better known as free radicals, that interact with biological molecules thereby increasing the peroxidation of carbohydrates, proteins and lipids and ultimately oxidative stress, leading to an exacerbation of diabetic complications. Free radicals are detoxified and rendered harmless by antioxidant defense systems, thus antioxidants are required to fight against oxidative stress and to prevent biological systems from damage caused by free radicals. It would appear that both endogenous and exogenous antioxidants are essential in avoiding pathophysiological complications caused by DM. Diabetes is the main cause for imbalances between reactive species and antioxidants in the biological system. Due to stress, age, genetic factors, immunodeficiency and various cell signaling abnormalities, oxidative stress is further increased. These factors interconnect with each other creating an environment that promotes the pathogenesis of various diseased conditions [6].

2. OXIDATIVE STRESS AND FREE RADICALS

Regulation of the redox state is critical for normal cellular functioning, and aerobic organisms have mechanisms in place by way of antioxidant systems to block and prevent the harmful effects of oxidants. Oxidative stress occurs when there is an imbalance between oxidants and antioxidants. The increased production of oxidant radicals over antioxidants plays a significant role in the progression of DM and its associated complications. These unstable free radicals are capable of damaging biological molecules resulting in glycoxidation, which is the oxidation of sugars, glycoproteins and glycolipids, and DNA hydroxylation [7, 8]. Free radical induced oxidative stress and its complications in the human

body are shown in Fig. (**1**).

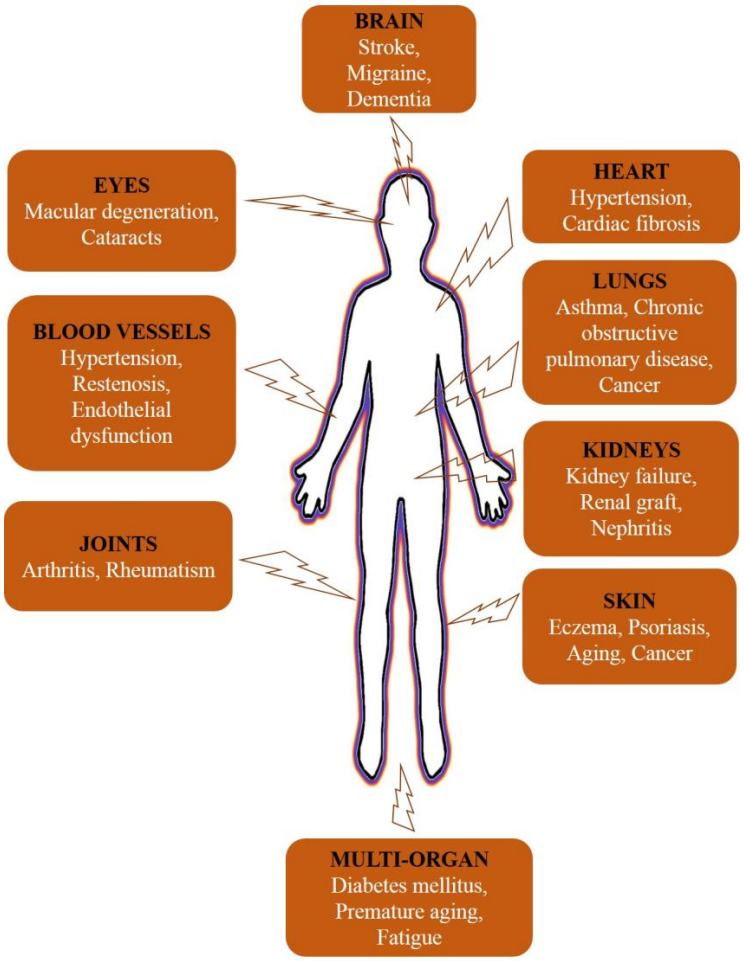

Fig. (1). Free radical induced oxidative stress and its complications in the human body. All most all the organs are affected by oxidative stress; the prolonged oxidative stress ultimately causes various pathophysiological conditions.

