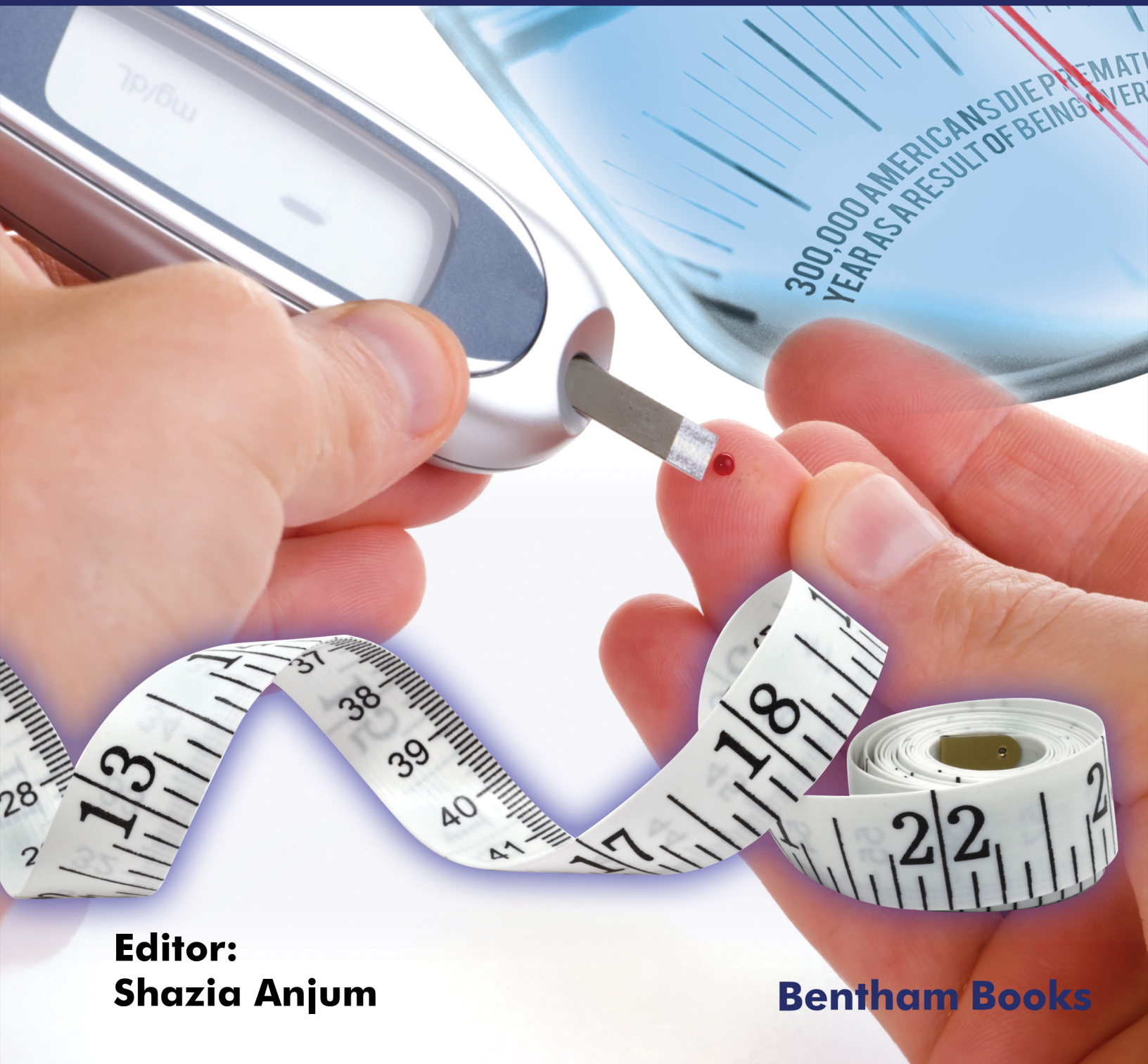
Frontiers in Clinical Drug Research

(Diabetes and Obesity)



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(Volume 7)

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PREFACE

Causes of diabetes are so complex but type II diabetes is directly linked with obesity at any time of your age particularly if you have excessive fats around your tummy. Obesity triggers your body's metabolism which causes fat tissues to release fats into your blood that directly affect insulin response and make you insulin sensitive- that's why obesity causes prediabetes. In order to understand this complex pathological disorder in our body and thereafter solutions to surpass this challenge, volume 7 of our eBook series is dedicated to cutting-edge articles on Diabetes or Obesity. The update can be found in the first chapter of this present volume that non-enzymatic glycation of proteins, lipids, and fatty acids speeds up due to persistent hyperglycemia and eventually causes associated secondary complications in diabetes.

The authors in the second chapter describe the current strategies of new drugs for diabetes management. For example, the development of novel therapeutic groups such as amylin analogs, incretin mimetics, GIP analogs, active peroxisome proliferator receptors, and dipeptidyl peptidase-4 inhibitors and as well as bioactive compounds from herbs.

The third chapter of this series deals with the debatable topic of using aspartame for T2D patients. More research is still needed to establish the pathological role of aspartame use in T2D.

Chapter four of this volume covers the research to investigate the psychological characteristics and adherence of children and adolescents with Type 2 diabetes. A joint venture of the Faculty of Medicine and Faculty of Arts has developed that mapping mental health and various therapeutic procedures, as well as their positive and negative effects, are of paramount importance for both diabetes and obesity.

The fifth chapter of this volume is about the clinical trials of new-generation anti-diabetic and lipid-lowering agents that also have simultaneously cardioprotective effects.

