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REVIEW

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Genetic factors and the role of pancreatic amylase in the pathogenesis of type 2 diabetes

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Abstract

This review article gives an insight into the genetic factors and the role of pancreatic amylase in type 2 diabetes (T2D). Diabetes is a non-communicable, multifactorial, heritable, complex, and irreversible disease of public health burden with a global prevalence rate of 6.28%, about 6% in sub-Saharan Africa, and 1.7% in Nigeria. T2D is recognized as the ninth leading cause of mortality worldwide. This disease is yet to be diagnosed in a significant number of people who live with it in underdeveloped and developing countries like Nigeria due to the lack of free or subsidized access to health care, especially medical checkups, inadequate health facilities, government policies, and negligence. Consequently, undiagnosed cases of T2D have contributed to the prevalence of this disease and its comorbidities -hypertension and chronic kidney disease. Obesity, age, race and ethnicity, inactivity, family history, underlying illness, and unhealthy diets are prominent undisputable predisposing factors of T2D. Pancreatic amylase is a type of amylase produced in the pancreas, known to hydrolyze starch and prone to mutations, but most of the genetic components, causative polymorphisms, and affected genes are yet unknown. Even as insulin secretion is found to be influenced by the loci, the causation of T2D cannot be inferred. Pancreatic amylase was observed to be the most relevant digestive enzyme, whose role is to bind to glycoprotein N-glycan to activate starch digestion. In a malfunctioning pancreas, little or no insulin is generated to keep the blood glucose at an appropriate level, thereby resulting in T2D.

Keywords Pancreatic amylase, Genetic aberration, Type 2 diabetes, Pathogenesis

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Introduction

Diabetes is one of the earliest diseases to be identified and it was first reported in 1500 BCE by Egyptians as "too great emptying of the urine" [1]. Diabetes is derived from the Latin word diabētēs, which itself is derived from the Ancient Greek term διαβήτης, meaning "a passer through; a siphon." The word "Mellitus" is coined from mellitus (Latin origin), which is translated as "mellite" (i.e., honey-sweet or sweetened with honey). The Latin term is derived from mell-, which is derived from mel, which means "honey" or "sweetness." When Thomas Willis observed the urine of a person suffering from diabetes had a sweet taste (glycosuria), he added the word "mellitus" to "diabetes" to give the condition a name in 1675.

Alarming statistics from the International Diabetes Foundation (IDF) show that there are approximately 537

million adults worldwide who are estimated to have diabetes (1 in 10 adults), and that figure has been predicted to rise to about 643 million in 2030 and 783 million in 2045, respectively [2]. Of the 8.75 million people with Type 1 diabetes in 2022, 1.52 million were under the age of 20. One in every 22 persons in Africa is anticipated to have diabetes, and between 2030 and 2045, that figure has been predicted to climb to 33 million (a 27% increase) and 55 million (a 56% increase). In 2021, diabetes causes 6.7 million mortalities, or one death in five seconds [3].

The National Diabetes Data Group created a consensus agreement in 1979 [4] that standardized the terminology and criteria for diabetes mellitus. One year later, the World Health Organization [5] approved this document. The two main kinds of diabetes were designated as insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) on the basis of their clinical manifestations. An international expert committee issued a report in June 1997 that contained updated guidelines for categorizing and diagnosing diabetes. The World Health Organization (WHO) and the American Diabetes Association (ADA) specialists worked together for more than two years to develop these new recommendations. Type 1 diabetes, type 2 diabetes, other specific kinds of diabetes, and gestational diabetes are the four categories of diabetes mellitus recognized under the new nomenclature system.

The characteristic feature of T1DM (formerly known as IDDM) is beta cell death brought on by the autoimmune destruction of the beta cells of the pancreas leading to a complete lack of insulin. Insulin resistance in cells that typically utilize insulin and an impairment in the beta cell's mechanism for secreting insulin are characteristics of type 2 diabetes mellitus (formerly known as NIDDM) [4]. The most prevalent kind of diabetes is T2DM and patients with this condition are predisposed to hypertension and chronic kidney disease. T2DM is prominent in people that are aged, obese, have a family history of diabetes, and/or living a sedentary lifestyle. As "other specific types," diabetic illnesses with multiple known etiologies are grouped- this classification includes patients with genetic aberrations of insulin action or beta-cell function, pancreatitis, or cystic fibrosis. When pregnant women are diagnosed with hyperglycemia, gestational diabetes mellitus might develop and might only last for the gestation period, although it increases their susceptibility to T2DM over time.

Amylases are enzymes that catalyze the hydrolysis of starch into low-molecular-weight sugars (maltose and dextrin). The three main kinds of amylase- alpha, beta, and gamma each distinctly hydrolyzes the carbohydrate molecule [6]. Humans, animals, plants, and microorganisms all have α-amylase. Microbes and plants have β-amylase. Animals and plants have γ-amylase [7]. While γ-amylase is secreted in the small intestine, amylase is mainly produced by the pancreas and salivary glands in animals. The α-amylase genes are prone to mutations (duplications and deletions), which causes copy number variations in various people. This results in a variety of processes through which various people react to dietary starch, as well as the ensuing blood glucose levels [8].

To lower blood sugar to physiological values, anti-diabetic therapeutic techniques are used, including but not limited to chemotherapies (insulin injections and oral drugs) and lifestyle modifications. Reducing postprandial hyperglycemia is one therapeutic strategy for treating early-stage diabetes. This is accomplished by delaying the absorption of glucose by inhibiting the digestive tract's amylase and glucosidase enzymes, which hydrolyze carbohydrates. Therefore, the inhibitors of these enzymes result in a reduction in the rate of glucose absorption, which in turn reduces the increase in blood glucose that occurs after a meal [9].

For this article, current trends of genetic aberration and the roles of pancreatic amylase in type 2 diabetes mellitus were studied. This research examined several original and review research articles to identify the genetic abnormalities and roles of pancreatic amylase in the pathogenesis of type 2 diabetes and also identify potential therapeutic approaches that target pancreatic amylase in the treatment of T2DM.

