Chapter 3

Update of Type 1 Diabetes

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Additional information is available at the end of the chapter

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1. Introduction

Diabetes is one of the fastest growing diseases. World health organization estimates that approximately 340 million people have type 1 diabetes and this number increases by 3-5% each year so the type 1 diabetes population reached 25 million by 2010. Type 1 diabetes is an autoimmune disease that is caused as a result of destruction of pancreatic β-cells. Several factors may contribute to the pathogenesis of type 1 diabetes. Genetic susceptibility of type 1 diabetes is determined by polymorphisms/mutations in multiple genes in both human and animal models.

The Major Histocomapatibility Complex (MHC) accounts for approximately 40% of the familial aggregation of type 1 diabetes and the insulin gene for only 10 % suggesting the existence of additional loci. The gene for "Protein Tyrosine Phosphatase, Non-receptor type 22 (lymphoid)."PTPN22, the lymphocyte signaling molecule, on chromosome 1p13.3–p13.1 is a confirmed locus that contributes to multiple autoimmune disorders, including type 1 diabetes. Diabetes associated Cytotoxic T - Lymphocyte Antigen 4 (CTLA-4) locus polymorphisms in most populations have relative risks less than 1.5. A fundamental question is whether there are genetic polymorphisms that confer major risk for type 1 diabetes, other than the Human Leukocyte Antigen (HLA) DR and DQ alleles (class II HLA alleles). Recently, genes outside MHC region have considered playing an important role in the onset of diabetes.

As accumulative report suggest the role of olfactory receptor in the pathogenesis of diabetic microvascular and other diabetic complications, undoubtedly, this haplotype specific alteration of type 1 diabetes risk is an independent risk for the disease and can address the promising MHC-linked gene other than DR/DQ. Moreover, there is nothing to hinder for that this might be a signal that identify the role of olfactory receptor gene in the pathogenesis of type 1 diabetes in patients who are prone to diabetic complications.

Diabetes is one of the fastest growing diseases. Diabetes affects today an estimated 371 million people world-wide compared to 366 million by the end of 2011. Of course this includes 20 million to 40 million of patients with type 1 diabetes. While type 1 diabetes accounts for 5% to 20% of those with diabetes, it is associated with higher morbidity, mortality and health care cost than the more prevalent type 2 diabetes. Overall, 4.8 million people died and $ 471 billion were spent due to diabetes in 2012 [1-2].

New figures indicate that the number of people living with diabetes is expected to rise from 371 million in 2012 to 552 million by 2030, if no urgent action is taken. This equates to approximately three new cases every ten seconds or almost ten million per year. International diabetes federation also estimated that almost half of the people with diabetes are unaware that they have diabetes [2].

In some of the poorest regions in the world such as Africa, where infectious diseases have traditionally been the focus of health care systems, diabetes cases are expected to increase by 90% by 2030. At least 78% of people in Africa are undiagnosed and do not know they are living with diabetes (Figure 1):

- 80% of people with diabetes live in low and middle income countries.
- 78,000 children develop type 1 diabetes every year
- The greatest number of people with diabetes is between 40-59 years of age [2].

2. Why is there an increasing trend in the incidence of diabetes?

In the past, most diabetics were known to have a genetic tendency towards the disease. However, that trend has rapidly given way in the past few decades to other causes, at least from a statistical perspective. These genetically-independent trends that explain the growth in the incidence of diabetes can be summarized as follows: (a) overall growth in population, (b) increased life expectancy resulting in a higher ratio of aged population more prone to diabetes, (c) increasing obesity trends, (d) unhealthy diets and (e) sedentary lifestyles.

In other words, diabetes has increasingly become a lifestyle-related disease as it afflicts young and old, in developed and developing nations, around the world. As the number of patients grows across the globe, there has never been a stronger and more urgent need for therapeutic measures that arrest the growth of the disease and alleviate its secondary manifestations.

