Diabetes types: Different etiology and similar therapeutic strategies complicate the clinical situation and worsen the outputs management.

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Abstract

Diabetes has been described since ancient times. Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) are the main types of diabetes. The present study reviewed the literature from different perspectives including historical perspectives of diabetes, pathogenesis of diabetes, treatment of diabetes, and the differences between T1DM and T2DM. I have discussed the involvement of neurological aspects in detail in view of the existing literature including my article. I also discussed how T1DM and T2DM have different etiologies and similar treatment patterns. I put emphasis on animal models used in studying diabetes and how these models do not mimic the reality of T1DM, and how information resulting from these studies did not participate in expanding our horizon on the progression of diabetes. Taken together, developing new animal diabetic models that mimic the reality of diabetes types is required to investigate the pathogenesis of diabetes.

Keywords: type 1 diabetes mellitus, Type 2 diabetes mellitus, Glucose, Insulin, Pathogenesis, Animal models.

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Introduction

The present study reviewed diabetes from different perspectives of view and included five sections in addition to conclusion part. The diabetes history was included as well as its pathogenesis and treatment.

Historical Perspectives of Diabetes

Diabetes Mellitus (DM) has been known since ancient Egyptian times and was mentioned in papyrus which was found by George Yepres in 1862, dating back to 1550 BC. The first cases of DM were reported more than 3500 years ago [1-3]. Since its discovery, DM has been associated with excessive urination. According to the study by Papaspyros [4], Apollonius Memphites, an Egyptian physician at around 230 BC, was the first to use the prefix "diabetes" to indicate the increased passage of urine and attributed its etiology to the kidney. The suggested treatments included dehydration and phlebotomy [4,5]. Later, in about 500 BC, the idea that DM is not a single disease was reported by Hindu-Indian physicians, who observed the phenomenon of urine sweetness. The patients continued to make urine, and they had a short life span. Actually, this was a description of clinical picture of Type 1 DM (T1DM). From China in AD 200, Tchang Tchong-King described the symptoms of excessive eating observed in people with diabetes. It has been observed in the literature that the triad of polydipsia, polyphagia and polyuria is the hallmarks of diabetes.

In medieval Persia, the Arab physician Ibn Sina (980-1037) was the first to confirm the clinical characteristics and some complications of diabetes, and in his book, The Law of Medicine, he described sexual dysfunction, food paralysis, and the sweet taste of urine [6]. He suggested that diabetes was a nervous system disorder along with the interaction of liver dysfunction. Seeking treatment, Avicenna prescribed the use of emetics and exercises to reduce the symptoms and advised against the use of diuretics [7].

The role of the pancreas as an etiology of diabetes was first reported by Johann Brunner in 1682 following partial pancreatectomy in a dog, with the observation that the dog was affected by life-threatening thirst, polydipsia and polyuria. This was the first step in the recognition of the role of the pancreas in the pathogenesis of diabetes [8]. Between the 18t h-19t h century, when biochemical and pathological understanding of diseases became more apparent, type 2 DM was identified and differentiated from theT1DM [9]. The idea of having glucose as the sugar type in the urine of patients with diabetes was reached in 1815 by a French Chemist, Michael [10]. In 1840, Bernard made a breakthrough in diabetes when he ligated the duct of the pancreas of a dog leading to degeneration of the pancreas and diabetes. Diabetic- associated complications including eyes, retinitis and retinopathy, were first reported by Henry Noyes in 1869. In 1875, William Dickinson hypothesized that diabetes was associated with alterations in the nervous system. Langerhans described new groups of cells in the pancreas, called "islet cells", as an endocrine gland [11].

Insulin resistance associated with T2DM is thought to lead to impaired β-cell function in the pancreas including the insulin [12]. In a further advance, Donald Steiner and Philip Oyer in 1967 found pro-insulin and described the underlying mechanisms explaining the synthesis of insulin from the β-cells of islets of Langerhans [13]. In a further discovery, Freychet et al. [14] found out insulin receptors on cell membranes. The

glycated hemoglobin (HbA1C) test was developed in 1979 to control blood sugar by measuring blood glucose over 3 months (the life span of red blood cells)[15].