Increased free radical formation directly stimulates the immune system, resulting in elevated pro-inflammatory cytokine levels and increased leukocyte infiltration. Increased inflammation and matrix metalloproteinase (MMP) provoke ageing, neurodegenerative disorders, polynephritis and autoimmune disorders. Many metals such as iron (Fe), copper (Cu), cobalt (Co) and nickel (Ni) are oxidized by reactive superoxide anions (O_2^-), resulting in the generation of toxic hydroxyl ions ($^{\bullet}OH$). These types of metallic ions boost free radical generation and augment its

CHAPTER 4

Administration of Nano Drugs in the Treatment of Diabetes Mellitus

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Abstract: Diabetes mellitus (DM) is a metabolic disorder which is the most alarming disease of the modern era, which occurs as a result of lack of insulin secretion or reduced insulin secretion or peripheral insulin resistance. Owing to the lifestyle changes, food habitus and stress, it has now become a pandemic. The incidence of diabetes is rapidly increasing worldwide at a dangerous rate. Over the past 30 years, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality, affecting the youth and middle-aged people. As per the WHO, 171 million cases were reported in 2000 and are expected to increase to 366 million by 2030. DM incidences continuous to rise and pose a serious threat to human health. DM prevalence is increasing due to lifestyle, ethnicity, and age. Insulin has remained the main treatment for Type 1 diabetes and many Type 2 diabetic patients since its discovery, through parenteral insulin administration. Nanoparticles (NPs), which are minute structures ranging from size 1 to 100nm, are being studied for the treatment of various diseases. Considering the versatility of NPs, it also gives hope for better treatment options in diabetes. Different strategies have been used to manipulate insulin by using NPs, such as encapsulated delivery, *etc*. The objective of this chapter is to resolve the issues concerned with the oral delivery of insulin and also to discuss possible routes for the administration and the use of NPs for the best delivery of insulin. Nanotechnology, as a promising field, has opened new ways for the treatment of DM.

Keywords: Diabetes, Nanoparticles, Nanomedicine, Oral therapy, Oral drug delivery.

INTRODUCTION TO THE ADMINISTRATION OF DRUGS BY ORAL ROUTE

The most common route of drug administration is the oral route. Since the gastro-

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intestinal tract has a highly absorptive surface, the majority of the drugs are administered orally. However, there are hindrances to this route as antigen inspecting and processing cells are found throughout the gastrointestinal tract (GIT) which cause immunogenic destruction of any compound administered for a longer period. Hence, nanoparticles (NPs) are used since they can be adjusted to increase or decrease bioadhesion to the mucosa and target the particular site [1]. Since mucus layers provide high protection for NP penetration, the residing time of NP is under trial for better results. Decreasing the residing time of NPs leads to failure to penetrate the mucus and trapping and clearance of medicine [2]. Human insulin is a protein composed of amino acids, it is basically a dimer having A and B chains linked by disulfide bonds [3]. When taken orally, this protein is degraded in the GIT before its action and absorption. To overcome this, it is given subcutaneously for better results.

Nanotechnology is the latest developing science with unique applications. Amazed by its properties, scientists have been extensively researching NPs for the development of newer options in the treatment of different diseases. NPs are minute structures with desirable properties having size 1-100 nm in any dimension. Due to their size, when compared to the larger molecules, they are better absorbed and uptaken by intestinal epithelium. As a result of minor modifications in the NP surface and hydrophobicity, the transport across the intestinal cells can be enhanced. The surface properties can be modified by nonspecific changes on the apical cell surface or by grafting a particular ligand targeting the intestinal cells [4,5] The features highlighted in the chapter are regarding the oral administration of the drugs using nanotechnology to bring about a change in anti-diabetic therapy and to help in the improvement of therapeutic efficacy.

DM is a metabolic disorder characterized by an impairment in the metabolism of carbohydrates, proteins and lipids leading to hyperglycemia resulting from the insufficiency of insulin or insulin resistance. DM is one of the fastest growing diseases expected to increase to about 366 million cases by year 2030 as per the predictions given by the WHO [6]. The etiology of diabetes varies due to the impairment in insulin production, reduced response to insulin by the body or insulin insensitivity [7]. Based on the etiology, it is categorized into:

TYPE 1: It is characterized by the absence of insulin production which is immune-mediated or idiopathic resulting from the destruction of β cells of the pancreas [7].

TYPE 2: It is characterized by relative insulin deficiency and insulin resistance resulting from genetic, environmental and behavioral risk factors (stress and lifestyle) [8, 9].

Also, there is a condition known as gestational DM, occurring from the changes in the hormones and body state during pregnancy (which usually resolves following delivery) [10].