The sixth chapter of this volume describes that the kidneys are a vulnerable target of diabesity. In this chapter, the epidemiology, pathophysiology, and treatment of diabesity–induced kidney disease are discussed. The special focus on the therapeutic targets and pharmacological management of diabesity-related kidney diseases is described herein.

I hope that the current volume of this series will provide updated information about the recent developments in Diabetes & Obesity treatment for interested researchers and pharmaceutical scientists. I would like to thank the editorial staff, particularly Mr. Mahmood Alam (Director Publications) and Ms. Asma Ahmed (Senior Manager Publications) for their dedicated efforts and the hard work.

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CHAPTER 1

Clinical and Diagnostic Implications of Glycated Albumin in Diabetes Mellitus: An Update

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Abstract: In diabetes mellitus (DM), non-enzymatic glycation of proteins, lipids, and fatty acids is accelerated due to persistent hyperglycemia and plays an important role in diabetes and its associated secondary complications. Glycation has the potential to alter the biological, structural, and functional properties of macromolecules. Glycated products (early and late) are both involved in provoking the immune-regulatory cells and generating autoantibodies in diabetic patients. More precisely, human serum albumin is the most abundant protein in circulation involved in glycation. Glycated albumin may accumulate in the body tissues of diabetic patients and participate in its secondary complications. This chapter compiles the studies focused on changes in the secondary and tertiary structure of proteins upon glucosylation. Various *in-vitro* and *in-vivo* approaches involved in investigating such changes are systematically reviewed. Besides, the potential role of glycated albumin in the pathogenesis of diabetes mellitus, as well as its applicability as a diagnostic marker in the progression of the disease, is also highlighted.

Keywords: Hyperglycemia, Non-enzymatic glycation, Glycated Albumin, Protein glycation, Diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder resulting from defects in insulin secretion and/ or action Author, or both. It is characterized by hyperglycemia, polydipsia, glucosuria, and polyuria. In type 1 diabetes, there is a complete absence of insulin, which affects the metabolism of proteins, carbohydrates, and fats. It is a very common autoimmune disease nowadays, afflicting millions of people in India and worldwide also. The disease occurs as a consequence of the organ-specific immune destruction of insulin-producing beta cells within the

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pancreas. However, type 2 diabetes mellitus is the result of the inability of islet beta cells to produce adequate insulin and has become an epidemic. The global prevalence of diabetes in 2011 was 366 million; however, by 2030, it is expected to reach 552 million [1]. Type 2 diabetes mellitus is highly prevalent and accounts for 90–95% of cases. In 21st century, diabetes will be a huge burden due to its increasing global prevalence and higher frequency of chronic complications (nephropathy, retinopathy, neuropathy, and cardiovascular disease), affecting various tissues, difficulty in controlling the disease, and its high cost. During diabetes, persistent hyperglycaemia leads to non-enzymatic glycation of various proteins such as haemoglobin, proteins of the erythrocyte membrane, insulin, human serum albumin (HSA), high and low-density lipoproteins, IgM, IgG, collagen, and histones [2, 3]. Proteins are glycated when glucose is chemically bound to amino groups of proteins without the help of an enzyme, which many structural and conformational changes in protein and proceeds to various micro and macro complications in diabetic patients [4].

Non-enzymatic Glycation

Prof. Louis Camille Maillard gave Millard reaction after his own studies describing the brown colour formed while heating carbohydrate and amine mixtures. It was first described during the early 20th century. Non-enzymatic glycation is a common chemical modification that involves the condensation of a carbohydrate's aldehyde group with either the epsilon group of lysine, hydroxylysine, side chains of arginine, cysteine, and histidine residues [5] or the alpha-amino group of a protein's N terminal amino acid [6]. Only open forms of sugars react with proteins, and a labile aldimine (Schiff base) is formed in a few hours by attaching protein amino group with sugar *via* nucleophilic attack. This product is reversible and can go back to glucose and protein again, or it can form ketoamine, which is slightly reversible. Further, this can undergo intermolecular rearrangement through acid_base catalysis to form 1_amino_1_deoxy fructose (fructosamine), a more stable early glycated product named amadori product in a few days. Both Schiff base and amadori products *in vivo* predominantly exist in the cyclic form [7]. Further, the stable amadori product gradually evolves to a heterogeneous population of fluorescent adducts with new cross-links, which are called advanced glycation end products (AGEs) by irreversible chemical reactions involving oxidation and fragmentation [8] (Fig. **1**). Thus, by subsequent degradation of amadori products and the fragmentation of Schiff base, alpha dicarbonyl compounds and alpha-keto aldehydes formed, respectively (Fig. **2**) [9]. Throughout the 1980s and 1990s, a large body of evidence has implicated that AGEs are mediators of various complications of diabetes and aging. The AGEs also interact with various AGE receptors as RAGEs and stimulate signaling pathways that are important to cause long_term complications in diabetic patients.

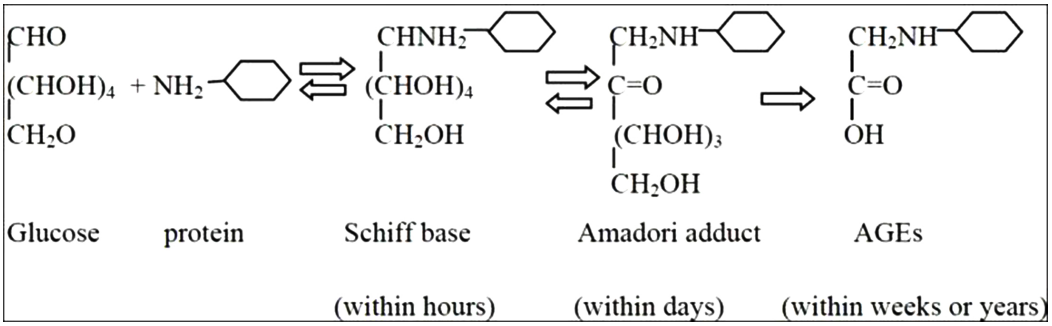

Fig. (1). Non-enzymatic glycation of protein by glucose and production of early and late glycation product. [Source; (Km Neelofar *et al*, 2015).