Depth Understanding of Type 1 Diabetes

Type 1 diabetes is a disease that was previously identified as insulin-dependent diabetes, which begins in childhood, appears at a young age or suffers from diabetes with basic insulin deficiency that requires daily insulin administration [16]. Type 1 diabetes is a chronic disease that requires insulin due to insulin abolition in pancreatic islet cells leading to increased levels of blood sugar and gradual functional loss and degeneration of various organs and tissues. High blood glucose concentrations activate oxidative stress resulting from the breakdown of macromolecules such as DNA, fats and proteins by the action of free radicals, accompanied by accelerated diabetes binding to non-enzymatic glycosylation or to protein and tissue damage in unhealthy people, but not in healthy people. The etiology of type 1 diabetes is unknown; and it shows symptoms such as excessive urination, constant hunger and thirst, visual changes, fatigue, and wasting that may ensue suddenly [17]. Although type 1 diabetes affects all age groups, several epidemiological studies have confirmed the features of the disease with clinical disease in childhood and adolescence, and sometimes difficulty differentiating from certain forms of Type 2 DM (T2DM) or autoimmune diabetes mellitus in adults [18]. Type 1 diabetes is an important and painful chronic disease that affects children at the global level, with 8 to 10 times the increased risk of death in children in developed regions, most of which die within a short period in developing countries [19], or which have not been adequately monitored, or registrars may elude healthcare personnel in developed countries. A 60 impairment of the internal gradient in the incidence of T1DM in addition to epidemic periods was ostensibly determined and reported. It is important for the investigation and characterization of the disease worldwide, the morbidity, mortality and healthcare of type 1 diabetes for collection and evaluation of health care of diabetes economics, promotion and local and global creation of training programs in diabetes epidemiology for prevention, reducing debilitating disorder and its complications [16,20,21].

The incidence of type 1 diabetes in childhood has reached increased worldwide near the end of the twentieth century, but the pathogenesis associated with augmentation has not been adequately reported and clarified [22]. The course of the diseases underlying type 1 diabetes temporarily changed with continuous evolution. The explanation of how type 1 diabetes spreads can provide ways to reverse it. Attempts have been made to eliminate the anomalies closely related to diabetes by the use of compounds derived from 1,3,4-Thiadiazine, resulting in decreased blood glucose and HbA1c levels and increased insulin levels in mice models. Type 1 diabetes tends to become a non-communicable disease with the most extensive discourse in the world, with Europe and the North America provides an astronomical increase in the burden of disease and created it as a model in the transformation of the present world path regarding health and healthcare. It cannot be prevented with prevalent and scarce and pervasive information and knowledge or to explain and clarify the burden and trends and differences in disease prevalence rates and consequences that can be seen in many countries [16].

Type 1 diabetes forms a chronic impairment of autoimmune metabolism with an expanding disorder characterized by defects of beta cells in the pancreas, associated with insulin deficiency and hyperglycemia. Environmental factors help precipitate autoimmune pathways in genetically susceptible children and adolescents. Type 1 diabetes is relatively less common than type 2 diabetes, but it causes increased morbidity and mortality rates compared to type 2 diabetes. Numerous reports of type 1 diabetes have indicated a high incidence [23]. Although childhood type 1 diabetes is more prevalent, about 25% of the cases are diagnosed among adults. In general, there are clinical features of type 1 diabetes, such as the classic new onset, hyperglycemia in the absence of acidosis, which is a common symptom in childhood, including the above symptoms, diabetic ketoacidosis, and silent or asymptomatic detection when some children are diagnosed with type 1 diabetes precedes the onset of clinical symptoms [24].