CLINICAL FEATURES OF DIABETES

Described as 3P, the symptoms of both type 1 and type 2 are polyphagia (excessive desire to eat) polydipsia (intense thirst) and polyuria (frequent urination and increased urinary frequency at night). In addition, there may be symptoms resulting from hyperglycemia and glycosuria, like fatigue, muscle cramps, impairment of vision, constipation and candidiasis [11].

Type 1 diabetes lasting for a longer period causes complications like micro and macrovascular diseases of heart, arteries and peripheral blood vessels [12 - 14]. Also, there is a higher risk of atherosclerosis in type 2 patients who also have other risk factors like hypertension, obesity and hyperlipidemia. Renal changes occur in longstanding uncontrolled diabetes, eventually leading to end-stage renal disease. There are also retinal and ocular changes in DM, such as early cataract and diabetic retinopathy, causing significant morbidity. Opportunistic infections, commonly of bacterial and fungal origin, are also common in DM.

Pathophysiology

Hyperglycemia induces physiological and behavioral responses in the body (as a result of hyperglycemia, insulin secretion is increased in coordination with the brain).

Type 1 DM

It arises from the autoimmune destruction of insulin-producing cells of the pancreas by CD4+ CD8+ T cells and macrophages. The features include immune-competent cells infiltrating pancreatic islets in the presence of islet cell-specific autoantibodies. Moreover, there is an association of the disease with the genes of class 2 MHC. Also, there are alterations in T cell-mediated immunoregulation and autoimmunity. 85% of the patients showed islet cell antibodies and anti-insulin antibodies in their blood even before receiving insulin therapy. In addition, there is an impairment or inappropriate response in glucagon which is not suppressed by hyperglycemia [15].

CHAPTER 5

SGLT-2 Inhibitors: An Evidence-Based Perspective

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Abstract: Diabetes mellitus (DM) is one of the most prevalent diseases of modern society. There are several therapeutic options available, but they also have many shortcomings. With the limitations and pitfalls of the existing therapies of diabetes, there is always a need for better drugs. This review is an attempt to give comprehensive details about the merits and demerits of a class of drugs called SGLT-2 inhibitors. SGLT-2 inhibitors act by increasing glucose excretion through urine and do not have any effect on insulin secretion, therefore, the risk of hypoglycemia is less. SGLT-2 inhibitors that are in clinical use are: dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin. Considering the benefits offered by SGLT-2 inhibitors over existing antidiabetics, they deserve an important place in the therapy of T2DM and are found to be useful in T1DM, as studies have suggested previously. Beneficial effects of these drugs extend beyond controlling hyperglycemia, *e.g*., reduction in body weight, reduction in blood pressure and a proven and appreciable reduction in cardiovascular adverse events, maintenance of arterial elasticity and decrease in visceral adipose tissue deposition. The demonstration of such beneficial effects in various clinical studies has established them as one of the important components of antidiabetic therapy. However, in the light of recent safety concerns raised on such molecules would help prescribers to take an informed decision about risks *versus* benefits while prescribing these agents to their patients.

Keywords: Canagliflozin, Dapagliflozin, Diabetes mellitus, Empagliflozin, Hyperglycemia, Mycotic genital infections, Osmotic diuresis, SGLT-2 inhibitors.

INTRODUCTION

Diabetes mellitus (DM) is currently one of the most prevalent diseases in the world. DM presently possesses a big global disease burden with an estimated prevalence of 422 million cases as per the WHO 2016 data and is likely to be doubled by the year 2030 [1, 2].

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Type 2 diabetes mellitus (T2DM) is a systemic disorder with characteristic hyperglycemia that results due to β cell dysfunction and/or insulin resistance in the peripheral tissues or both [3]. In the present scenario with an increase in the population, the incidence of the disease is increasing day by day. Factors such as age, urbanization, and a sedentary lifestyle, are usually common risk factors. The strongest risk for hyperglycemia and insulin resistance can be attributed to obesity which can be further possibly related to subclinical inflammation and increased oxidative stress which culminates into damaging the β-cells in the pancreas [4, 5].