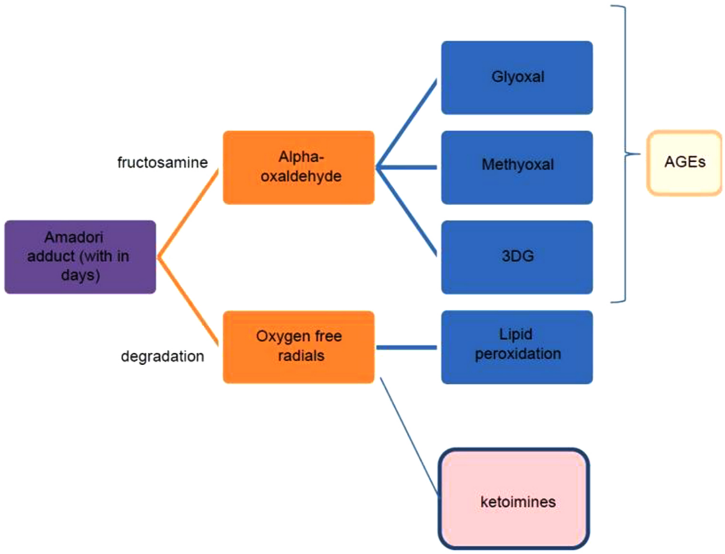

Fig. (2). Amadori adduct fate (Km Neelofar *et al*, 2015).

Non-enzymatic Glycation in Diabetes

Recent studies demonstrate that non-enzymatic glycation is accelerated during hyperglycemia, and its products are aggressively involved in the pathogenesis of diabetes. In diabetes, persistent hyperglycemia leads to non-enzymatic glycation of various proteins such as hemoglobin, proteins of the erythrocyte membrane, insulin, IgG, IgM, human serum albumin, high and low-density lipoproteins, collagen, and histones. Non-enzymatic glycation is also found in normal conditions, but in diabetes, it is increased [10]. Glycated serum proteins consider a marker for hyperglycaemia in diabetes mellitus. Our research studies have shown that early glycation products induced significant changes in albumin structure and function [11]. Glycated proteins are involved in disease pathogenesis by

CHAPTER 2

Current Strategies of New Drugs for Diabetes Management

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Abstract: Several aspects need to be explored in drug therapy for diabetes patients. Some specific glucose-reducing medicines are present, while other medicines are associated with unintentional changes in hyperglycemia. Diabetes is a developing epidemic that has caused significant socioeconomic problems in several countries throughout the world. Despite scientific discoveries, greater healthcare services, and higher literacy rates, the disease continues to plague many industries, particularly developing countries. The current trends show an increase in premature mortality, which threatens world prosperity. Experimental and technical improvements have been made in sulphonylureas, alpha-glucosidase inhibitors, biguanides, and thiazolidinediones, all of which are beneficial in lowering glucose levels. The latest drug research techniques have led to the development of novel therapeutic groups such as amylin analogs, incretin mimetics, GIP analogs, active peroxisome proliferator receptors, and dipeptidyl peptidase-4 inhibitors as targets for future diabetes therapy medications. Furthermore, drug development and detection for diabetes treatment have been revolutionized by identifying and investigating bioactive compounds from herbs. This chapter discusses vital fields of clinical diabetology regarding opportunities for stem cells and nanotechnology as next-generation therapies, with an emphasis on evolving developments and reviews why plant-derived products are reliably common for treating and managing diabetes.

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Keywords: Diabetes, Emerging Trends, Herbal Formulations, Glucose-lowering Drugs.

INTRODUCTION

Diabetes mellitus (DM) is a complicated metabolic condition identical to elevated blood glucose levels or hyperglycemia, resulting from insulin secretion deficiencies, intervention, or both, as displayed in Fig. (**1**). The persistent metabolic disproportion related to this condition places the patient at increased danger of long-standing macro and microvascular problems, leading to repeated hospitalization and complications, including an elevated danger of cardiovascular disease, unless high-quality treatment is provided [1].

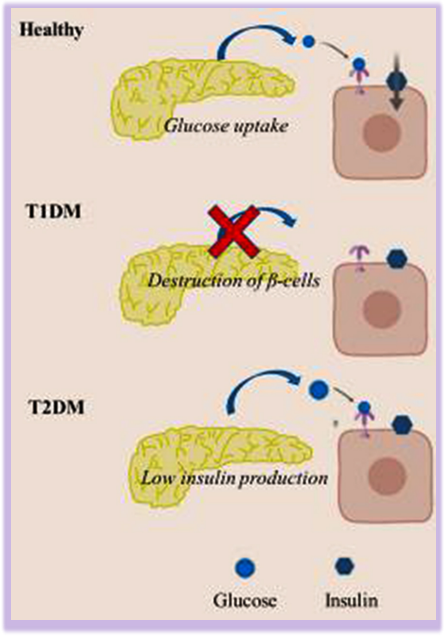

Fig. (1). Diabetes mellitus and its types.