Regulation of pancreatic amylase

About 30 enzymes make up the family of glycoside hydrolases known as amylase (EC 3.2.1.1), which can be distinguished from one another by their unique characteristics [10]. Alpha amylase (1,4-α-D-glucanglucanohydrolases) results in nonselective, random endohydrolysis of α-(14) glycosidic bonds in amylose and amylopectin. According to Wild et al. 1954, this amylase generates "limit dextrins" from amylopectin as well as maltose, maltotriose, and higher oligosaccharides from amylose.

There are two isozymes of pancreatic amylase, each of which is approximately 56 KDa in size and has 496 amino acids in length. On chromosome 1, two genes for pancreatic amylase (*AMY2A* and *AMY2B*) exist [11]. According to Brayer, G.D. et al. in 1995, human amylase is made up of three structural domains, this was proofed based on research done using X-ray crystallography [12]. The largest domain is A and it comprises residues 1–99 and 169–404 and forms a core eight-stranded parallel β-barrel with the active site residues- Asp-197, Glu-233, and Asp-300 at one end. A bonded chloride ion interacts with Arg-195, Asn-298, and Arg-337 also in this area. The smallest domain is B (residues 100–168) and it forms a calcium-binding site against the wall of Domain

A's β-barrel. Asn-100, Arg-158, Asp-167, and His-201 are protein groups that interact with calcium. Domain C (residues 405–496) has an antiparallel structure and is only tangentially related to Domains A and B. Moreover, there is a post translational modification of the N-terminal glutamine residue of human pancreatic amylase to generate a stable pyrrolidone derivative that protects against digestion by proteases [12].

Human pancreatic amylase is constitutively expressed, and its activity rises postprandially, resulting in postprandial hyperglycemia. Thus, the regulation of the enzyme's expression and activity is critical to the levels of blood glucose. Joachim et al. 1989 investigated the involvement of glucocorticosteroids in the modulation of pancreatic amylase in rats. They discovered that adrenalectomy reduces amylase activity by 70%, demonstrating that corticosterone directly modulates amylase expression in the rat pancreas.

Giorgi et al. 1984 conducted another study on the effect of dietary content on the regulation of amylase activity. Three groups of rats were fed diets containing 75%, 20%, and 11% carbohydrates, respectively. The amount of amylase mRNA expressed by the rats on a high carbohydrate diet was nine times higher than that of the rats on a low carbohydrate diet and twice that of the intermediate group. Furthermore, amylase mRNA-directed synthesis was 35%, 14%, and 4% in high, intermediate, and low carbohydrate-fed rats, respectively, and a similar trend was observed in the rate of amylase synthesis following [^{3}H] phenylalanine injection (Fig. 1). These findings suggest that dietary changes influence the expression of pancreatic amylase genes at the transcriptional and post-transcriptional levels.

Roles of pancreatic amylase in Type 2 diabetes

Amylase is a Greek word derived from "amylone," which refers to starch. They can be found in the pancreas and salivary glands of humans as well as in other tissues, but in small quantities. During digestion, it cleaves starch into smaller polysaccharides at an interval of 1 to 4 alpha linkages [13, 14]. Key endocrine cells that collectively make up a tiny but significant portion of the pancreas are found in the islets of Langerhans. The key types of the islets include b, a, d, F, and e cells, which release hormones involving grehlin, pancreatic polypeptide, somatostatin, glucagon, and insulin, among others.

Through controlling hormones and, in specific, glucose homeostasis, these cells collaborate to regulate energy metabolism. The majority of the islet volume, or around 70%, is made up of pancreatic B-cells [15], make up the majority of the islets. Lower blood amylase has long been recognized as a sign of diffuse pancreatic degeneration caused by chronic pancreatitis and other severe pancreatic diseases [16].

Decreased serum amylase levels have been linked, according to recent investigations, to metabolic syndrome and diabetes [17–19]. Amylase dysfunction is linked to insulin shortage in people with type 1 diabetes and, fewer times, in people with type 2 diabetes [20–22], as well as the origins of insulin resistance in obese animal models [23, 24]. For an obvious medical diagnosis, it often helps to differentiate between both kinds of serum

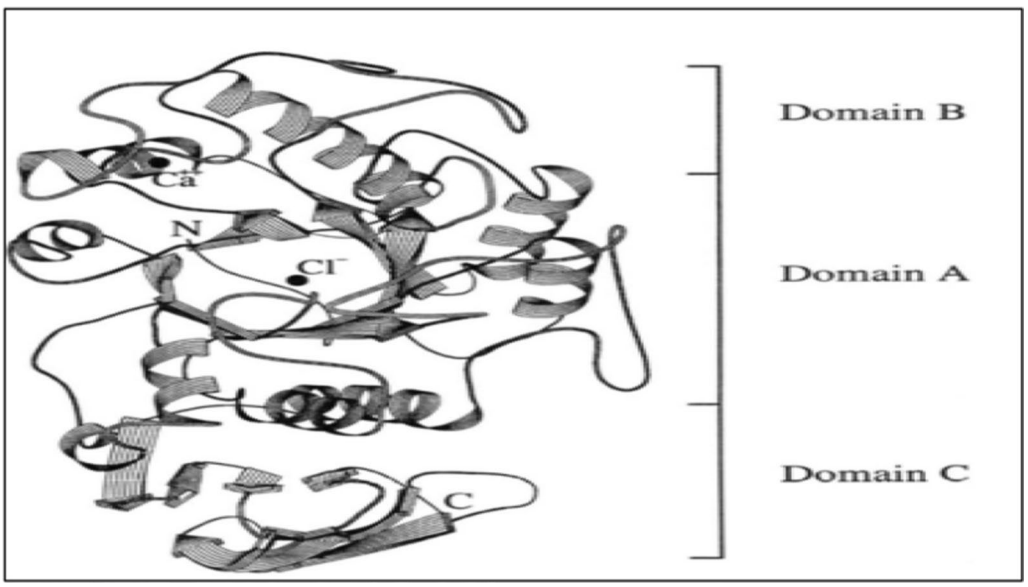

Fig. 1 3D structure of human pancreatic amylase (AMY2A; 56.01 KDa) [12]

amylase because they may be divided into pancreatic-type and salivary-type amylases.