Need for New Targets

Antidiabetic drugs in the treatment of T2DM predominantly act by increasing insulin release from the pancreas, increasing the peripheral insulin sensitivity, negatively regulating glucagon secretion, modulating hepatic glucose production or blocking the intestinal glucose uptake [6]. With the progression of disease in T2DM patients, there is a worsening function of the pancreatic β-cells and/or associated with increased insulin resistance, there is perpetually a persistent need for exploring newer drug targets and treatment strategies to control/cure the disease [7]. Several conventional antidiabetics are available, which come with multiple pitfalls, *e.g.,* many sulfonylureas are associated with variable cardiovascular disease (CVD) risk and mortality outcomes [8, 9]. Weight gain is an issue commonly related to thiazolidinediones and sulfonylurea which can further turn out to be a burden in T2DM [10]. In the newly developed agents, Glucagon-like peptide 1 (GLP- 1) analogues are associated with gastroparesis and risk of thyroid cancer in animal models [11, 12]. The side effects of pancreatitis with GLP-1 analogue were initially concerned, but a recent study has confirmed it to be negative [13]. Earlier, Dipeptidyl peptidase 4 (DPP-4) inhibitors, have been reported to cause nasopharyngitis, upper respiratory tract infection, headache and pancreatitis but recent evidence shows there is no risk of increased infections or pancreatitis with these drugs [14, 15]. The limitations of existing therapies serve as a ground for the development of newer molecules which can help improve glycemic control in T2DM without the danger of hypoglycemia, weight gain, improve β-cell function and decrease complications associated with diabetes [16].

Glucose Handling by Kidneys

In normoglycemic individuals having a mean plasma glucose concentration of -5.5 mmol/L and a normal glomerular filtration rate (GFR) of 125 ml/min/1.73 m^2 in adults, the kidney plays a significant role in glucose homeostasis by reabsorption of about 160–180 g of glucose that kidneys filter each day [17, 18]. A normal individual has a very minute or no glucose in the urine. Kidneys maintain this glucose homeostasis because almost 99% of the filtered glucose gets

reabsorbed by the proximal tubule and returns to the blood. Kidneys also contribute to gluconeogenesis and help to maintain the blood glucose level, both the mechanisms are independent of each other [19]. Sustained hyperglycemia as in DM leads to defects in the absorption of glucose which leads to glucosuria. Hyperglycemia enhances the amounts of glucose filtered and increases the reabsorption of glucose.

Role Of SGLT-2 In Kidneys

About 80-90% of the glucose load is reabsorbed from the proximal tubule by the high-capacity sodium-glucose cotransporter 2 (SGLT2). Whereas, remaining 10–20% glucose is absorbed by SGLT1 which is more in the distal parts of the proximal convoluted tubule (PCT) [20].

SGLT-2 Inhibitors- A Targeted Approach to Curb Hyperglycaemia

History

Phlorizin was the first developed SGLT-2 inhibitor, which was extracted from the apple tree bark in 1835. The development of phlorizin was terminated because of its non-selective nature, its rapid degradation by *lactase-phlorizin hydrolase* in the intestine and poor absorption from the gastrointestinal tract led to its low bioavailability and local gastrointestinal (GI) adverse effects like diarrhea [21]. Similarly, sergliflozin also failed in clinical development because of low bioavailability and short half-life [22].

With the increasing importance of this target, continued researches led to the development of novel selective SGLT-2 inhibitors. SGLT-1 selectivity increases GI adverse effects like diarrhea, so to increase the SGLT-2: SGLT-1 selectivity and to minimize the GI adverse effects, the chemical structure of phlorizin was modified [23]. The C-link between the glucose and phenol moiety in phlorizin was replaced by O-link which imparted greater resistance to β-glucosidase and other enzymes leading to greater oral bioavailability of the newer molecules [24]. The molecular modifications increased the SGLT-2 selectivity and half-life [24].

SGLT-2 inhibitors

The mechanism of glucose control in DM is by blockade SGLT-2 inhibition, which leads to an increase in glucose excretion through the urine. As these molecules do not have any effect on insulin secretion, therefore, the risk of hypoglycemia is less, the loss of glucose leads to calorie deficit, which would decrease the body weight, an effect which is instrumental in DM [25, 26].

SUBJECT INDEX

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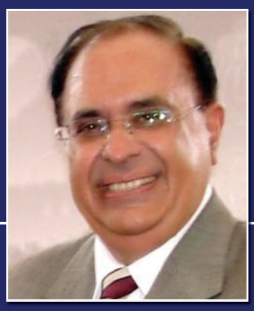

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Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.