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REVIEW

Type 1 diabetes mellitus: An update

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Abstract
Globally, the number of children with Type 1 diabetes mellitus (T1DM) has been rising at a much faster pace than expected. Despite an advanced diabetes care system, we have not yet succeeded in either preventing the disease or treating complications of diabetes. Therefore, the negative effects tend to be greater among children with a young age at onset. Consequently, the global financial burden of diabetes is increasing at an exponential rate and accounts for about 11% of the total budget on health.

Several studies have confirmed the increasing incidence of Type 1 diabetes mellitus, linking it with sedentary life style. T1DM, being one of the most prevalent chronic health conditions in children under the age of 18 years is considered as one of thrust areas of research. Hence, this article is aimed to provide an overview of the major advances in our understanding of the etiology, pathogenesis and clinical management of DM in children with the focus being on T1DM. The incidence, prevalence, burden on health budget and prevention and prediction of childhood diabetes, which may facilitate the researchers in the field of diabetes is documented in this review. Although T1DM cannot yet be prevented successfully, ongoing clinical trials on designer insulin and innovative strategies such as herbal formulae may bring some hope through advanced research techniques.

Keywords: *diabetes mellitus, juvenile diabetes, insulin, blood glucose, insulin autoantibodies*

Introduction
Diabetes mellitus is one of the major areas of research and Type 1 diabetes (T1DM) in particular. Many researchers are focusing on studies related to pathogenesis, epidemiological studies, newer insulin formulations and alternative therapies in T1DM. An effort is made to provide collective information regarding recent advances and trends in diabetes research, which may help researchers focusing on T1DM related studies. In general, diabetes mellitus is a clinical syndrome, characterized by hyperglycemia due to an absolute or relative deficiency of insulin or non-responsiveness of tissues for insulin. The minimum defining characteristic feature to identify diabetes mellitus is chronic and sustained elevation of circulating glucose concentrations in the plasma. Diabetes mellitus can be classified into two main types such as Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus.[1] T1DM is an autoimmune disease characterized by pancreatic β-cell destruction and an absolute deficiency of insulin and most commonly develops in childhood, and progresses with ageing. It accounts for approximately 5% to 10% of all cases of diabetes, and is the most common subtype diagnosed in patients younger than 20 years of age. In the recent past the term juvenile diabetes or insulin dependent diabetes mellitus (IDDM) has been replaced by Type 1 diabetes mellitus (T1DM). Since the disease can develop at any age, including late adulthood, the appellation "juvenile diabetes" is now considered obsolete. Similarly, the older moniker "insulin-dependent diabetes mellitus" has been excluded from the recent classification of diabetes because insulin dependence is not a consistent distinguishing feature. Nevertheless, most patients with T1DM depend on insulin for survival, without insulin they develop serious metabolic complications such as ketoacidosis and coma.[2]

In 1997, the American Diabetes Association proposed the etiological classification of diabetes into four major types and is T1DM, T2DM (non-insulin dependent diabetes mellitus or NIDDM), gestational and secondary to other diseases. T1DM is further classified as immune mediated (Ia) with insulin autoantibodies (IAA) and idiopathic (Ib) without IAA. Other subtypes of diabetes include MODY (maturity onset of diabetes of the young), LADA (latent autoimmune diabetes in adults).

Diabetes is a potentially devastating metabolic syndrome, as long standing dysmetabolism is frequently associated with permanent and irreversible, structural and functional changes in the body, the vascular system being particularly susceptible.[3] Dysmetabolism in turn will lead to the development of complications of diabetes, such as nephropathy, angiopathy, retinopathy, peripheral neuropathy and encephalopathy; which cause substantial morbidity and disability, even contributing to the mortality, by causing renal failure, and cerebrovascular accidents among others.[4]

Pathogenesis of Type 1 diabetes

T1DM is a 'T' cell mediated autoimmune disease, in which islet destruction is caused primarily by immune effector cells reacting against endogenous β-cell antigens. As with most autoimmune diseases, the pathogenesis of T1DM represents an interplay of genetic susceptibility and environmental factors.

Autoimmunity

A role for antibodies in T1DM is suspected because of the observation that autoantibodies against islet antigens are found in the vast majority of patients with T1DM, as well as autopsies of patients who died following diabetes. In fact, autoantibodies directed against islet constituents precede the onset of clinical disease by many years and can be used to predict it; they are present in 95% of newly presenting patients. Several islet antigens have been characterized, and these include insulin itself, the enzyme glutamic acid decarboxylase (GAD), protein tyrosine phosphatase (IA-2) and the cation transporter ZnT8.[3] Islet cell antibodies are detected by a fluorescent antibody technique which detects binding of autoantibodies to islet cells.