Nevertheless, while pancreatic alpha-amylase is the most essential breaking-down enzyme, evaluating the serum amylase level is helpful in identifying the pathophysiology of many diseases [25–27]. Pancreatic amylase, also known as 1,4-glucan-4-hydrolase (E.C.3.2.1.1), is a significant treatment option for the digestive system. Starch is first hydrolyzed by this enzyme into maltose, which is then further broken down by α-glucosidases into glucose. Therefore, the postprandial hyperglycemia glucose surge is tightly controlled by the delay in starch hydrolysis brought about by lowering the activity of α-amylase.

Without insulin, glucose cannot get into the cell, which is the predominant type of energy that cells need. When the pancreas is functioning normally, the right quantity of insulin is created to deliver glucose to the cells. However, when the pancreas is abnormal, either a small amount of insulin is produced, or the insulin that is produced does not reach the bodily cells which results in an insufficient level of blood glucose and T2D [28]. Diabetes is a well-known group of endocrine diseases that develop as a result of a relative lack of insulin, a hormone, or disruptions in how it interacts with an organism's cells, and eventually cause an ongoing spike in the amount of glucose in the blood and the development of hyperglycemia [12]. The human pancreatic -amylase's function is to attach selectively to glycoprotein N-glycans in the brush-border membrane to initiate starch digestion, but at high concentrations, it dramatically reduces SGLT1's ability to take up glucose [27]. The suppression of HPA by ligands, which lowers postprandial blood glucose levels, has recently been recognized as one of the scientifically validated management strategies for type 2 diabetes [28, 29].

Genetic factors of pancreatic amylase leading to type 2 diabetes

The amylase gene, like several other human genes, is located in a structurally complex locus with genetic mutations such as inversions, duplications, deletions, and translocations [30]. Amylase genes (*AMY*) code for amylase enzymes, which break down starch into maltose and dextrin. Mutations in the genes encoding pancreatic amylase (*AMY2B*) have been identified, they are primarily associated with differences in amylase production and activity levels, as well as variations in carbohydrate metabolism.

Amylase mRNA makes up 20% of the pancreatic mRNA and it is the most prevalent enzyme in pancreatic acinar cells [31]. As demonstrated by Korc et al. in 1981, amylase mRNA is reduced in the pancreas of diabetic mice and recovered by treatment with insulin, demonstrating the insulin dependence of amylase expression.

The pancreas is a mixed exocrine–endocrine gland, with the exocrine portion of the gland making up the greatest volume of 84%. Ductal cells and blood vessels make up around 4% of the volume; while, the endocrine part makes up 2% of the volume. The other part is occupied by an extracellular matrix of 10%. Further, the acinar tissue in the pancreas is in the close vicinity of the islets. Due to this close morphological relationship, functional interactions are likely to occur between the exocrine and endocrine pancreas in any disease that affect this organ [32].

Research has shown that the pancreatic exocrine function may be influenced by the pancreatic endocrine hormones. In type 2 diabetes mellitus, there are multiple defects in the insulin secretion and the signaling which may adversely affect the enzyme synthesis and in the exocrine pancreas [15]. Also, the secretion of pancreatic juice is controlled by the autonomic nervous system and by naturally occurring gut hormones, cholecystokinin and secretin. This mechanism is observed to be disturbed in diabetes due to the common complications of autonomic neuropathy and the microvascular complications which are prominent in diabetes mellitus.

The only pancreatic-specific gene whose expression has been shown to be diminished in diabetic pancreas is pancreatic and duodenal homeobox 1 (*Pdx1*). Although they are also expressed exclusively in the pancreas, elastase, trypsin, chymotrypsin, lipase, and ribonuclease but are unaffected in diabetic mice [33]. Further, diabetic animals have been observed to have lower levels of pancreas-specific genes, which is not sufficient to cause type 2 diabetes.

One of the profound indicators of recent natural selection in the human population is copy number variation (CNV) of the starch-digesting *AMY* genes. According to Wood et al., in 2017, there are three amylase genes; *AMY1 (AMY1-CN), AMY2A (AMY2A-CN),* and *AMY2B (AMY2B-CN)*. Salivary amylase is encoded by *AMY1-CN*, which can have 1 to 20 copies. About 1 to more than 6 copies of pancreatic amylase are encoded by the genes *AMY2A-CN* and *AMY2B-CN* [34].

The hydrolysis of starch and glycogen's alpha bonds by *AMY1-CN* has been shown to be favorably correlated with salivary amylase activity, and it starts the process of starch breakdown in the mouth. Many human amylase genes are race-specific, and it is assumed that these three CNV genes influence how the body reacts to starch. Hence, they have been identified to be associated with diabetes and obesity [9, 35].

Human pancreatic amylase (HPA) is a crucial target for the prevention and treatment of type 2 diabetes,

according to Pajic et al. [40], HPA is an essential enzyme that plays a key role in the digestion of starch, making it a key target for the management of postprandial blood sugar [36, 37].The combined effort of genome-wide association studies (GWAS) and international collaboration have substantially described the genes involved in the pathogenesis of T2D. More than 403 loci have been associated with T2D but most of the genetic components of this disease, the causative variants, and the affected genes are yet unknown [38–40]. Insulin secretion is influenced by most of the loci [39].

An article by Rakhee et al. illuminated the relationship between type 2 diabetes and pancreatic amylase, the research identified that significantly low serum levels were found in the diabetic patients in comparison with the healthy controls; hence, it was concluded that in T2D, wherever the blood glucose level was higher, the serum amylase activity was observed to be significantly lower [41]. This illustrates the disorderliness in the endocrine–exocrine axis of the pancreas as a disease which affected any portion of an organ would affect the adjoining area of that organ functionally.