Middle East & North Africa: 1 in 9 adults in this region have diabetes; More than half of people with diabetes in this region don't know they have it. Europe: 1 out of every 3 dollars spent on diabetes healthcare was spent in this region; 21.2 million people in this region have diabetes and don't know it. Western Pacific: 1 in 3 adults with diabetes lives in this region; 6 of the top 10 countries for diabetes prevalence are Pacific Islands. South & Central America: Only 5% of all healthcare dollars for diabetes were spent in this region; 1 in 11 adults in this region has diabetes. Africa: Over the next 20 years, the number of people with diabetes in the region will almost double; This region has the highest mortality rate due to diabetes. South East Asia: 1

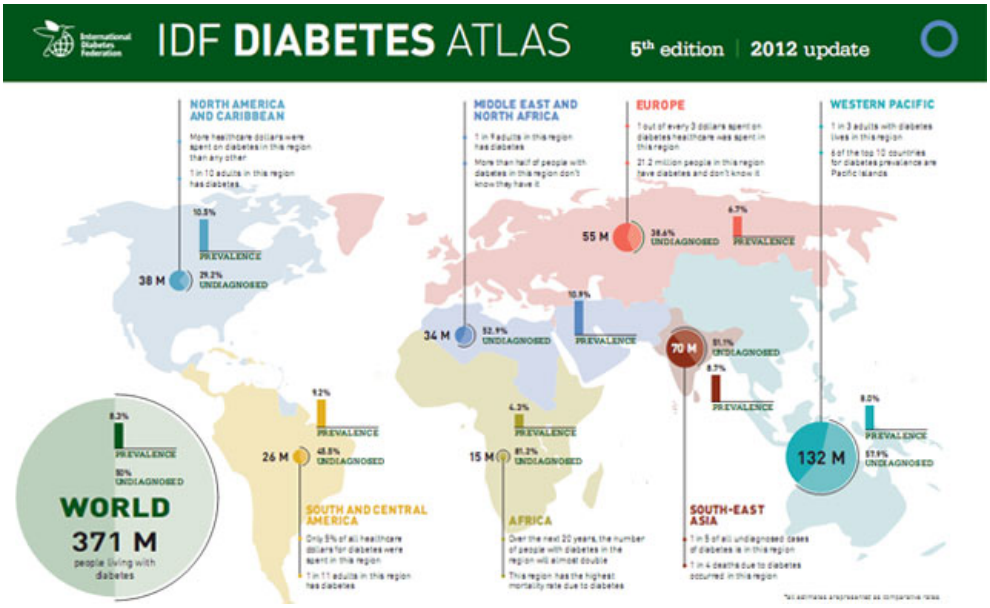

Figure 1. According to international diabetes federation5th edition; 2012the number of diabetes increases to 371 million. North America & Caribean: More healthcare dollars were spent on diabetes in this region than any other; 1 in 10 adults in this region has diabetes.

in 5 of all undiagnosed cases of diabetes is in this region; 1 in 4 deaths due to diabetes occurred in this region [2]

2.1. Pathogenesis

Type 1 diabetes develops slowly and progressive abnormalities in beta cell-function herald what appears to be a sudden development of hyperglycemia. Rising the hemoglobin A1c test (HbA1c) in the normal range[3], impaired fasting or glucose tolerance, as well as loss of first phase insulin secretion usually precede overt diabetes. The exact beta cell mass remaining at diagnosis is poorly defined and there are almost no studies of insulitis prior to diabetes onset [4]. For patients with long-term type 1 diabetes there is evidence of some beta cell function remaining (C-peptide secretion) though beta cell mass is usually decreased to less than 1% of normal [5]. At present methods to image/quantitate beta cell mass and insulitis are only beginning to be developed. In particular Positron Emission Tomography (PET) scanning utilizing a labeled amine (dihydrotetrabenazine) may provide the first method to image islet mass [6] and this is now being evaluated in man. A number of techniques are being evaluated to image insulitis [7].