Many of the advances in T1DM pathogenesis have emerged from extensive studies of the non-obese diabetic (NOD) mouse model, which shares features of autoimmune islet destruction observed in the human disease. The observation that treatment with immunosuppressive agents such as cyclosporine prolongs beta-cell survival in newly diagnosed patients has confirmed that the disease is immune-mediated. However, it is not clear if the autoantibodies are involved in causing injury or are produced as a consequence of islet injury.[5]

Although the clinical onset of type 1 diabetes is often abrupt, the autoimmune process usually starts many years before the disease becomes evident, with progressive loss of insulin reserves over time. The classic manifestations of the disease (hyperglycemia and ketosis) occur late in its course, after more than 90% of the β cells have been destroyed. The fundamental immune abnormality in T1DM is a failure of self-tolerance in T-cells.[6] This failure of tolerance may be a result of some combination of defective clonal deletion of self-reactive T cells in the thymus, as well as defects in the functions of regulatory T cells or resistance of effector T cells to suppression by regulatory cells. Thus, autoreactive T-cells not only survive but are poised to respond to self-antigens. The initial activation of these cells is thought to occur in the peri pancreatic lymph nodes, perhaps in response to antigens that are released from damaged islets. The activated T cells then traffic to the pancreas, where they cause β cell injury. Multiple T-cell populations have been implicated in this damage, including TH1 cells (which may injure β cells by secreted cytokines, including IFN-γ and TNF), and CD8+ CTLs (which directly kill β cells). The islet auto-antigens that are the targets of immune attack may include insulin itself, as well as β-cell enzyme glutamic acid decarboxylase (GAD) and islet cell auto antigen 512 (ICA512).[5, 7]

Genetic susceptibility

Type 1DM and T2DM are genetically substantially different. Genome-wide association studies have broadly widened our understanding of the genetic susceptibility to T1DM and more than a dozen genes or gene regions have been identified to date. These studies have confirmed that by far the greatest genetic contribution comes from the significant susceptibility locus (*IDDM1* locus) in the HLA class II gene located at 6p21.3, contributing about 50 per cent of the inherited risk for T1DM. The *HLA-DR* and *HLA-DQ* loci in the class II region have the strongest influence on T1DM risk. Since HLA class II molecules participate in antigen presentation, the mechanism of HLA-influenced susceptibility inT1DM is believed to involve antigen presentation to CD4+ cell, thymic selection, and immune responsiveness. [8-11]

Non-HLA loci also play a role in the genetic susceptibility to T1DM. *IDDM2* (INS-VNTR, variable number of tandem repeats) located in the insulin gene promoter on chromosome 11p15.5consists of tandem repeat. Recent studies have also demonstrated an association between T1DM and*CTLA4* (cytotoxic T lymphocyte-associated 4, *IDDM12*) located within the 2q31-q33 region, exhibiting the strongest association with T1DM. *SUMO4* located in the *IDDM5* locus on chromosome 6q25 is believed to play a role in pathogenesis of T1DM via its role in apoptosis of pancreatic b cells.[12-14]

Environmental factors

Although the incidence of childhood T1DM is increasing worldwide at an alarming pace, Northern Europe has the highest rate of 2-3% each year, suggesting that environmental factors are involved in its pathogenesis. Islet autoantibodies appear in the first few years of life, indicating prenatal or early postnatal interactions with the environment.

Circumstantial epidemiologic evidence suggests that exposure to a protein in cow's milk (bovine albumin peptide) in neonates may trigger the autoimmune process, subsequently resulting in TIDM and this may increase the risk about 1.5 times.[15] Recent studies have provided some strong evidence that dietary intake of the *N*-nitroso compounds found in smoked/cured meats is diabetogenic in susceptible individuals, producing beta cell damage by the same mechanism as streptozotocin.[16] Many other chemicals, such as rodenticide vacor, have also been implicated in beta cell damage.

Recent epidemiological and experimental evidence has strengthened the hypothesis of a viral etiology of T1DM in some cases. A viral etiology was initially suspected due to the seasonal variation in the onset of the disease (October–March). During these months, v iral diseases, such as mumps, congenital rubella, retrovirus, cytomegalovirus (CMV), Epstein-

Barr virus and Coxsackie B_4 virus infections are much more prevalent and these viruses are capable of infecting pancreatic beta cells and inducing DM. [17, 18] It has also been suggested that a cleaner environment (the hygiene hypothesis) with less early stimulation of the immune system in childhood may increase susceptibility for T1DM, as for atopic/allergic conditions.