Therefore, poor diet, sedentary behavior, obesity, and insulin resistance are common lifestyle variables that contribute to type 2 diabetes in addition to genetic susceptibility. Genetic factors can contribute to an individual's susceptibility to developing the condition, but it is usually the result of the interaction between multiple genes and environmental influences. Some rare genetic diabetes types, such as maturity-onset diabetes of the young (MODY), is caused by unique gene mutations. However, these genetic mutations usually affect other components of glucose metabolism, such as pancreatic beta cells or insulin receptors, rather than pancreatic amylase. All the reviewed articles showed that the understanding of genetics factors of diabetes is continually evolving, and new research may reveal unknown associations; therefore, type 2 diabetes is not directly caused by a genetic mutation of the pancreatic amylase (Fig. 2).

This figure shows how more pancreatic amylase copies are kept in species that consume a lot of starch, how

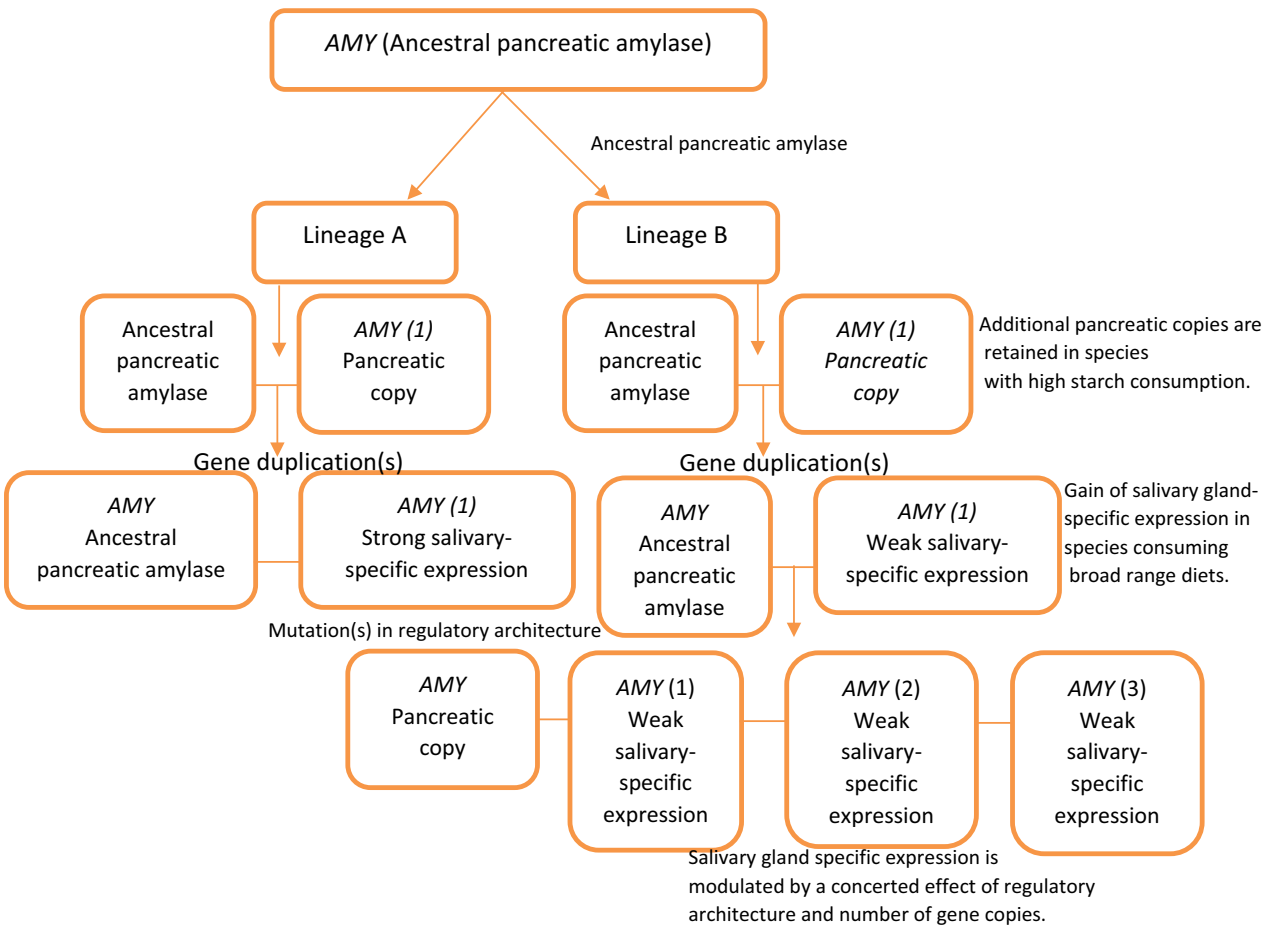

Fig. 2 Evolutionary expression of pancreatic amylase gene

salivary gland-specific expression increases in species that consume a varied diet, and how the effects of regulatory sites and gene copy number ultimately modulate salivary gland-specific expression.

Pathogenesis of type 2 diabetes

Type 2 diabetes (T2D) is an ailment caused by multiple factors, each of which differs from one individual to another [42]. Insulin resistance is the main cause of elevated glucose synthesis in the liver and reduced glucose absorption in muscle and fat tissues at a set insulin level in T2D. Abnormal β-cells also lead to a decrease in insulin biosynthesis, which is not sufficient for sustaining standard glucose levels [43].