A large body of evidence indicates that the development of type 1 diabetes is determined by a balance between pathogenic and regulatory T lymphocytes [8]. A fundamental question is whether there is a primary autoantigen for initial T cell autoreactivity with subsequent

recognition of multiple islet antigens. A number of investigators have addressed in the Non-Obese Diabetic (NOD) mouse (spontaneously develops type 1 diabetes) the importance of immune reactivity to insulin with the dramatic finding that eliminating immune responses to insulin blocks development of diabetes and insulitis, and importantly immune responses to downstream autoantigens such as the Islet specific molecule Glucose-6-phosphatase catalytic subunit-Related Protein(IGRP) [9]. Knocking out both insulin genes (mice in contrast to humans have two insulin genes) with introduction of a mutated insulin with alanine rather than tyrosine at position 16 of the insulin B chain prevents development of diabetes [10]. Recognition of this B-chain peptide of insulin by T lymphocytes depends upon a "non-stringent" T cell receptor with conservation of only the alpha chain sequence (Valpha and Jalpha) and not the N-region of the alpha chain, or the Beta chain [11].

As in other immune diseases both genetic factors as well as environmental factors contribute in the pathogenesis of the disease (Figure 2). Environmental factors exert their effects ones genetic susceptibility factors already exist.

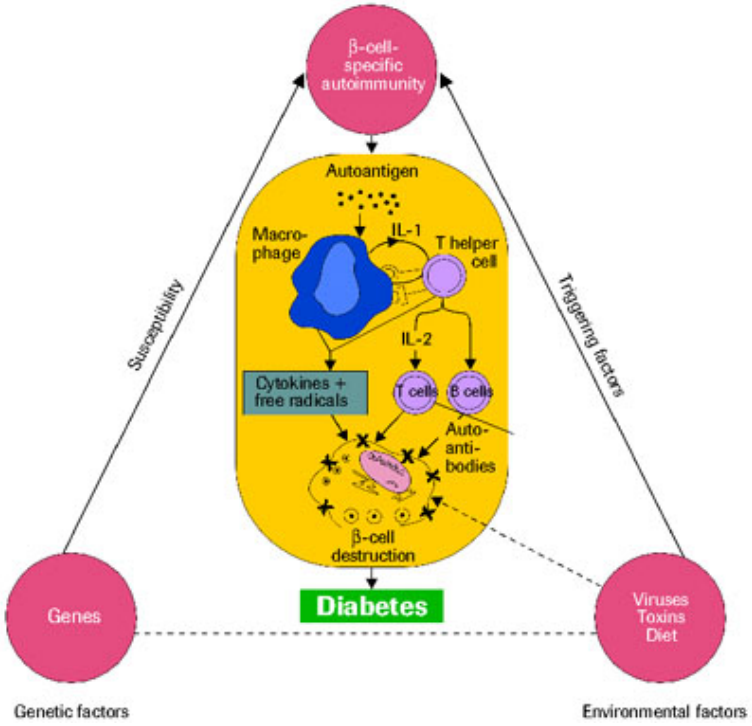

Figure 2. A schematic figure shows how environmental factors trigger TYPE 1 DIABETES onset in genetically susceptible persons which ends to the process of β-cell-specific autoimmunity processes which lead to the destruction of pancreatic β-cell. As antigen presenting cell is triggered by auto antigens it releases intiinfalmatory cytokines eg IL-1 that signals T-helper 1 class to activate B-cell and T cell in order to release autoantibodies to attach pancreatic β-cell.

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3. Genetic factors

A mutation of the Forkhead bOX Protein 3 (FOXP3 gene, a transcription factor that controls the development of regulatory T cells is a cause of neonatal diabetes [12]. The syndrome is termed IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome. As reflected in the name, children with disorder suffer from overwhelming autoimmunity and usually die as infants. Of note bone marrow transplantation can reverse disease. IPEX syndrome is rare, as is neonatal diabetes. In the differential diagnosis of neonatal diabetes it must be recognized that half of children developing permanent neonatal diabetes have a mutation of the Kir6.2 molecule of the sulfonylurea receptor. These children with their non-autoimmune form of diabetes can be treated with oral sulfonylurea therapy.