Clinical presentation of diabetes

These can be broadly discussed under three main headings; acute, sub-acute or asymptomatic.

Acute symptoms include polyuria, polydipsia and polyphagia. If these early symptoms are not recognized and treated, ketonuria is often present and may progress to ketoacidosis. Sub-acute presentation includes symptoms such as lack of energy, visual blurring, or pruritus vulvae in women. Asymptomatic diabetes includes glycosuria or hyperglycemia and may be detected on routine examination in individuals who have no symptoms of ill-health. Glycosuria is not diagnostic of diabetes but indicates the need for further investigations. About 1% of the population has renal glycosuria. Evidence of weight loss, dehydration, characteristic retinopathy and acetone smelling breath may be present on physical examination at diagnosis.

WHO recommendations for the diagnostic criteria for diabetes

The World Health Organization (WHO) has published guidelines for the diagnosis and classification of diabetes since 1965 and these were reviewed and published as the guidelines for the Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications in 1998. Since then information relevant to the diagnosis of diabetes has become available, which helped the researchers conducting diabetes related studies in particular. A joint WHO and International Diabetes Federation (IDF) Technical Advisory Group meeting Geneva to review and update the current WHO guidelines again in November 2005.[19] After consideration of available data and recent recommendations made by other organizations, the group made the following criterion as shown in Table 1.

Mortality and Morbidity

Globally, diabetes is likely to be the fifth leading cause of death. Excess mortality attributable to diabetes accounted for 2-3% of deaths in poorest countries and over 8% in the USA, Canada, and the Middle East.[20] Worldwide, 3.2 million deaths are attributable to diabetes every year. One in 20 deaths is attributable to diabetes; 8700 deaths every day; six deaths every minute. [21] WHO projects that diabetes death will double between 2005 and 2030. The overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes.

Diabetes is associated with excess mortality and morbidity as well. Over time, diabetes can damage various organs of the body, heart and brain in particular. The incidence of ischemic heart disease and stroke was 181.5 and 126.2 per 1,000 person-years, respectively, which was higher than the incidence of all other diabetes-related complications.[22]

- Diabetes increases the risk of heart disease and stroke. 50% of people with diabetes die of primarily heart disease and stroke.
- Diabetic nephropathy: 10-20% of people with diabetes die of kidney failure.
- Diabetic retinopathy: After 15 years of diabetes, approximately 2% of people become blind, and about 10% develop severe visual impairment.
- Diabetic neuropathy affects up to 50% of people with diabetes including common symptoms like tingling, pain, numbness, or weakness in the feet and hands.
- Combined with reduced blood flow, neuropathy in the feet increases the chance of foot ulcers and eventual limb amputation.[23]

Prevalence and incidence

The prevalence of diabetes is increasing in an epidemic-like fashion and it was estimated to be 2.8% in 2000 and 4.4% in 2030 for all age groups worldwide. Thus the total number of diabetics is projected to rise from 171 million in 2000 to 366 million in 2030.[24] The 171 million cases of diabetes reported worldwide in 2000, is 11% higher than the previous estimate of 154 million. [25] Given the increasing prevalence of diabetes, it is likely that these figures provide an underestimate of future diabetes prevalence, as many undiagnosed cases are not accounted.

The trend of incidents of diabetes estimated for continents showed statistically significant increases all over the world. [26-29] The incidence of T1DM ranged from 1.9 to 7.0/100,000/year in Africa, 0.13 to 10/100,000/year in Asia, approximately 4.4/100,000/year in Australasia, 3.4 to 36/100,000/year in Europe, 2.62 to 20.18/100,000/year in the Middle East, 7.61 to 25.7/100,000/year in North America, and 1.27 to 18/100,000/year in South America.[30] The epidemiology of T2DM is equally bleak. The prevalence of T2DM ranged from 0.3 to 17.9% in Africa, 1.2 to 14.6% in Asia, 0.7 to 11.6% in Europe, 4.6 to 40% in the Middle East, 6.69 to 28.2% in North America, and 2.01 to 17.4% in South America.[30]

The prevalence of diabetes is increasingly sharply in the developing world as people adopt more sedentary life styles, with India and China being the largest contributors to the world's diabetic load. India is the “diabetes capital of the world”, as

every 4th diabetic patient is an Indian. India was home to around 31.7 million diabetics in 2000 and estimated to rise up to about 79.4 million in 2030.[24] The study undertaken by Madras IDDM Registry group suggests that the incidence of T1DM in south India is approximately 10.5 cases / 100,000 per year.[31] T1DM is the commonest form of DM in children (1.7 of 1000 children) and the second most common chronic disease during childhood around the globe. [32]