The various factors that initiate the pathogenesis of type 2 diabetes in individuals are illustrated below;

Insulin resistance

The pathological condition known as insulin resistance occurs when the body's cells lose their sensitivity to the insulin hormone and are unable to recognize insulin [44]. When glycemia concentrations increase beyond 5 mM in healthy people, beta-cells in the pancreatic islets of Langerhans biosynthesize and release insulin. In the islets, beta-cells make up around 70% of the total cell population, and alpha-cells, which secrete glucagon (make up about 20%) [45]. Then, after binding to the insulin receptor (IR), GLUT4 receptors are stimulated to transport from intracellular vesicles to the plasma membrane, enabling glucose absorption into tissues. Adipose tissue, skeletal and cardiac muscle, are the main locations of GLUT4 [46]. Subsequently, glucose can either be converted to either glycogen or fat for energy conservation, or it can be delivered into the cell via GLUT4 from the circulation and catabolized in the cell for ATP synthesis, which makes energy available for intracellular functions [47].

A large number of the islet beta-cells in individuals with T2D go through programmed cell death, and the role of the remaining cells is jeopardized. This significantly lowers the amount of insulin in the blood. Moreover, there is reduced GLUT4 shift to the membrane due to weakened insulin activity, causing reduced glucose assimilation from the blood in peripheral tissues. Hyperglycemia and hyperlipidemia occur due to reduced insulin levels and activity (Fig. 3), consequently, the patient starts exhibiting T2D-associated symptoms [48].

Comparing the phenotypes of individuals with type 2 diabetes with those who are healthy. In healthy individuals, insulin freely binds to the insulin receptor, this initiates the glucose to cleave to GLUT4. GLUT4 serves as a carrier or transporter of glucose into the cell. Glucose is absorbed into the cell for the synthesis of ATP (universal energy currency for cells). In type 2 diabetic patients,

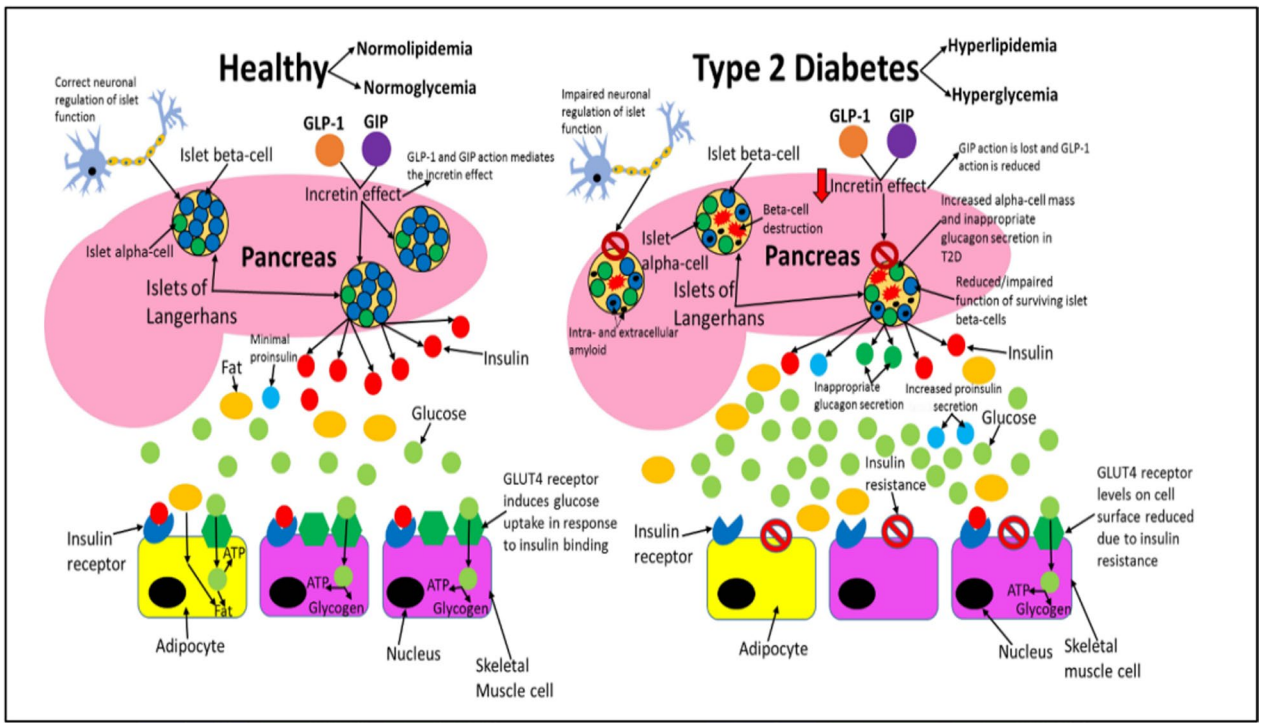

Fig. 3 Comparison of type 2 diabetic and non-diabetic (healthy) phenotypes [47, 48]

excess free fatty acids (hyperlipidemia) bind to the surface of the insulin receptor, thereby inhibiting the binding of insulin (a condition known as insulin resistance). The blockage of the insulin receptor surface by free fatty acids prevents glucose from binding with GLUT4. Excess glucose migrates in the blood leading to hyperglycemia. Prolonged hyperglycemia leads to type 2 diabetes.

Diminution of beta cell mass and beta cell damage

Beta cell (β-cell) death also promotes the emergence of type 2 diabetes by promoting necrosis and islet inflammation. Excess free fatty acids (FFA) cause islet inflammation (insulitis), which impairs insulin synthesis by causing β-cell on the islet of Langerhans to collapse metabolically. Cytokines are produced as a result of this metabolic collapse, which mobilizes immune cells to the islet of Langerhans, where they gather. The mobilization of immune cells to the islet of Langerhans triggers beta cell malfunction and impairs insulin synthesis [49].

Beta cells are the predominant cell type (approximately 70%) in non-diabetic people and are located both centrally and peripherally. The islets' periphery contains non-beta cells, which make up about 30% of the total cell population (20% alpha cells and 10% other cell types). Islet structural components are altered in people with type 2 diabetes, with significantly fewer beta cells, more alpha cells, more delta cells, migration of alpha and delta cells into the center, extracellular amyloid plaque deposits, intracellular islet amyloid polypeptide (IAPP) (commonly known as amylin) oligomers in beta cells, and larger alpha cells (Fig. 4). The altered islet structural component in T2D leads to different intra-islet paracrine signaling, which damages metabolic homeostasis [50].