Though more common than IPEX syndrome, the Autoimmune Polyendocrine Syndrome Type 1 (APS-1) syndrome is also rare. It results from a mutation of the "autoimmune regulator" AIRE gene, another transcription factor [13]. Approximately 15% of patients with this syndrome develop autoimmune diabetes. The leading hypothesis as to etiology (e.g. Addison's disease, mucocutaneous candidiasis, and hypoparathyroidism) is that AIRE controls expression of autoantigens and negative selection of autoreactive T lymphocytes within the thymus. A very recent dramatic discovery is the demonstration that essentially 100% of patients with Autoimmune Polyendocrine Syndrome type 1 (APS-1) have autoantibodies reacting with interferon alpha and other interferons. Such autoantibodies are extremely rare and essentially not found in patients with type 1 diabetes or Addison's disease outside of the syndrome.

Patients with type 1 diabetes and their relatives are at risk for development of thyroid autoimmunity, celiac disease, Addison's disease, pernicious anemia and a series of other autoimmune disorders [14]. Approximately 1/20 patients with type 1 diabetes have celiac disease by biopsy though the majority have no symptoms [15]. These asymptomatic individuals are usually detected with screening for transglutaminase autoantibodies. The level of transglutaminase autoantibodies relates to the probability of a positive biopsy and it is important for clinicians to know the threshold for likely positive biopsy for the assay they employ [16]. There remains controversy as to whether asymptomatic celiac disease when detected should be treated with a gluten free diet and large clinical trials are needed to address this question.

3.1. MHC genes

Type 1 diabetes has become one of the most intensively studied polygenic disorders. There are MHC as well as non-MHC genes or loci candidate to contribute in the genetic susceptibility to type 1 diabetes pathogenesis. According to the recent version of the National Center for Biotechnology Information (NCBI) map viewer these genes are located on all human chromosomes [17] (Figure 3). The strongest associations with both susceptibility and protection from type 1 diabetes are HLA DR and DQ molecules. For instance DQB1*0602 alleles are associated with dominant protection and DR3-DQ2 molecules (DQB1*0201) and DR4-DQ8 (DQB1*0302) with susceptibility [18].

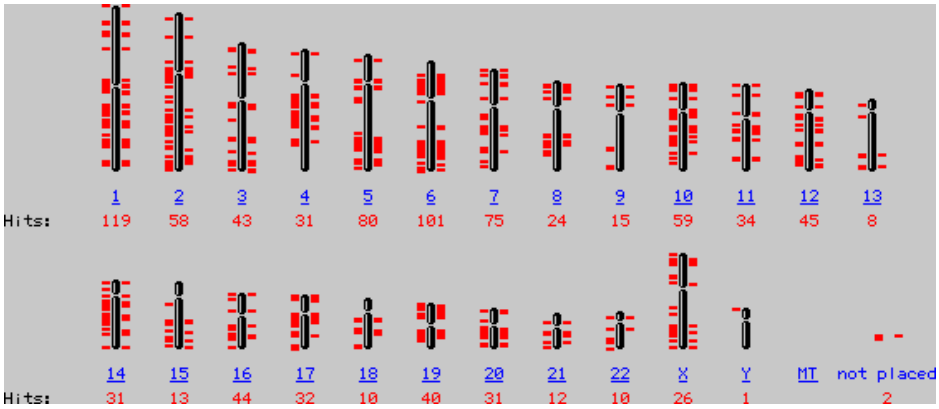

Figure 3. A schematic projection of type 1 diabetes susceptible genes location according to 2012 version of NCBI map viewer. Type 1 diabetes susceptible genes were reported on all chromosome of human[17].