Pathogenesis of T1DM

T1DM is a chronic autoimmune disease characterized by high levels of glucose in the blood (hyperglycemia), which is caused by insulin deficiency that occurs as a result of the loss of is cells from pancreatic islets [25]. T1DM is one of the most prevalent endocrine and metabolic conditions that occur in childhood. The majority of patients suffer from the loss of β cells as a result of autoimmunity related to T1DM, these patients have autoimmune T1DM.

A small group of patients with T1DM does not show the existence of immunological reactions or autoantibodies, and the underlying cause of beta cell destruction is idiopathic. It is expected that genetic predisposition is likely to be the causative reason [26]. The existence of autoantibodies among patients with TDM1 precedes the onset of the disease by several months or years. These autoantibodies are not thought to be pathogenic, but they act as biomarkers of autoimmunity development. The distinctive T1DM-linked antibodies are those that target insulin, 65 kDa glutamic acid decarboxylase (GAD65; also known as glutamate decarboxylase 2), insulin-bound protein 2 (IA2) or zinc transporter 8 (ZNT8) [27,28]. People with specific HLA genotypes (coding for MHC proteins), that is, HLA-DR and HLA-DQ (HLADR-DQ) genotypes, are at an increased risk of developing two or more antibodies and T1DM [29].

Normally, the first cell-targeting autoantibodies to appear during early childhood target insulin or GAD65 (*i.e.,* anti-insulin antibodies or anti-GAD65 autoantibodies), but these autoantibodies may be present, whereas IA2 is rare or the first antibody ZNT8. It is not clear what triggers the first appearance of a cell-directed autoantibody, but it has come under scrutiny in numerous studies in children followed from birth [30].

It has been suggested that the pathogenesis of T1DM is a continued process that can be subdivided into stages according to autoantibody detection and progression toward beta cell destruction, dysglycemia, and finally symptoms associated with hyperglycemia [31]. What remains to be determined are the cell-directed autoimmune pathogens, which likely include a combination of environmental and genetic factors that trigger or enable an autoimmune response against beta cells. This event often occurs years before the eventual development of dysglycemia and symptoms [32].

Neonatal screening for-cell autoantibodies in children born in families with a mother or father infected with T1DM, and in the general population, provided a better understanding of when these autoantibodies appeared and allowed for factor analysis. Genetic and environmental-this may explain the emergence of the first antibody directed at islets [28,29,33]. Although this has not been proven, it is generally believed that autoantibodies are produced due to continuous exposure to cellular autoantibodies. The first autoantibodies detected usually target insulin or GAD65; The order of appearance of these two autoantibodies is related to age and genetic difference [27,28]. The peak incidence of insulin autoantibody development occurs between one and two years of age and this autoantibody usually appears first in children who have the HLA DR4 DQ8 haplotype. As the development of autoantibodies against insulin is rare before 6 months of age, it is likely that environmental exposures before 1 year of age are relevant to the etiology of insulin autoimmunity [25].

It is possible that various factors are involved in the aetiology of GAD65 autoantibodies, as children who first develop these autoantibodies are usually older than 1 year and have HLA DR3 DQ2 hplotype [34]. Other autoantibodies can develop after insulin or GAD65 autoantibodies: autoantibodies that target protein molecules similar to tyrosine phosphatase IA2 and IA2β, or ZNT8 [35]. These proteins are found in the membrane of the secretory vesicles.

ZNT8 transports zinc ions from the cytoplasm into the secretory vesicles, but the functions of IA2 and IA2β remain elucidation. The membranes of secretory vesicles are the places where these proteins exist. ZNT8 transports zinc ions from the cytoplasm to the secretory vesicles, but the functions of IA2 and IA2β remain to be elucidated. The appearance of the IA2 autoantibody as a second or third antibody significantly increases a person's risk of reaching stage 3 of the disease [36]. ZNT8 autoantibodies from three different ZNT8 species, containing tryptophan, arginine, or glutamine at amino acid position 325, appear to appear later during stage 1 and stage 2 [37]. At the time of clinical diagnosis, patients may have autoantibodies against ZNT8 specific to only one of the variants; A single amino acid at position 325 appears to dictate the autoantibody reaction against ZNT8 [38]. Hyperglycemia mainly affects the retina, peripheral nerves, and renal glomeruli. These cells share an inability to regulate glucose uptake in the presence of increased levels of extracellular glucose. The pathological effects of hyperglycemia are caused by the overproduction of superoxide by the electron transport chain in the mitochondria, leading to oxidative stress [39-41]. Retinopathy in T1DM is characterized by impaired blood flow in the retinal vessels and this induces compensatory proliferation of the retinal vessels. The new vessels are very fragile and permeable, characteristics that cause bleeding and protein leakage into the retina. Retinal perfusion is steadily decreasing and can eventually lead to blindness [32].