Diabetes is a common and significant global public health concern. According to the International Association of Diabetes (IDF), around 463 million adult diabetes patients were documented worldwide in 2019, which is around 9.3 percent of adults aged 20-79 years, and the number of diabetes patients is still rising [2]. The selection and implementation of glucose control therapy rely on a variety of factors, such as the condition of hyperglycemia, the underlying liver and kidney functions, hypoglycemic risk, the body mass index, capacity to regulate blood

glucose, and drug cost. Type 2 diabetes therapeutics include stimulus for insulin release by GLP analogs such as liraglutide and exenatide [3, 4], insulin injection to balance β-cell defects, inhibition of dipeptidyl peptidase-4 (DPP-4) by sitagliptin, and improved islets survival [5, 6] and islet cell regeneration through islet neogenesis associated protein (INGAP) peptide therapy aiming at islet cell regeneration [7].

Diabetes has become a threat to people's health and is a significant global problem for health and society. A timely clinical concern is diabetes care. Along with diet variety and appropriate workouts, antidiabetic medications are important approaches in the treatment of diabetes. Several hypoglycemic agents, like insulin and insulin analogs, biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 (DPP4), glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, are currently used in the treatment of diabetes [8]. However, almost half of patients with diabetes cannot achieve treatment goals, including glycemic control, even over 10 years [9 - 11]. A big confusion about the suitable choice and screening of antidiabetic drugs because of the various hypoglycemic drugs is the accessibility and the possibility that the same hypoglycemic agent may contribute to different beneficial responses in each individual. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) also propose individualized diabetes attention and precision medicine applications [12, 13]. Providing medication that relates to the genetic knowledge of individuals through pharmacogenomics is one way to achieve precision medicine and direct the proper use of antidiabetic agents [14, 15].

Strategies for the treatment of pharmacologic agents (leptin, β-3-agonists) can increase the resistance of glucose uptake by effectively reducing visceral fat. A function for macrophage fatty-inhibitors (thiazolidinediones, CCR2 antagonists) in treating insulin resistance and vascular disease is also strengthened in different reported studies. Thus, two research lines worth exploring include (i) the interpretation of the visceral fat secretory biology to determine key mediators of the Mets and (ii) drug production for modulative delivery of body fat [16]. Some new kinds of hypoglycemic medicines, such as GLP-1, DPP-IV inhibitors, amylin inhibitors, peroxisome proliferators, and activated receivers, have also been developed and recorded. Any active molecules and bioactive compounds purified from herbs and seeds add to the war on diabetes. These plant components have overturned the production of medicines and led to the discovery of diabetes drugs. Several recent studies have been conducted on important fields of diabetes, focusing more on the statin-based method of diabetes treatment and next-generation antidiabetic stem cell therapy [17].

CHAPTER 3

Diabetes Type II: Should Aspartame be a Concern?

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Abstract: Blood sugar levels have to be controlled by individuals with type II diabetes (T2D) to preserve health and longevity. For such people, artificial sweeteners (including aspartame) are proposed sugar substitutes. In particular, the protection of aspartame has long been the point of discussion. Although it is such a problematic product, T2D patients are advised by many physicians to use it during a managed diet and as part of a treatment modality. Aspartame is 200 times sweeter than sugar and has a marginal effect on blood glucose levels. It is recommended for use so that T2D can regulate carbohydrate consumption and blood sugar levels. Previous studies, however, indicate that aspartame consumption may increase a person's risk of gaining weight instead of losing weight, resulting in intolerance to blood glucose in T2D. By increasing the levels of cortisol, aspartame can act as a biochemical stressor. It may cause systemic oxidative stress by creating excess free radicals, altering the gut's microbial activity, and interacting with the receptor N-methyl D-aspartate (NMDA), resulting in insulin deficiency or tolerance. Due to the lack of reliable evidence, aspartame and its derivatives are safe for T2D yet are still debatable. In the already stressful physiology of T2D, more research is needed to provide indications and raise concerns that aspartame may worsen the prevalence of pathological physiology.

Keyword: Aspartame, Aspartic acid, Methyl alcohol, Phenylalanine.

BACKGROUND

Non-nutritive sweeteners are commonly used by people who want to minimize their average daily calorie consumption, lose weight, and maintain a balanced diet [1]. Non-nutritive sweeteners elicited physiological responses, although inconsistent, but failed to reduce blood glucose levels [2]. Aspartame is a non-nutritive sweetener that has gotten a lot of attention because of its extreme sweetness, 200–300 times sweeter from sucrose [3]. The European Food Safety

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Authority (EFSA) recommends 40 mg/kg.BW/day of aspartame, while the Food and Drug Administration (FDA) recommends 50 mg/kg.BW/day [4, 5]. Health-conscious people and diabetic patients use aspartame products, but their safety is a major concern (Fig. **1**).