Contrast between pancreatic islet structural components in non-diabetic (healthy) people and people with type 2 diabetes (T2D). In healthy people, beta cells on the islet of Langerhans outnumber the alpha and delta cells. Beta cells on the islet of Langerhans are the point where insulin is secreted. The proper function of beta cells on the islet of Langerhans allows the proper absorption of glucose into the cell. In type 2 diabetic patients, excess free fatty acids (FFA) cause islet inflammation (insulitis), which leads to the production of cytokines. The synthesis of cytokines initiates the release of immune bodies to the islet of Langerhans, which destroys the beta cells. The structural composition of the islet of Langerhans changes, thereby increasing alpha and delta cells. This triggers beta-cell dysfunction and impairs insulin secretion (insulin resistance) leading to type 2 diabetes.

Genetic factors

Genetic background can also be a major factor in the etiology of type 2 diabetes in some individuals. The likelihood of being a type 2 diabetic patient is higher in individuals with one diabetic parent, and this percentage increases if both parents are type 2 diabetic patients.

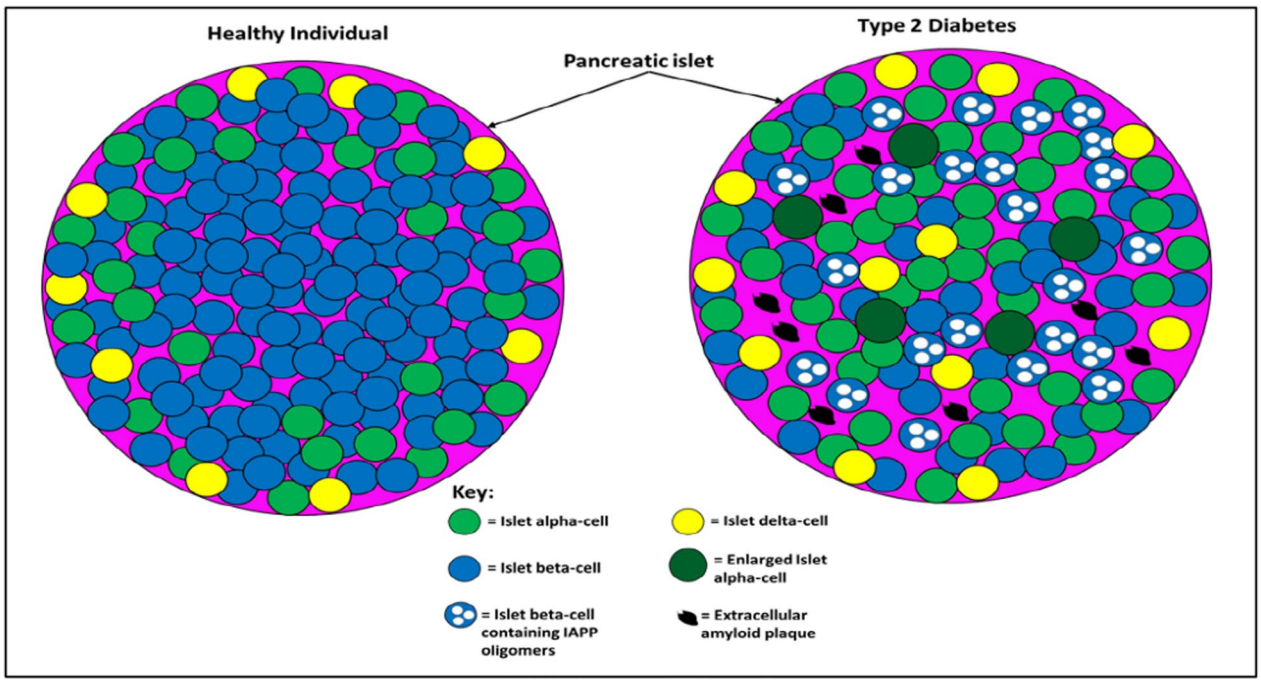

Fig. 4 Islet structural component of non-diabetic individuals in relation to the altered form in individuals with type 2 diabetes [50]

Likewise, the probability of having T2DM also rises by approximately 70% in identical or monozygotic twins (twins formed from a single fertilized ovum) than in fraternal or dizygotic twins (twins formed from two egg cells that have been separately fertilized) [51]. Through the process of the purifying selection method, specific genes (alleles) that are prone to T2DM are aloof at low occurrence and these hereditary genes can be used for screening and early diagnosis in families with a record of T2DM [52].

Obesity

Increased amounts of cytokines and fatty acids are characteristics of obesity, and it is alleged that these increased levels cause insulin resistance [53]. Islet beta-cells can preserve metabolic homeostasis and normoglycemia after the onset of insulin resistance by secreting more insulin or by replicating the amount of insulin [54]. Due to enhanced regeneration of tissues (neogenesis), obesity is alleged to cause approximately a 50% increase in islet beta-cell volume. The increase in islet beta-cell volume is to enhance the amount of insulin secretion due to insulin resistance [55]. It has been scientifically proven that the accumulation of excess free fatty acids (especially in individuals with excess fat around their abdomen) blocks the surface of insulin receptors leading to insulin resistance. Excess glucose moves freely in the blood because the insulin secreted is not able to bind with insulin receptors, thereby inhibiting the binding of glucose with GLUT4. GLUT4 (glucose transporter type 4) receptor levels on the cell surface are reduced due to insulin resistance, as a result of this, a prolonged increase in glucose in the blood leads to type 2 diabetes [56].

Therapeutics that target pancreatic amylase in type 2 diabetes

Reducing diet-dependent blood glucose rise is a popular treatment strategy to prevent and treat diabetes. This can be accomplished by inhibiting digestive enzymes like alpha-amylase and alpha-glucosidase, both of which break down dietary carbohydrates in the stomach [56, 57].

