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Mechanisms of Diabetes Mellitus Progression: A Review

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Abstract

This review was tailored on the description, types and progression of diabetes mellitus. Diabetes is a non-infectious disease of sugar metabolism that is characterized by elevated blood glucose concentration above normal level; referred technically as hyperglycaemia. It has been shown that excessive thirst, fatigue, hunger, weight loss, blurry visions, frequent urination constitutes the symptoms of diabetes. The disease has three broad classifications which include; type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes mellitus depending on the underlying factors causing it. For the type 1 diabetes mellitus, insulin is not produced at all duet to deformities of β cells present in the pancreas, in the type 2 diabetes, insulin is produced but not sensitive to glucose which would have helped cells to internalize it while the gestational diabetes is usually in women due to pregnancy. In any case, life-threatening complications may result. The possible mechanisms for unabated diabetes progression may be due chiefly to oxidative-based stress due to the accumulation and activities of reactive oxygen species-induced hyperglycaemia, activation of protein kinase C (PKC), elevated inflow of bio-precursors and substrates in the pathway leading to hexosamine biosynthesis, production of advanced glycation end-product (AGEs), altered polyol pathway flux and altered gene expression leading to beta cell death and reduced insulin secretion. In order to detect and stop its progression to unbearable complications, individuals should look out for these symptoms and go for early medical check-ups and diagnosis so that diabetes mellitus and its attending complications may be averted.

Keywords: Diabetes, Beta cells, Pancreas, Insulin

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Introduction

The term “Diabetes” refers to a collection of metabolic disorders characterized by long-lasting hyperglycaemia beyond acceptable range arising from either the inability of the pancreatic cells to secrete adequate amount of insulin or body cells not sensitive to the insulin produced [1] because it is the sensitivity of cells to the insulin that will make it possible for glucose to get into the cells. Prominent symptoms due to diabetic conditions may include, excessive thirst, fatigue, hunger, weight loss, blurry visions, frequent urination as often noticed in most diabetic persons.

The word “diabetes” originated from Greek and it means a siphon depicting the frequent passage of water (urine) like a siphon. Later, the Latin description “mellitus” meaning sweetened or honey-like was added to it. Combining the two together, the term diabetes mellitus was literarily used to denote a disease condition which was associated with the persistent passage of sweetened urine [2]. The type 2 diabetes mellitus is observed to have up to about 90% of the total cases and the risk rising constantly.

Diabetic conditions usually lead to the impairment of the body’s ability to metabolize food due to the fact that either the pancreatic cells do not make adequate insulin or the body cannot use the available insulin properly. Hypoglycaemia (i.e., low blood glucose level) is most commonly observed in diabetic patients compared to their non-diabetic counterparts, when the body is supplied with excessive insulin amidst too little food, a delayed meal, or excessive exercise [3]. On the other hand, when insulin in the body gets too little amidst high amount of food, or too little exercise, hyperglycaemia (i.e., high blood glucose level) arises. [4]. Stress may also be a contributory factor to hyperglycaemia. Hyperglycaemic state (diabetes mellitus) arises when the glucose (sugar) concentration in blood is beyond 180 mg/dl (10 mmol/l) [5].

Categories of Diabetes

Type 1: It is a type of diabetes mellitus that occurs because the pancreatic cells cannot synthesize and secrete the necessary amount of insulin, reason being that the beta cells have been lost [1]. The paucity of beta cells in this case is as a result of an auto-immune response which caused their destruction [6].

The type 1 diabetes is an autoimmune disease situation in which the beta cells of the pancreatic cells fail to produce sufficient amount of insulin; a hormone that enables cells to internalize and use blood sugar (glucose) for energy [7], thereby reducing its concentration in blood. Consequent upon the failure, the cells become starved of their energy source, especially cells that depend on glucose for energy and in turn there will be excessive glucose concentration in the blood. This is then followed by life threatening conditions of hypoglycaemia and hyperglycaemia [8]. When hypoglycaemia develops, cells do not get adequate supply of glucose and the individual may manifest symptoms such as confusion, loss of consciousness, coma and even death when the situation persist for too long in organs like the brain [9]. Although the rate of β-cell destruction may vary among individuals due to varying genetic and physiological make-ups. The rapidly progressive form of T1DM is majorly encountered in children but may also occur in adults [1].

Type 2: This type of diabetes mellitus starts with insulin resistance, a situation in which body cells become insensitive to insulin and fail to recognize it properly [1], hence failing to respond to it properly. As the disease progresses, a total depletion of insulin may eventually become the case [10]. This type of diabetes was referred to as "non-insulin-dependent diabetes mellitus" or "adult-onset diabetes" in the past. The implicated factor responsible for it may be due to too much body weight or inadequate exercise or a combination of the two [1].

The disease (type 2 diabetes) is a progressive and continuous disease condition chiefly characterized by risks such as stroke, myocardial infarction, microvascular events, and even death due to the resulting hyperglycaemia [11]. The major cause of the disease as has been documented in many literatures is a decline in beta cell function and deteriorating cases of insulin resistance [12]. Clinical manifestations include

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deteriorations in multiple biochemical parameters, including A1C, fasting plasma glucose (FPG), and postprandial glucose level [13]. Here, insulin is produced but cannot function.