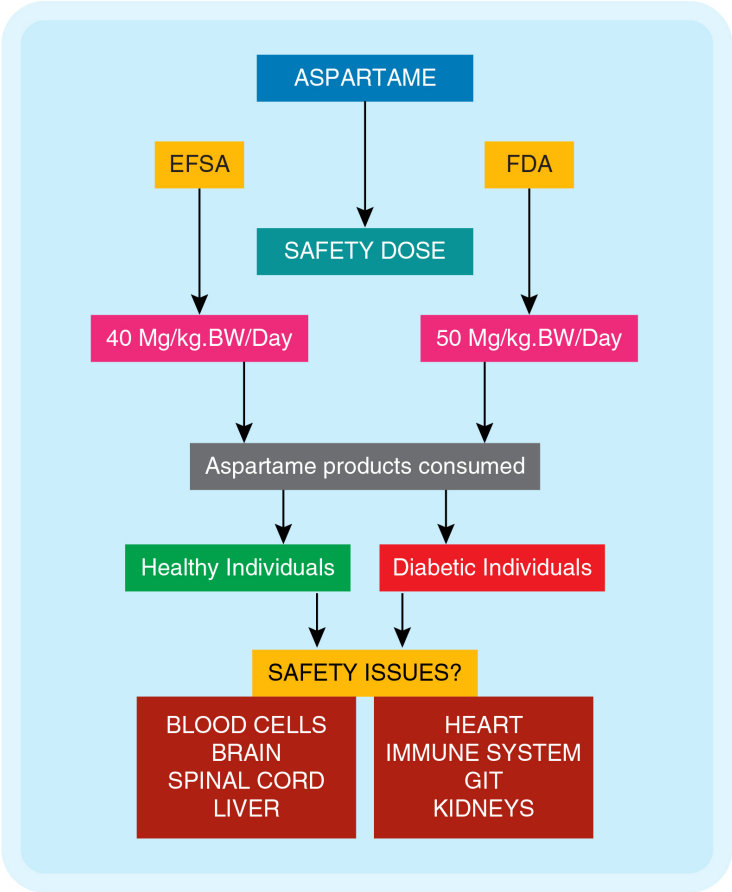

Fig. (1). Safety dosage of aspartame and safety issues.

Diabetes mellitus, *i.e.*, type II diabetes (T2D), is a metabolic disorder in which the pancreas fails to produce sufficient insulin. The body cells fail to respond to the insulin produced correctly. This results in chronic hyperglycemia (high blood glucose levels) and disturbances in carbohydrate, fat, and protein metabolism. In the long run, this may lead to symptoms of this disorder such as retinopathy, nephropathy; neuropathy; and an elevated risk of cardiovascular disease. A balanced diet, daily physical activity, and pharmacotherapy are all recommended for diabetes management. As for many people, the most critical component of the treatment regimen for diabetes is deciding on what to eat.

Aspartame and Weight Management

Although aspartame is suggested to help people lose weight by reducing their food intake and limiting their calorie intake [6], compared to natural sweeteners like sucrose, aspartame may have no impact on food consumption, satiety levels, or postprandial glucose levels. It may also not affect postprandial insulin levels [7]. Although aspartame can help with weight loss by lowering caloric intake when compared to sucrose [6], there is evidence that rats can compensate for the calorie reduction by overeating, resulting in increased body weight and adiposity [8]. It is well known that type 2 diabetes (T2D) and obesity have a troubling relationship [9].

Humans with a higher BMI were found to consume diet carbonated drinks containing aspartame [10, 11]. The increasing use of aspartame (*e.g.*, Diet Coke) in food items has been related to weight gain [12]. Aspartame is thought to disrupt appetite control and contribute to weight gain. It does not stimulate the food reward pathways in the same way that natural sweeteners do but instead encourages sugar craving and sugar dependency, leading to weight gain [12]. For some people, eating dietary foods justifies consuming excess calories from other kinds of food. As a result, it's impossible to say if obesity is linked to the usage of artificial sweeteners (including aspartame) or just to eat too many calories [13].

Weight changes are typically connected to insulin receptors or insulin resistance changes [14]. Increased insulin and glucose levels are linked to weight gain [15]. Chronically high insulin levels are linked to a loss of insulin sensitivity [16], leading to insulin resistance [14]. Insulin resistance is believed to be related to elevated blood sugar, triglycerides, blood clots, insomnia, and cardiovascular and neurological disease [17 - 19].

Although replacing added sugars in foods and beverages with aspartame has the potential to improve body weight and glucose control. The American Diabetes Association and the American Heart Association said in a scientific statement that evidence for their long-term benefits in reducing caloric and added sugar intake is limited.

Aspartame and Glucose Intolerance

Glucose intolerance is commonly accepted as a precursor to T2D [20]. In human [7, 21, 22] and animal studies [23-25], the role of aspartame in maintaining an average blood glucose level is debatable. Although no major variations in blood glucose levels were found [7, 22], it did not sustain an average level. It increased blood glucose levels [23, 25, 26]. Gut enzymes (esterase and peptidase) easily break down aspartame into its three metabolic components: phenylalanine (50%),

CHAPTER 4

Mental Health, Adherence, and Self-Management Among Children with Diabetes

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Abstract: Nowadays, the investigation of mental health is a popular and important topic. Several national and international researchers have been trying to discover the different mechanisms, effects and efficacy among healthy people and patients diagnosed with chronic diseases. It is particularly important to monitor this phenomenon in childhood and adolescence regularly. The developmental processes are further hampered by the physical, mental, social and spiritual development due to the different illnesses. Therefore, it is clear that mapping mental health and various therapeutic procedures, as well as their positive and negative effects, are of paramount importance in diabetes and obesity.

In this research, after analysing the scales of ten international questionnaires, a complex Diabetes Adherence Questionnaire with 58 statements was created, the characteristics and subscales of which (1. Self-management; 2. Emotional feedback - emotional reactions associated with blood sugar level measurement; 3. Social support - parents and family; 4. Social support - peer relationships; 5. Denial of the disease; 6. Positive consequences of adherence; 7. Negative consequences of adherence, pain, discomfort, burden; 8. Relationship with the medical team; 9. Concern about the future) are described in the present book chapter. We also introduce our latest research findings on the relationship between adherence and mental health, covering self-evaluated health and quality of life, satisfaction with life, subjective well-being, vision and depression, stating that positive variables show a positive while negative variables correlate negatively with adherence.

Keywords: T1DM, Adherence, Denial of the disease, Depression,, Diabetes Adherence Questionnaire, Emotional feedback, Negative adherence (the burden of the treatment), Positive adherence, Quality of life, Self-management, Self-rated

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health, Social support (medical team) vision (worries), Social support (parents and family), Social support (peer relationships).