How to Differentiate T1DM from T2DM

It is not always easy to distinguish between DM1 patients and those with DM2. Although DM1 often has a childhood onset, it can occur in adulthood; in these cases, it is often confused with T2DM. Adults usually have mild symptoms, and it is not always possible to classify patients based solely on hyperglycemia. The distribution of BMI between children and adults with DM1 disease is usually similar to the distribution of BMI in the general population [42,43]. Therefore, it is estimated that about 20% to 40% of children who have T1DM are overweight, although they are seldom overweight or obese as most young adults with T2DM. In fact, the average BMI among children and youth with T1DM is likely to be less than that of children and youth with T2DM [44]. It has been reported that despite the consideration that ketoacidosis is likely to be more common in T1DM than in T2DM, about 30% of T2DM patients in Africa could have ketosis at the onset of disease due to cytotoxicity caused by hyperglycemia, leading to low levels of insulin and peptide C (a marker of insulin production) [45]. However, obese adolescents with clinical features of T2DM could have evidence of autoimmunity [46]. Accordingly, new terms such as "type 1.5 diabetes", or "double", "hybrid" or "mixed" diabetes have been emerged [47]. Various studies have been conducted to suppress immunological reactions hoping to find therapeutic agents for TIDM, but no success has been achieved [48-50].

Treatment of Diabetes

According to American Diabetes Association, for most patients who have type 1 diabetes, multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion are the appropriate therapeutic options accompanied with educational programs on how to match insulin doses intake with pre-meal carbohydrate and glucose intake and planned physical activity.

There are other treatments for type 1 diabetes, not insulin-based treatments. Pramlintide is one of these choices, it is based on b-cell peptide amylin and it is recommended for use in adults with type 1 diabetes [51]. Metformin can be added in adults with type 1 diabetes [52,53]. Other trials showed the benefits of adding the Glucagon-Like Peptide 1 (GLP-1) Receptor Agonist (RA) to insulin treatment [54]. Other studies have indicated that the addition of a Sodium–Glucose Cotransporter 2 (SGLT2) inhibitor to insulin treatment is beneficial in enhancing A1C and body weight in comparison with insulin treatment alone [55]. Surgical approaches including the transplantation of pancreas and islet have been reported to be effective if successful, but the need for lifelong immunosuppression to avoid immune rejection [56].

Metformin is the first therapeutic options for patients with type 2 diabetes. Lifestyle modifications can be accompanied with metformin [57]. Metformin is associated with vitamin B12 deficiency and it increases the symptoms of neuropathy [58]. In case metformin alone is not sufficient to maintain glucose levels within normal limits, or if glucose level exceeds 300 mg/dL, then insulin is recommended to be added with metformin [59].

Taken into consideration that type 2 diabetes progresses over time, glycemic control using one treatment can't cope with this progression and further combinations of treatments are required [60].

