SMART INSULIN: A TOOL FOR EFFECTIVE MANAGEMENT OF HYPOGLYCEMIA AND DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus management is associated with the episodes of hypoglycemia. The hypoglycemia complications associated are higher in elderly and also in some cases of type 1 diabetes subjects. Furthermore, prolong insulin deficiency and longer disease duration increase the risk of hypoglycemia in type 2 diabetes mellitus. Diabetes and its associated complications is the possible cause of morbidity and mortality worldwide. This calls for a resolute action in part of its therapeutic potential. To curb the increased episodes of diabetes and its associated complications, cost-effective and minimal tedious interventions are needed for its efficient management and to slow down its rate of prevalence. The epidemiological analysis of diabetes mellitus episodes enables the researchers to develop the smart insulin. Smart insulin is the best option to minimize the episodes of hypoglycemia and diabetes associated complications. Besides associated micro-vascular and macro-vascular complications with diabetes, hypoglycemia is among the most important complication in patients relying on insulin action. It is commonly prevalent in elderly population, type 1 diabetic subjects and with those having co-morbidities. Subsequent episodes of hypoglycemia may lead to even deaths. Smart insulin is also known as glucose-responsive insulin that is being designed on the situation and need. It automatically turns on when the glucose level reaches to maximum and, it turn off when glucose level reaches to normal. This insulin could make a remarkable history and ensure for a perfect glycemic control throughout the life span. The smart insulin working depends on the principle of sensing of glucose. When the

concentration of glucose is low a signal goes to some binding element having biodegradable material that attached to insulin molecules and prohibits its action. During high glucose concentration the binding element attached to insulin detached and enables the insulin to perform its function.

KEYWORDS: Diabetes mellitus; hypoglycemia; smart insulin.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders with multiple aetiologies characterized by hyperglycemia along with impairment of carbohydrate, fat and proteins metabolism. It results from an imbalance of insulin secretion, insulin action or both. Hyperglycaemia in diabetes is associated with micro vascular disturbances and dysfunction of eyes, kidneys, nerves and heart together with an increased risk of macro vascular disease. Statistical data clearly signifies that 63% global deaths (36 million) were caused in 2008 by four major NCDs; diabetes, cancer, cardiovascular diseases and chronic respiratory diseases.[1] It is also estimated that by 2020, NCDs mortality will be increased globally by 15%, with 20% in low to middle-income countries.[2] Alcohol consumption, tobacco smoking, unhealthy diet, and inactiveness may lead to four common metabolic conditions; high blood pressure, obesity, hyperglycemia along with raised cholesterol level. The criteria of diagnosis of diabetes mellitus are defined by guideline of by American Diabetes Association (ADA).[3]

Classification of Diabetes Mellitus

The first globally accepted classification of diabetes mellitus was published by World Health Organization in 1980,[4] modified in 1985.[5] The American Diabetes Association (ADA) categorized diabetes in varied classical forms to differentiate individuals with diabetes mellitus.

(a) Type 1 diabetes mellitus

Type 1 diabetes accounts for only 5-10% of diabetic people. Previously this form of diabetes was popularly known as insulin dependent diabetes, juvenile onset diabetes results from destruction of pancreatic beta cells via the cellular mediated autoimmune mechanism. The prime participants for this destruction include auto-antibodies to insulin, GAD65 and tyrosine phosphatases IA-2. Islets of type1A diabetic patients' overexpress class I HLA antigens, rarely class II HLA molecules. The HLA alleles i.e. HLA- DR/DQ may either predispose or be protective. The rate of destruction of islets cells varies from high children to slow adults.

Ketoacidosis may be the first symptoms that appear in diabetes patients with this class. Other classical symptoms include mild or severe hyperglycemia followed by infection and other stress.