INTRODUCTION

According to the latest statistics of the International Diabetes Atlas, Type 1 Diabetes (T1DM) is one of the fastest-growing global health problems of the 21st century [1, 2]. Epidemiological surveys show that its incidence and prevalence are continuously increasing worldwide, affecting all age groups, regardless of gender and socio-economic background. As diabetes has a significant impact on children's physical health and their mental, emotional, and social development [3, 4], continuous and in-depth exploration of T1DM and related factors is of paramount importance. Chronic diseases such as diabetes require adequate adherence to the treatment protocol, in this case, regular insulin dosage, blood glucose measurement, and proper diet [5]. However, its quality can be supported or hindered by several intra- and interpersonal as well as environmental factors [6]. Adherence, which is 'the individual's behaviour in accordance with recommendations agreed with a health care professional in medication, diet, and lifestyle change', is thus a complex phenomenon that also requires a complex definition to study. However, the questionnaires and other research methods applied in international practice to study adherence do not cover adherence in complexity but focus only on one spectrum. Thus, we aimed to create a complex Diabetes Adherence Questionnaire with 58 statements [7]. In this chapter, after introducing the most relevant literature and previous research findings, we present the above-mentioned questionnaire and the most important findings of these topics.

MENTAL HEALTH AND T1DM

Quality Of Health And Diabetes

The concept of quality of life (QoL) has come to the fore in psychology and medicine in recent decades. The term quality of life, interpreted from a psychological point of view, is based on positive psychology and is associated with the subjective well-being and the affective dimension of quality of life [8, 9]. In addition to the general satisfaction, the cognitive components of the quality of life also mean an area-specific assessment related to individual satisfaction, performance, and health [10]. Quality of life is determined by the subjective assessment of the individuals' life and how good or bad they feel about it. Thus, the multidimensional construct that integrates physical, psychological, and social well-being includes both cognitive and emotional elements [11, 12]. First, the study and improvement of quality of life among children with certain somatic diseases, *e.g*. diabetes, cardiac disease and epilepsy, have appeared. Concern-ing

the quality of life, the subjective assessment of an individual's general health, impairments, and routine functioning are significant [13]. When examining the phenomenon, the aspect described for adults is of outstanding importance, according to which an objective external observer is essential in addition to the child's own judgment, so we cannot rely only on the children's subjective evaluation. The use of proxy reports, *i.e*. data based on the opinion of the external reviewer (mostly the parent), is recommended to get a more precise and reliable picture of the situation of children and adolescents. However, parents are 'not entirely' external and objective evaluators, as they have a unique and close relationship with their children. In the case of psychiatric illnesses, both children and parents have reported poorer quality of life than their healthy peers [14, 15]. It is interesting to note that the children's perceptions of themselves and the parents of their children often differ [16, 17]. According to Cummings [18], a comparison of objective and subjective data is essential, and although a weak relationship between objective and subjective indicators can be demonstrated, none can be neglected when examining children [19, 20].

Several studies have examined the extent to which children agree with their parents' perceptions concerning their quality of life [21, 22]. A stronger correlation has been demonstrated concerning the objective areas (*e.g*., school performance), while a weaker relationship could be detected concerning the child's assessment of the psychological and social situation. Assessing the quality of life of a child can also be influenced by examining the similarities between the evaluation of the parent and the child among both healthy or chronically ill children [23]. Jozefiak *et al*. [22] reported that in the case of healthy children, parents perceive a much more positive status concerning the child's quality of life in almost all areas (except family and friendships) than the children themselves. Hwang *et al*. [24] found that chronically ill adolescents rated their quality of life less poorly than their parents. The reason for this can be that they do not have as much insight into their problems as their parents, so they do not always experience their illness as critical.

Therefore, quality of life is a key factor in gaining a better understanding and more effective treatment concerning people with chronic illnesses. Pediatric health practice also increasingly recognises the importance of integrating illness-specific health-related quality of life (HRQoL) testing into an increasingly holistic approach to disease management [25]. For T1DM, in order to achieve optimal glycemic control, children face serious challenges in their daily lives: having at least 1500 insulin injections within a year, blood glucose measurement with 1000 finger sticks, absence from school of at least 7-15 days due to clinical follow-up examinations, regular contact with the care team, constant self-discipline, and self-control over adherence to the diet. These aspects raise the question of how the

CHAPTER 5

Recent Trials on the Cardioprotective Effects of New Generation Anti-diabetic and Lipid-Lowering Agents

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Abstract: Diabetes and hyperlipidemia are global epidemics that significantly increase the morbidity and mortality of the affected population. Several medications have been utilized to mitigate the risk of diabetes and hyperlipidemia. Insulin, alpha-glucosidase inhibitors, thiazolidinediones have been used for decades as antidiabetic medications. Statins are a cornerstone in hyperlipidemia management. Omega□3 fatty acid supplementation has been used to treat hypertriglyceridemia with debatable effects on cardiovascular outcomes.

In the past decade, multiple new discoveries have revolutionized the management of these disorders. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a class of oral anti-diabetic drugs with a unique mechanism of action. SGLT2 was proven to reduce cardiovascular events, including hospitalization for heart failure, with this benefit extending to patients without diabetes. PCSK9 inhibitors are a new class of antihyperlipidemic that significantly lowers plasma LDL-C on top of the conventional treatment.

In this book chapter, we review the history of diabetes and hyperlipidemia medications and discuss the new classes of lipid-lowering and anti-diabetic medications and their associated cardioprotective benefits.