Synthetic medications

Acarbose, voglibose, and miglitol are just a few of the synthetic medications that have been developed to target alpha-amylase as a form of treatment strategy [58]. A potential preventive strategy for hyperglycemia is the use of pancreatic amylase and glucosidase inhibitors, which reduce the rate of carbohydrate digestion and thereby stop glucose release into the bloodstream. However, chemical and synthetic pancreatic amylase inhibitors can have certain unfavorable side effects, including bloating, diarrhea, and stomach pain [59].

Alpha amylase inhibitors (AIs) mostly function as carbohydrate blockers, reducing the digestibility and absorption of carbohydrates [62]. In medicine, amylase inhibitors are used to treat diseases such as hyperglycemia, diabetes, and obesity. Furthermore, oftentimes pancreatic amylase inhibitors inhibit these enzymes by blocking their carbohydrate binding sites [63].

Phytochemicals

When compared to synthetic medications, phytochemicals are superior for the treatment of diabetes since they are more effective and have fewer negative effects. Several pancreatic amylase inhibitors have been discovered in nature and described in the literature [56, 60, 61].

In a review by Payan [64], Ardalani et al. [65], they synthesized data from the literature and identified 104 plants whose anti-diabetic properties of their roots have been evaluated from various in vivo diabetes studies between 2001 and 2019. It was observed that saponins, terpenoids, and anthraquinones have inhibitory effects on pancreatic amylase in the treatment of diabetes.

In a study published by Ardalani et al. [65], Gong et al. [66], they found that the consumption of whole cereals may be associated with the induction of hypoglycemia in vitro through the inhibition of pancreatic amylase by phenols, peptides, nonstarch polysaccharides, and lipids. However, the mechanism of inhibition needs to be studied to elucidate the structure–function relationships between the ligands and pancreatic amylase.

Ogunyemi et al. in [62], conducted an in silico study to determine the inhibitory potentials of four steroidal pregnanes from *Gongronema latifolium*: (marsectohexol) (P1), 3-O-[6-deoxy-3-O-methyl-β-D-allopyranosyl-(1→14)-β-D-oleandropyranosyl]-11,12-di-O-tigloyl-17-β-marsdenin (P2), 3-O-[6-deoxy-3-O-methyl-β-D-allopyranosyl-(1→4)-β-D-oleandropyranosyl]-17-β-marsdenin (P3), and 3-O-[6-deoxy-3-O-methyl-β-D-allopyranosyl-(1→4)-β-D-canaropyranosyl]-17-β-marsdenin) (P4) on pancreatic amylase. The stability of the interaction of these compounds with pancreatic amylase was compared with the stability of the pure enzyme in both static and dynamic states based on five parameters: Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), Radius of Gyration (RoG), Number of Hydrogen Bonds, and Solvent Accessible Surface Area (SASA). It was observed these compounds bound to the pancreatic amylase binding sites with high affinity with hydrogen bonds, and hydrophobic interactions using specific Asp, Glu, and Tyr residues at the binding sites (Fig. 2). Also in a dynamic state, it was observed that the interactions

of these compounds with pancreatic amylase were stable over time across the five parameters measured. These suggest that the preganes are potentially a stable inhibitor of pancreatic amylase and this may be confirmed by using in vivo experimental studies.

Ogunyemi et al. [62] supplemented the in silico study with an in vivo study to evaluate the oral starch tolerance test of rats with a steroidal pregnane (marsectohexol) extracted from *G. latifolium*. They fasted sixteen albino rats and divided them into four groups of four rats per group. The rats were orally treated with 10 mg/kg marsectohexol (P1), 20 mg/kg marsectohexol (P1), DMSO (negative control), and 10 mg/kg acarbose (positive control). The blood glucose level was measured (0 min) after 10 min before the arts were fed with 3.0 g/kg starch. Afterward, the blood glucose level was measured at 30, 60, and 120 min with a glucometer. They observed that marsectohexol (P1) and acarbose caused a significant decrease in blood glucose level suggesting the inhibitory potential of this steroidal pregnane on alpha-amylase (Figs. 5 and 6).

Conclusion

Facts gathered from different research studies have stated clearly that human pancreatic amylase (HPA) is a significant factor in the prevention and management of type 2 diabetes.

Human pancreatic amylase is integrally expressed, and its activity rises postprandially (after meals), resulting in postprandial hyperglycemia. It has been recommended that dietary changes influence the expression of pancreatic amylase genes at the transcriptional and post-transcriptional levels. Although the regulation of HPA expression and activity is crucial to the levels of blood glucose, there is no proven fact that HPA has an influence on the pathogenesis of T2DM.

Previous research investigated the contribution of glucocorticosteroids to the modulation of pancreatic amylase in rats. It has also been established that some specific phytochemical constituents (such as saponins, terpenoids, and anthraquinones) present in plants possess inhibitory effects on HPA.

Future perspectives

All the reviewed articles consulted to compose this review showed that the understanding of genetics and diabetes is continually evolving, and new research may reveal unknown associations of HPA in the etiology of T2DM; therefore, T2DM is not directly caused by a genetic mutation of the human pancreatic amylase. Although, HPA regulation helps reduce blood glucose levels in individuals with T2DM. Therefore, there is a need for intensive research to understand the mechanisms that inhibit HPA to avoid postprandial hyperglycemia in T2DM patients.

This review also shows that there is need for computational study to effectively explore the potent human pancreatic α-amylase (HPA) inhibitor. The computational approach helps to determine inhibitors with similar binding affinity and stability to acarbose which can act potential molecule for HPA inhibition. From this review, it is clear that a good ADMET study for the HPA inhibitors is required for drug discovery against type 2 diabetes.