(b) Type 2 Diabetes mellitus

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes (>90-95% of total diabetic patients) and currently a major cause of morbidity and mortality. T2DM is generally viewed as a clinical syndrome with variable phenotypic expression (β- cells insufficiency and insulin resistance) however, in most instances, the exact cause seems to be polygenic in nature and is yet unknown. The complexity of the pathogenesis of T2DM reflects the heterogeneous genetic, pathologic, environmental and metabolic abnormalities that exist in the different patient, but the ultimate expression of the hyperglycemic state involves some combination of impaired insulin secretion from the β-cells of pancreas, insulin resistance and increased glucose production. People with this diabetes form are insulin resistant.[6] Nevertheless, such patients with this form of diabetes are at high risk of development of macro-vascular and micro-vascular complications.[7] The majority of patients with this form of diabetes mellitus are obese thereby causing insulin resistance.[8] Those patients who are not obese may represent fat deposition in abdominal region changing into central obesity.[9] Ketoacidosis in association with infections is frequently associated with this form of diabetes.[10]

(c) Maturity Onset of Diabetes in Young

Several forms of diabetes mellitus may be linked up with monogenic defects in beta cells function, characterized by the onset of mild hyperglycemia at an early stage (>25 Years). They have usually inherited autosomal dominant pattern. This form of diabetes referred to as maturity onset diabetes of young (MODY) and is associated with impaired insulin secretion and insulin action.[11] Abnormalities at chromosome 12 genetic loci have now been characterized and are closely associated with hepatic nuclear transcription factor HNF1 alpha.[12] Another form is linked with mutations in the glucokinase gene at chromosome 7p that in turn impairs insulin secretion and glucose-6-phosphate metabolism.[13] A recent variant in IPF-1 mutations have been contributing to pancreatic agenesis.[14] Genetic inability to convert proinsulin into functional insulin have identified in several patients due to inherited autosomal dominance.[15] Similarly, mutations were found in insulin molecules along with impaired insulin receptors.[16]

(d) Gestational Diabetes (GDM)

Gestational diabetes is glucose intolerance resulting in hyperglycemia with onset or first recognition during pregnancy. After deliberations in 2008-2009, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) including American Diabetes Association (ADA) recommended that high-risk women found to have diabetes mellitus at their prenatal visit with standard diagnostic criteria, receive a diagnosis of overt, not gestational diabetes. Insulin resistance may be the probable cause for GDM, as pregnancy hormones (placental) along with other unknown (fat depositions) factors binds with insulin receptors causing insulin resistance.[17]

Epidemiology of Diabetes Mellitus

(a) World Scenario

The global prevalence of diabetes mellitus in the adult population in 2015 by International Diabetes Federation (IDF) estimates that almost 415 million people suffer from diabetes mellitus with owning a prevalence rate of 8.3 %. North America and Caribbean region with a higher prevalence rate of 11% (44.3 million people). Western Pacific has 153.2 million diabetes population with a rate of 8.6%. According to IDF, out of 12 people, 1 is diagnosed with diabetes and 1 out 2 people has undiagnosed diabetes.

The results of the World Health Organization (WHO) in the past decade have seen a march in the prevalence of worldwide diabetes from 100 million a decade ago to 135 million in 1995, 151 million by 2000, and a projected numbers of 221 million by 2010. In 2011, IDF set the figure at 366 million (8.3%) that will rise to 552 million (9.9%) by 2030. As per current scenario of diabetes prevalence, only one-quarter of the rural area is suffering from diabetes compared to the urban area of Bangladesh, Bhutan, India, Maldives, Nepal and Sri Lanka.[18]

(b) Indian Scenario

Diabetes mellitus in India shows the scary value of >62 million diabetic individuals.[19] In the year 2000, India topped the outmost position with 31.7 million people with diabetes mellitus among other countries around the globe followed by China (20.8 million) and the United States (17.7 million) on second and third position respectively. Wild et al clearly state the prevalence of diabetes mellitus to double globally from 171 million in 2020 to 366 million in 2030.[20] Preliminary results obtained by Indian Council of Medical Research (ICMR), revealed that lower mass of population is affected by diabetes in states of Northern India (Chandigarh 0.12 million, Jharkhand 0.96 million) as compared to Maharashtra (9.2 million)