Gestational Diabetes Mellitus

Unlike the type 1 and type 2 diabetes mellitus which are pathophysiologic conditions, gestational diabetes mellitus is due to pregnancy, hence only common in pregnant women [14].

In the case of the type 1 type of diabetes, the pancreatic cells do not make any insulin at all, hence it must be taken through injections [1]. While in type 2 diabetes, the cells don't respond normally to insulin (a state called insulin resistance). Consequently, the pancreatic cells are overly stimulated into synthesizing higher amount of the hormone, insulin. As these progresses with time, there is elevated blood glucose concentration thereby paving the way for an onset of the type II due to insulin insensitivity [16]. Gestational diabetes usually disappears after the birth of the baby [19].

Other classifications of Diabetes mellitus include, monogenic defects of β-cell function which is caused by specific gene mutations, has several clinical manifestations requiring different treatment, some occurring in the neonatal period, others by early adulthood**.** Monogenic defects in insulin action: This is caused by specific gene mutations and have features of severe insulin resistance without obesity; diabetes develops when β-cells do not compensate for insulin resistance [1]. In such circumstances, it may be necessary to trace the particular gene that has undergone a mutation before proper ameliorative measures could be administered.

Diseases of the exocrine pancreas: Various conditions that affect the pancreas can result in hyperglycaemia (trauma, tumor, inflammation, etc.)**.** Endocrine disorders can also cause diabetes in diseases conditions with excess secretion of hormones that are insulin antagonists [1]. Hormone-based therapy and protein engineering may be the only way to a solution.

Drug- or chemical-induced: Some medicines and chemicals impair insulin secretion or action, some can destroy β-cells leading to Diabetes mellitus [1].

Infection-related diabetes: Some viruses have been associated with direct β-cell destruction. A situation that may lead to what is referred to as viral-induced or infection-induced diabetes mellitus [1].

Uncommon specific forms of immune-mediated diabetes: This type of diabetes mellitus is associated with rare immune-mediated diseases. Other genetic syndromes sometimes associated with diabetes: Many genetic disorders and chromosomal abnormalities increase the risk of diabetes [1].

The term "Unclassified diabetes" is used to describe diabetes that does not clearly fit into other categories. This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis [1]. The mechanisms of induction and progression of such types of diabetes mellitus may possibly not have been elucidated.

Diabetes Mellitus Progression

This is a set of related diseases characterized by the body's inability to regulate the amount of glucose concentration in the blood, thereby leading to its excessive accumulation in blood. Usually, blood circulation distributes glucose molecules to provide the needed metabolic energy to perform all the body's metabolic functions [20].The liver metabolically processes and converts food substances into glucose [21], sometimes and stores the excess glucose in form of glycogen. Hormonal activities help the body to release glucose molecules into the circulating bloodstream for onward circulation and delivery to cells. Hormones are also involved in regulating the amount of glucose released in the blood, the major glucose-regulatory hormone is insulin. It is produced by the pancreatic cells; the pancreatic cells make up the pancreas; which is a small organ between the stomach and liver [22]. The pancreatic cells also make other important enzymes released directly into the digestive system that helps metabolize food substances. Insulin enables cells to internalize glucose from the

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bloodstream [23], a process that keep blood glucose concentrations in check by ensuring that the amount of glucose in blood does not exceed an acceptable metabolic threshold.

Problems in glucose metabolizing processes such as inadequate or total absence of insulin secretion, defective insulin receptor proteins and glucose transporter proteins, a decrease in peripheral glucose use and defective term known as glucose toxicity which is a gradual, time-related onset of irreversible lesion action due to non-expression of insulin receptor proteins or lack of sensitivity of expressed insulin from the pancreatic beta cells to the excessive glucose concentrations (hyperglycaemia) results in non-physiological and potentially irreversible β-cell damage, defect in glucose metabolizing enzymes leading to their inactivity. Lipolysis (lipid breakdown), gluconeogenesis (glucose synthesis from non-carbohydrate sources), glycogenolysis to release glucose and many other metabolic factors responsible for the imbalance in glucose metabolism or loss of glucose homeostasis such as imposed on the hormonal system resulting to hyperglycaemia (elevated glucose concentration beyond normal level) [24].

Some of the well-studied biochemical pathways and cellular metabolic mechanisms for glucose elevation and subsequent toxicity include glucose autoxidation which resulting from oxidative stress in the presence of reactive oxygen species-induced hyperglycaemia, protein kinase C (PKC) activation, a surge through the hexosamine biosynthesis pathway (HBP), appearance of advanced glycation end-product (AGEs), altered polyol pathway flux and altered gene expression [25].

All the aforementioned biochemical pathways have something in common which is the formation of highly reactive oxygen intermediates (ROIs) or reactive oxygen species (ROS) which in excess amount and on prolonged exposure induce chronic oxidative stress on the pancreatic β-cell number, and causes defective insulin gene expression and insulin secretion as well as increase pancreatic β-cell products [26].

Conclusion

It has already been established scientifically that diabetes mellitus is a disease of abnormality in glucose metabolism involving the destruction of alpha and beta cells of the pancreas resulting to the type 1 and 2 respectively. The danger is that diabetes mellitus can progress to life threatening complications. A number of early warning symptoms have been listed. It is therefore pertinent that individuals look out for these symptoms and go for early medical check-ups and diagnosis so that diabetes mellitus and its attending complications may be averted.

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