Burden on health budget

The global financial burden of the Diabetes is increasing steadily at an exponential rate. Globally, healthcare expenditures for diabetes are expected to account up to 11% of the total health budget. [33] Due to the high costs associated with management of diabetic complications, diabetic patients are more than twice as costly to manage as non-diabetic patients. Consequently, diabetes imposes a large economic burden on the national healthcare budgets and economies. The American Diabetes Association (ADA) in 2008 estimated the total costs of diabetes to be US$174 billion annually and the average direct treatment costs in US, Europe and other developed countries are thought to cover a range from US$4000 to 12,000 per patient per year, although it is quite lower in poor countries.[34,35] Besides the direct treatment costs, diabetes also imposes a huge impact on national economies in the form of lost work days, lower productivity at work, permanent disability, higher mortality rates and, therefore, foregone economic wealth. Indirect costs may have a share on total costs as high as 30%.[36,37] Thus the long-term complications associated with diabetes either directly or indirectly carries a crushing burden of morbidity, mortality and health care budget.

Prediction and prevention strategies for type 1 diabetes

T1DM is one of the most prevalent chronic health conditions in children under the age of 18 years.[38] Many researchers strongly support the concept that T1DM results from interactions between various environmental and genetic factors. Hence T1DM should be a preventable disease theoretically, if environmental triggers and temporal sequence of their interaction with corresponding gene is identified at an earlier stage. Accurate quantification of the risk for developing T1DM in a given individual is necessary to be successful in prevention strategies. Currently, prediction strategies involve measurement of autoantibodies namely, ICA, IAA, GAD65, IA-2A/ICA512[39] and genotyping for at risk HLA haplotypes (*e.g.*, DR3-DQ2/DR4-DQ8). The presence of two or three of these antibodies represents a predictive value of 50 and 80 percent, respectively for developing the disease within 5 years. The risk of diabetes increases with numbers and titers of antibodies and is modified by HLA genotype. [40-42]

First phase insulin response (FPIR) to an intravenous glucose tolerance test (IVGTT) is one more good predictor of T1DM, which indicates the beta cell function in islets of pancreas, especially in individuals with positive autoantibodies and genetic susceptibility. Reduced FPIR (less than45 mU/ml) with the presence of one antibody signifies a 92 percent prediction for the development of diabetes within 5 years.[43]

Prevention strategies for T1DM can be classified into two major categories as primary and secondary prevention strategies. Primary strategy includes the prevention of T1DM prior to the onset of clinical diabetes mellitus or prior to the development of autoimmunity to the islet or prevention prior to development of significant beta cell loss.

Secondary prevention strategy seeks to prevent further loss of beta cell after onset of clinical disease. Prevention strategies in individuals without autoimmunity seek to eliminate potential triggers like cow's milk in individuals with genetic susceptibility to develop diabetes.[44, 45, 46] Several therapies are available to prevent the onset of disease after beta cell loss. Immunosuppressive agents such as cyclosporine A, corticosteriods and plasmapheresis could delay the onset of clinical diabetes.[47] Nicotinamide, the oxygen-free radical scavenger, was reported to improve metabolic control. The active form of vitamin D, 1,25 $(OH)_2$ D3 has immunomodulatory actions and prevents development of T1DM in animal models. Supplement of vitamin D (2000 U/day) has been reported to reduce the relative risk of T1DM.[48,49] After the onset of disease (secondary prevention), several approaches aim to ameliorate the disease by preventing further beta cell damage and thus prolong the honeymoon phase. Methotrexate, anti-thymocyte globulin, oral insulin, BCG vaccine, and Q fever vaccine failed to exhibit protective effects again further decline in beta cell function. Other innovative approaches such as Ala-Ala anti-CD3, deglycosylate anti-CD3, oral IFN-g, heat shock protein peptide, insulin B, anti-IL2 receptor, and mycophenolate mofetil are the subject of multicenter trials.[50] Furthermore, islet transplantation is in the early stages as is stem cell therapy.

In summary, although this disease cannot yet be prevented successfully, it can be predicted well before the onset of diabetes and the ability to predict will facilitate prevention when this becomes possible. Newer insulin and other alternative therapies like herbal medicine should be screened, which would permit prevention and a meaningful reduction in the number of new cases of this disease worldwide.

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