The Detailed Roles of Genetics in Diabetes

Diabetes Type 1 (T1D) T1D is an autoimmune disease characterized by the loss of insulin-producing beta cells in the pancreas. Both cellular and humoral immunity are involved. Although the cause of T1D is unknown, inherited genetic elements have been identified as being involved in its development [61]. According to twin studies, monozygotic twins have a concordance of 43%, while dizygotic twins have a concordance of only 7% [62]. Two genetic areas in the human genome have been identified as having a consistent link to T1D. These are the MHC gene locus on chromosome 6 (locus 6p21.3) and the insulin gene locus on chromosome 11 (locus INS) (locus 11p15). With the 1970s, the MHC region was discovered to be involved in T1D genetic predisposition [63]. Following that, this genomic region was separated into three primary groups, with mutations of human leukocyte antigen (HLA) class II genes, such as HLA-DQ, HLA-DP, and HLA-DR genes, being identified as key T1D risk factors [64]. In fact, rather than single variations, a synergy of so-called DR3DQ2 and DR4-DQ8 haplotypes (standing for DRB1*03:01DQA1*05:01-DQB1*02:01 and DRB1*04:01/04:04-DQA1*03:01DQB1*03:02, respectively) has been discovered to produce these effects.

These two haplotypes are held by 90% of patients compared to 30% of controls, and 40% of patients have both compared to 3% of controls (odds ratio 14 30). Immune cells such as macrophages, dendritic cells, B cells, and T cells mostly express HLA Class II molecules. HLA molecules are antigen-presenting cell surface receptors that play a role in the immune system. HLA molecules modulate regulatory T cells (Tregs) and conventional T cell activation in the immune system by delivering antigens to T cells [65]. Antigen binding and presentation specificity may thus play a role in HLA contribution to T1D susceptibility [66]. Indeed, Single-Nucleotide Polymorphism (SNP) data imputation of amino acids corroborated Ala57's key involvement in the peptide-binding groove of the HLA-DQb1 chain and identified independent impacts at positions 13 and 71 of the HLA-DRb1 chain [67]. Specific HLA alleles could influence central negative selection of self-reactive T lymphocytes in the thymus and peripheral activation of beta-cell antigen-presenting dendritic cells in pancreatic nodes, leading to beta-cell activation and eventually destruction, by influencing effective antigen-binding. The MHC is thought to account for 50% of T1D heritability [68], although HLA class II genes were found to account for roughly 30%. As a result, HLA class I alleles, such as HLA-A*24 and HLA-B*39, have been linked to T1D independently [69]. To explain the missing heritability, researchers looked at non-MHC areas of the human genome. The INS gene was linked to T1D as early as 1984 [70]. T1D was also linked to candidate genes for Cytotoxic T-Lymphocyte Antigen-4 (CTLA4) [71], Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22) [72], and Interleukin-2 Alpha Chain Receptor (IL-2ACR) [73]. Then, between 2002 and 2010, major Genome-Wide Association Studies (GWAS) (which scan the entire genome using SNPs) were done, particularly by the Type 1 Diabetes Genetics Consortium (T1DGC), which collected over 6,000 T1D samples. There have been 52 association signals detected thus far [74]. All linked mutations are non-protein-coding, except for the HLA and five genes outside the MHC, including PTPN22, IFIH1, CTSH, TYK2, and FUT2, which were recently confirmed by targeted deep sequencing of 301 candidate genes [75]. The majority of GWAS hits are associated with or near genes involved in immunological processes, such as BACH2, C1QTNF6, CCR5, CD69, CD226, CLEC16A, CTSH, ERBB3, GPR183, IFIH1, IKZF1, IL2/IL21, IL2RA, IL7R, IL10, IL18RAP, IL27, ITGB7, PTPN2, PTPN22, PRKCQ, SH2B IFIH1, PTPN2, CTSH, and CLEC16A, as well as GLIS3, are all highly expressed inside pancreatic beta-cells and have been linked to inflammation and apoptosis [76]. The destruction of pancreatic beta cells is caused by immune cells entering the endocrine islets [77]. In the beta cell, a substantial number of genes connected to susceptibility loci are expressed, and pro-inflammatory cytokines influence their expression [78].

Conclusion

This study investigated diabetes from various perspectives including historic points, pathogenesis, and treatment. Treatment strategies imply that both types of diabetes will have similar patterns, which may lead to a very basic question, if diabetes is a developmental disease or not.

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