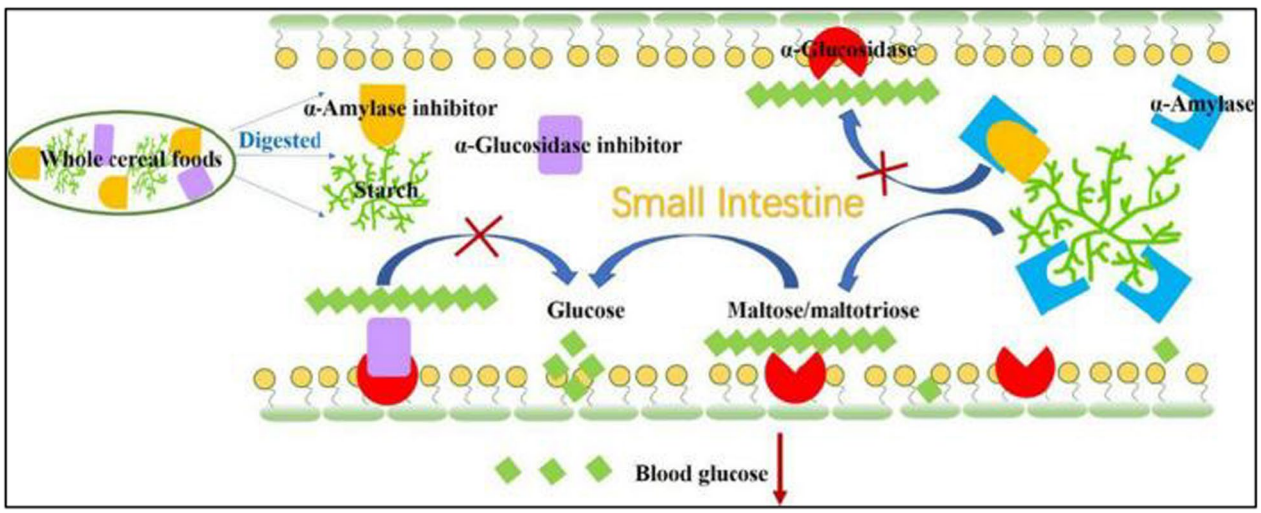

Fig. 5 Predicted inhibitory mechanism of action of whole cereal on pancreatic amylase [66]

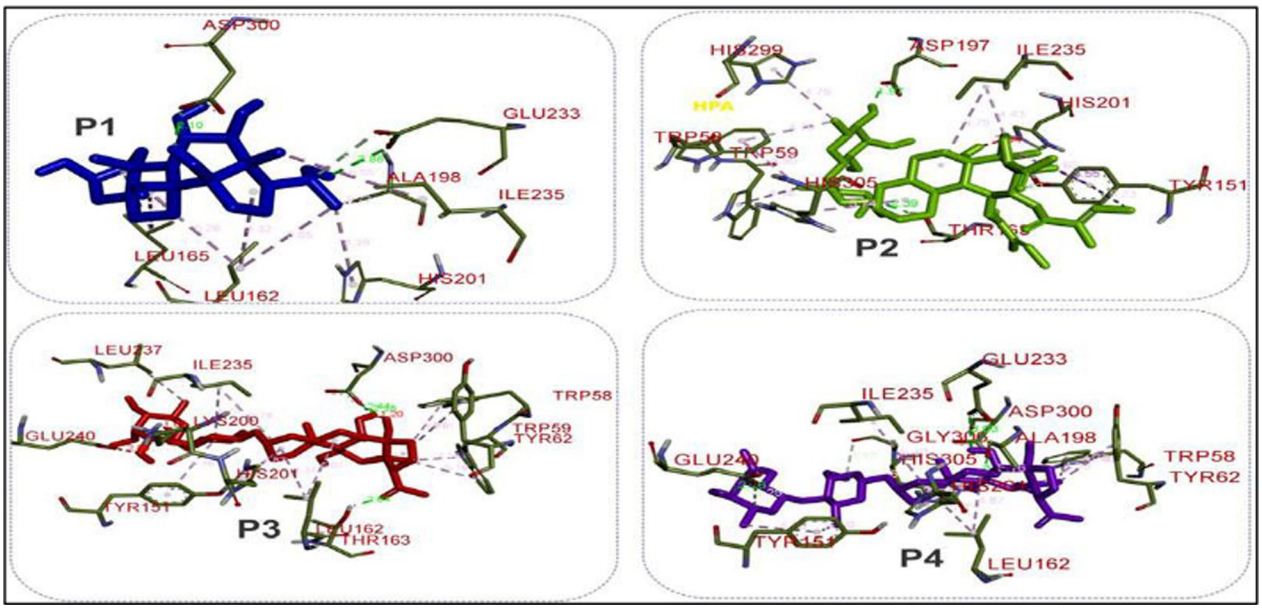

Fig. 6 Interactions between pregnanes from Gongronema latifolium with pancreatic amylase showing the specific amino acids residues at the binding sites (Asp, Glu, Tyr) [62]

Abbreviations

T2D	Type 2 diabetes
T2DM	Type 2 diabetes mellitus
T1DM	Type 1 diabetes mellitus
HPA	Human pancreatic amylase
AMY	Amylase gene
Pdx1	Duodenal homeobox 1
WHO	World health organization
ATP	Adenosine tris phosphate
IDF	International diabetes foundation
NIDDM	Non-insulin-dependent diabetes mellitus
IDDM	Insulin-dependent diabetes mellitus
CNV	Copy number variation
AMY1 (AMY1-CN) AMY2A (AMY2A-CN) AMY2B (AMY2B-CN)	Different types of amylase gene
GWAS	Genome wide association studies
MODY	Maturity-onset diabetes of the young
IR	Insulin receptor
GLUT4	Glucose transporter type 4
FFA	Free fatty acids
IAPP	Intracellular islet amyloid polypeptide
RMSD	Root mean square deviation
RMSF	Root mean square fluctuation
RoG	Radius of gyration
SASA	Solvent accessible surface area
ADA	American diabetes association
ADMET	Absorption, distribution, metabolism, excretion, and toxicity

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