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Keywords: Anti-diabetic, Cardioprotective, Cardiovascular, Diabetes mellitus, DPP4, Heart failure, Incretin, Lipid, Lipid lowering, Medications, Outcomes, SGLT.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with diabetes mellitus (DM) [1, 2]. Diabetic patients suffer from microvascular and macrovascular complications, with coronary heart disease (CHD) being the most common cardiovascular disease in diabetic patients.

Data from the UK and Canada suggest a 3% to 5% yearly decline in the rates of acute myocardial infarction (MI), stroke, cardiovascular mortality (CVM), and all-cause mortality (ACM) in patients with diabetes since the early 1990s [2]. However, patients with Type-1 Diabetes Mellitus (T1DM) and Type-2 Diabetes Mellitus (T2DM) still experience a significantly higher cardiovascular risk than the general population [2 - 5], highlighting the importance of cardioprotective medications.

Besides glycemic control, taking additional risk factors into account is also an essential component of the patient's management plan. Smoking, higher LDL levels, and a higher body mass index (BMI) are important risk factors that a holistic patient approach should consider, along with controlling plasma glucose and HbA1c levels [2].

The cardiovascular (CV) safety and benefits of novel anti-diabetic medications have been the focus of recent studies due to the heightened mortality risk in this patient population and the scarcity of evidence linking more traditional anti-diabetics to improved hard cardiovascular outcomes, such as cardiovascular mortality and major adverse cardiovascular events (including strokes and MI) [6]. This improvement in outcomes is essential because reductions in surrogate measures, such as HbA1c, are ultimately not as directly relevant to the patient as their risk of death or stroke. In addition, recent advances in lipidology have further added to the clinician's arsenal of lipid-lowering drugs, which also play a vital role in risk reduction in a variety of relatively high-risk patient populations—including those with diabetes. This chapter will discuss the newer formulations of insulin, anti-diabetic, and lipid-lowering medications and summarize each class' landmark trials, a summary of which is illustrated in Tables **1** and **2**.

Table 1. Summary of landmark clinical trials focusing on anti-diabetes medications over the past decade.

Anti-Diabetic Drugs							
SGLT2 Inhibitors							
Trial, Authors, Publication Date,	**Recruitment Period**	**Patient Population**	**Intervention (Drug Name, Dose)**	**Control**	**Sample Size (Intervention vs Control)**	**Main Outcome(s)**	
						Clinically-oriented hard outcomes	**Surrogate Outcomes**
EMPA-REG Trial, Zinman *et al.*, 2015 (4)	2010 to 2013	T2DM with established cardiovascular disease with an HbA1c of ≥7% and less than 10% (If they had received glucose-lowering medications within the last 12 weeks) or 9% (If they had not received such medications within the last 12 weeks)	Empagliflozin, 10 or 25mg	Placebo	4687 vs 2333	− 0.86 HR of CVM, MI or stroke − 38% RRD of CVM − 35% RRD of HF Hospitalization − 32% RRD of ACM	− An HbA1c reduction of 0.24% in the 10mg group and 0.36% in the 25mg group at 206 weeks
CANVAS, Neal *et al.*, 2017(5)	2009 to 2011 and 2014 to 2017	T2DM with an HbA1c of between 7 and 10.5% and a history of symptomatic ASCVD (Aged ≥ 30 years) or ≥2 risk factors for cardiovascular disease (Aged ≥50 years)	Canagliflozin, 100 or 300mg	Placebo	5795 vs 4347	− 0.86 HR of CVM, MI or stroke − HR of 0.73 for albuminuria progression.	− A mean HbA1c reduction of 0.58%.
CREDENCE, Perkovic *et al.*, 2019(6)	2014 to 2017	T2DM with an HbA1c of 6.5 to 12%** and albuminuric CKD (GFR of between 30 and 90ml/min/1.73m^2 in addition to an UACR of between 300 and 5000)	Canagliflozin, 100mg	Placebo	2202 vs 2199	− 0.7 HR of End-stage KD, Creatinine doubling, or CVM, or renal mortality − 0.8 HR of CVM, MI or stroke − 0.61 HR of HF Hospitalization	− Overall mean HbA1c reduction of 0.31% throughout the trial
DECLARE-TIMI 58, Wiviott *et al.*, 2019(7)	2013 to 2018	T2DM with an HbA1c of between 6.5 and 12%, a creatinine clearance of ≥60ml/min, and a history of ASCVD or multiple risk factors thereof.	Dapagliflozin, 10mg	Placebo	8582 vs 8578	− 0.83 HR of CVM or HF hospitalization − No statistically significant differences in MACE − No statistically significant differences in CVM	− Average Mean HbA1c reduction of 0.42%
DAPA-HF, McMurray *et al.*, 2019(8)	2017 to 2018	Heart Failure with NYHA class II-IV and LVEF ≤40%	Dapagliflozin, 10mg	Placebo	2373 vs 2371	− 0.74 HR of HF worsening (Hospitalization or IV therapy) or CVM − 0.82 HR of CVM − 0.83 HR of ACM − Similar effects in both diabetics and non-diabetics	− N/A
VERTIS, Cosentino *et al.*, 2020 (9)	2013 to 2019	T2DM with an HbA1c of between 7 and 10.5%, established ASCVD, and with a significant proportion of HF/EF ≤45% (23.7 and 60.7% respectively)	Ertugliflozin, 5 or 15mg	Placebo	5499 vs 2747	− RR of 0.7 for HF hospitalization − No statistically significant differences in CVM	− N/A

CHAPTER 6

Diabesity and the Kidney

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Abstract: Diabetes Mellitus and obesity, now coined as "Diabesity", is a worldwide epidemic that imposes a huge burden on healthcare and society. Diabesity has been associated with poor outcomes and increased morbidity and mortality. The kidneys are a vulnerable target of diabesity. In this chapter, we discuss the epidemiology, pathophysiology, and treatment of diabesity–induced kidney disease. We specifically focus on the therapeutic targets and pharmacological management of diabesity-related kidney diseases.