Type 1 diabetes is a T cell organ specific autoimmune disease [19] with approximately 40% of the familial aggregation accounted for by the MHC region [20-21]. Nevertheless, it is generally assumed that the positive predictive value of MHC alleles is relatively low given the complex genetics and potential multiple environmental factors hypothesized to contribute to diabetes risk. However, approximately 1/2 to 1/3 of U.S. children who develop type 1 diabetes prior to age 15 have the highest risk DR/DQ genotype (HLA-DRB1*03-DQA1*0501-DQB1*0201/ DRB1*04-DQA1*0301-DQB1*0302, DR3-DQB1*02-01/DR4-DQB1*0302) [22-25]. Pursuing the hypothesis that additional major determinants of Type 1 diabetes risk (in addition to DR/ DQ genes) are within or close to the MHC region, highly conserved HLA-F [24-32].

Recently, OR gene have been associated with different diseases which support the hypothesis of the importance of OR in CNS in addition to smell [33]. Increasing studies suggest significant association among SNP in OR genes that link autoimmunity, psychiatric disorders, and smell impairment [33-36].

Interestingly, a large cluster of the human OR family 14, subfamily J and member 1gene (OR14J1) were found in proximity to the HLA-F, and so they were called “MHC-linked” OR-genes [1, 37-38]. Olfactory Receptor (OR) is our Central Nervous System (CNS) external messenger which translates the information from the odorant into neural pulses, a window for our mind. In addition, the important role of CNS in the pathogenesis of type 1 diabetes any variation in the genetic make-up of the OR might lead to the destruction of its function and notably malfunction of the CNS. The OR14J1C allele of OR gene in the conserved region of HLA-F showed a significant association with type 1 diabetes, except the known diabetogenic DQ/DR genes [39].

3.2. Non–MHC genes

Although important, the MHC susceptibility genes are not sufficient to induce type 1 diabetes, suggesting polygenic inheritance in most cases [40]. An important component of the suscept-

ibility to type 1 diabetes resides in certain non-MHC genes that have an effect only in the presence of the appropriate MHC alleles.

In particular, polymorphisms of a promoter of the insulin gene and an amino acid change of PTPN22 are associated with the risk of TYPE 1 DIABETES in multiple populations [4-6]. A repeat sequence in the 5' region of the insulin gene is associated with greater insulin expression in the thymus and it is hypothesized that this contributes to decreasing the development of diabetes [7]. The polymorphism of the lymphocyte-specific tyrosine phosphatase gene influences T cell receptor signaling, and the same polymorphism is a major risk factor for multiple autoimmune disorders [8].

A polymorphism in the cytotoxic T-lymphocyte-associated antigen-4 gene was shown to be associated with the risk of type 1 diabetes in a meta-analysis of 33 studies involving over 5000 patients [9]. Other genes are implicated in risk for type 1 diabetes (eg, CTLA-4) [10] and other genetic loci, but their influence is very small, or so small that replication has been difficult.

Additional evidence for the role of non-MHC genes comes from studies in NOD (nonobese diabetic) mice. These mice develop spontaneous autoimmune diabetes with striking similarities to type 1 diabetes in humans [11]. Autoimmune infiltration of the islets of Langerhans (insulitis) begins at about 50 days of age and clinical diabetes appears at about 120 days.

Interferon (IFN-γ)+ T cells (Th1 cells) appear to be an important mediator of the insulitis in NOD mice, and destruction of the islet cells can be slowed by the administration of anti- IFN-γ antibodies. IFN-γ -inducing factor (IGIF; also called interleukin (IL)-18) and IL-12 are potent inducers of IFN-γ, and the progression of insulitis begins in parallel with increased release of these two cytokines(kent et al 2005). IGIF gene expression is upregulated in NOD mice, and the location of the IGIF gene suggests that it is a candidate gene for susceptibility to type 1 diabetes [41].Genetically altered (knockout) mice deficient in IL-18 had hyperphagia, obesity, hyperinsulinemia, and hyperglycemia; intracerebral administration of recombinant IL-18 decreased food intake and reversed hyperglycemia (Bach 2002). A new locus associated with type 1 diabetes, has been identified near the gene encoding the p40 subunit of IL12B in NOD mice [42].