and Tamil Nadu (4.8 Million).[21] National urban Survey revealed the statistical figure of 11.7% in Kolkata (Eastern India), 6.1% in Kashmir Valley (Northern India),[22] 11.6% in New Delhi (Northern India), 9.3% in Mumbai (West India), 13.5% in Chennai (South India), 16.6% in Hyderabad (South India), 12.4 % in Bangalore (South India).[18] Kashmir Valley has undiagnosed diabetes prevalence rate of 4.25%.[22] The difference in urban and rural prevalence rate of diabetes was reported by the study of ICMR as 2.1% and 1.5% respectively.[23] A later study showed a prevalence rate of urban (8.2%) and rural (2.4%).[18] A study on the prevalence of diabetes in India study (PODIS) also reported the prevalence rate of diabetes in urban and rural population as 4.7% and 2.0 % respectively according to ADA criteria[24] and 5.6% and 2.7% respectively according to WHO criteria.[24]

Economic Burden of Diabetes Mellitus

Diabetes imposes a huge economic and social burden on the national healthcare system accounting for 11.6% of total healthcare expenditure budget of the World 2010 (International Diabetes Federation, 2010). In 2010 diabetes management and treatment need 376 billion USD that will enhance up to 490 billion USD in 2030. A report of International Diabetes Federation (IDF) on the economic status of diabetes published in 2010, described that more than 80% of the worldwide healthcare expenditure spent in World's richest countries. Statistical figures on global healthcare expenditure on diabetes showed that the North American and Caribbean region spend alone USD214 billion in 2010, African region with USD1.4 billion, United States of America with USD198 billion and India with the expenditure of USD2.8 billion. In another report of IDF, North America, and Caribbean Region spent together a sum of USD310 billion.[25,26]

Hypoglycemia: a consequence of insulin

Hypoglycemia can be redefined on the basis of confirmation by measurement of plasma glucose of ≤3.9mmol/L and/or self-reported probable hypoglycemic symptom. Incidence of severe hypoglycemia even requires aid of another helping person to deliver the treatment. Hypoglycemia is a well known common side occurring event during insulin therapy and also remains the leading role in management of glucose control in insulin derived diabetes management. Hypoglycemia in certain cases can be counteracted by behavioral, hormonal and metabolic events. If this episode of hypoglycemia occurs in healthy subjects, the counter mechanism involves a gradual decrease in endogenous insulin release and co-release of glucagon, adrenalin (epinephrine), cortisol and growth hormone. Patients presenting type 1

diabetes completely depends on exogenous insulin and can't reduce the source of endogenous insulin generation during the episodes of hypoglycemia. Hormonal responses in the episodes of hypoglycemia have prominent metabolic effects in normal populations that lead to increased endogenous glucose secretion.

Smart management of hypoglycemia

Smart insulin is basically a combination of biodegradable polymer and insulin. At a moment insulin become insoluble because of component that invited by glucose, and take aside of those components from the hormone allowing it to become active. To control over the arising cases of hypoglycemia rather taking insulin directly via injections. The advantageous scientific technology associated with smart insulin is self regulating release and non release depends on glucose concentration at a specific range to certain level by recognizing plasma – molecular indicator. Smart insulin is also known as glucose-responsive insulin that is being designed on the situation and need. It automatically turns on when the glucose level reaches to maximum and, it turn off when glucose level reaches to normal. This insulin could make a remarkable history and ensure for a perfect glycemic control throughout the life span. The smart insulin working depends on the principle of sensing of glucose. When the concentration of glucose is low a signal goes to some binding element having biodegradable material that attached to insulin molecules and prohibits its action. During high glucose concentration the binding element attached to insulin detached and enables the insulin to perform its function. Insulin unlocks glucose entry to cells that in turn delivers the energy. The flexibility & innovative technology to control & self regulate the insulin secretion as with glucose level high and low smart insulin become a best managing tool over hypoglycemia (low blood sugar).

CONCLUSION

Hypoglycemia is an important limiting factor in strict glycemic management of diabetes mellitus especially in insulin controlled environment. The choice of smart insulin in an effective approach for the management of insulin responsive hypoglycemia in diabetes and maintain good glycemic control.

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