Keywords: Chronic kidney disease, Diabesity, Diabetes, Diabetic kidney disease, Kidney failure, Obesity.

INTRODUCTION

Diabetes Mellitus (DM) and obesity, now coined as "Diabesity", is a worldwide epidemic that imposes a huge burden on healthcare and society [1]. Five million deaths in 2015 were attributed to DM in people aged 20–79 years, representing 12.8% of the global all-cause mortality. In 2010, the prevalence of diabetes worldwide was 284 million people, which represented nearly 6.4% of the whole world population and is estimated to reach 642 million by 2040 [2, 3].

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Insulin resistance is the cornerstone of the pathophysiology of diabesity. For every kilogram rise in body weight, there is an increased risk of diabetes by 4.5%. Poor dietary habits, lack of exercise, and other risk factors lead to hyperinsulinemia, insulin resistance (IR), and atherogenic dyslipidemia, *i.e.*, hypertriglyceridemia, low high-density lipoprotein (HDL-C), and increased low-density lipoprotein (LDL-C).

Diabesity predisposes to cardiovascular morbidity and other comorbidities, such as hypertension, endothelial dysfunction, metabolic syndrome, and obstructive sleep apnea. Moreover, diabesity is linked with polycystic ovarian syndrome and various malignancies, such as breast, endometrial, and prostate cancer [3, 4].

The kidney is the most important target of microvascular damage in DM. Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD) worldwide. It is now considered as a "medical catastrophe of worldwide dimension" [5]. Diabetes that affects the kidneys used to be known as Diabetic Nephropathy, however, DKD is now the new term used to encompass a whole spectrum of nephro-pathology induced by DM, since it has been introduced by the Kidney Disease Outcomes Quality Initiative (KDOQI) in 2007 [6].

Genetically speaking, DM can be categorized into a monogenic form, including neonatal and maturity-onset diabetes of the young (MODY), and a polygenic form that includes classic Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). Studies have shown that DKD in T2DM has not been strictly linked to poor glycemic control as it was more likely to develop in patients with a strong family history of cardiovascular disease [7].

Obesity presents a systemic pro-inflammatory state that promotes IR and DM [8]. Obesity-associated nephropathy is characterized by increased kidney weight and hypertrophy of individual nephrons, increased glomerular size, and reduced glomerular density in the cortex, as well as the number of glomerular capillaries [9].

It's always challenging in patients suffering from diabetes and kidney disease to distinguish between those wit non-diabetic CKD [10]. Therefore, despite numerous studies relying on nephro-pathology to differentiate DKD from non-DKD, it remains sometimes difficult to determine the exact incidence of DKD.

In addition to the current advances in understanding DKD, there are some concerns that physicians have regarding optimizing the diagnostic process and future propositions in its management. The natural course of DKD could be divided into five stages: increased glomerular filtration rate (GFR) initially with hyperfiltration, the 'silent' phase, the 'incipient' phase, the 'overt' phase, and

eventually the development of ESKD. Nevertheless, not all patients obviously follow the same course of complications [11].

DKD screening should be done yearly in T1DM starting 5 years after diagnosis and at the time of diagnosis for all patients with T2DM then annually thereafter. Diabetic retinopathy is strongly suggestive of DKD in the presence of albuminuria. To confirm the diagnosis of DKD, albuminuria or reduced estimated GFR (eGFR) should be present in two abnormal measurements at least 3 months apart [12].

The atypical presentation that may denote non-diabetic kidney disease includes sudden onset of low eGFR, rapidly decreasing eGFR, an abrupt increase in albuminuria, development of nephrotic-range proteinuria, development of nephritic syndrome, refractory hypertension, signs or symptoms of another systemic disease, and > 30% eGFR decline within 2–3 months of initiation of a renin-angiotensin system inhibitor [12, 13].

According to the American Diabetes Association, glycemic targets should be tailored to age and other comorbidities. Strict glycemic control, such as hemoglobin A1c (HbA1c) <6.5%, is important for young patients with early diabetes, and those who have not yet developed complications. On the other hand, HbA1c targets up to 8% are allowed for patients with longstanding DM, older age, micro-and macrovascular complications, and limited life expectancy. Similarly, the National Kidney Foundation (NKF)–KDOQI and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend a target HbA1c of about 7% to prevent or delay the progression of the microvascular complications of diabetes. However, patients at risk for hypoglycemia, should not target less than that.

Conventional therapy of DKD includes good hyperglycemic control, control of hypertension and hyperlipidemia, antiproteinuric drugs, and close monitoring for micro and macrovascular complications with appropriate management to slow their progression.

Anti-diabetic medications also have an impact on weight in addition to glycemic control. Recent clinical trials on patients with DKD revealed that Sodium-Glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA) were capable of improving long-term kidney-related outcomes of DKD in the outpatient clinic [5, 14]. Newer agents to treat obesity are emerging, with efficacy and safety being tested in randomized controlled trials.

SUBJECT INDEX

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As recognition of her contributions to science, she has been awarded with 03 International awards like Fellowship from Islamic World Academy of Sciences, Postdoctoral fellowship from Ministry of Culture and Education, Spain and a Young Chemist Award from Third World Academy of Sciences, Italy. She also has several national awards on her credit.