It was initially thought that, in contrast to Th1 cells, Th2 cells (which produce IL-4, -5, -10, and -13) protected against the onset and progression of type 1 diabetes. However, Th2 cells also are capable of inducing islet-cell destruction, and therefore the onset and progression of type 1 diabetes are probably under the control of both Th1 and Th2 cells [1,43].

In our extensive cytokine gene polymorphisms effect on type 1 diabetes immunogenetics (44-46]we have shown clearly that a single nucleotide polymorphism (SNP) in the genetic of IL-4 gene, however, would contribute to the domination of T-h-1 cell to Th2 (IL-4) [46], lack of action of IL-4, the th2 cytokine initiator. Further, a Single Nucleotide Polymorphism (SNP) in the Transforming Growth Factor (TGF)-β gene ends up to lower production of TGF- β protein level. That may contribute to the lack of immunosuppressive effect of TGF- β in the pathogenesis of type 1 diabetes [47].

4. Environmental factors

During the last decades, the incidence of type 1 diabetes has increased significantly, reaching percentages of 3% annually worldwide. This increase suggests that besides genetic factors environmental perturbations (including viral infections) are also involved in the pathogenesis of type 1 diabetes.

There is a number of environmental factors contribute to the marked global variation in the incidence of type 1 diabetes. Evidence suggests that the incidence is lower in the tropics compared with further north or south of the equator.

Assuming that the observation that there is a direct relationship between incidence of type 1 diabetes and equatorial distance, a number of environmental factors appear to be protective against the development of an autoimmune pathological process. Ultra violet radiation results in increased levels of vitamin D, which is an important modulator of the immune system. Detailed studies have shown not only that lower levels of circulating vitamin D predispose to autoimmunity, but that vitamin D supplementation may also reduce the risk of developing type 1 diabetes (vitamin D). Further data are required to establish the clinical utility and cost-effectiveness of such interventions, including the demonstration of these positive effects over a longer period of time.

Other dietary considerations may also be important, with avoidance of cow's milk at an early age seemingly providing protection against autoimmunity. Again, it is unclear as to whether or not use of hydrolysed infant formulae instead of cow's milk for weaning will be of significant clinical benefit, as long-term prospective data of this type are lacking. However, the fact that cereal exposure at a young age may also provoke increased autoimmune activity reinforces the notion that antigen ingestion may affect immune system function.

The role for infectious agents in type 1 diabetes remains unclear, as there are variations on the hygiene hypothesis which suggest that certain infections may prove protective whereas others may be pathogenic. Certainly, evidence in animal models convincingly demonstrates an association between viral antigens and autoimmunity and human biopsies have shown viral particles in the pancreas of type 1 diabetes patients. However, there is a lack of data demonstrating a causal effect for viral infections. Furthermore, the intriguing prospect that parasitic infections may protect against type 1 diabetes requires further study, so that molecular mechanisms may be elucidated for therapeutic purposes.

Future research needs to be conducted on a large scale, with the inclusion of both randomised and prospective studies in order to establish the link between environmental factors and type 1 diabetes pathogenesis. In particular, long-term follow-up of infants is required to assess the true benefits of interventional trials. In addition, consideration of the interaction of genetics with environmental factors is necessary to complete the picture, as it is likely that both mechanisms are involved in determining geographical variation of disease [18, 48].

Environmental influences are another important factor in the development of type 1 diabetes. This has been illustrated in twin studies; less than 50 percent of monozygotic twins of probands

with type 1 diabetes develop diabetes [49-50]. These observations are most likely explained by environmental factors such as viruses and dietary antigens.

5. Autoimmunity

Islet Cell Autoantibodies (ICAs) were first detected in serum from patients with autoimmune polyendocrine deficiency; they have subsequently been identified in 70 to 80 percent of patients with newly diagnosed type 1 diabetes and in prediabetic subjects (American Diabetic Association 1997). Measurement of serum ICA by staining of frozen sections of human pancreas was the major screening test used to identify subjects at risk for clinical diabetes but currently, large studies utilize a series of radioassays for autoantibodies reacting with specific islet autoantigens.

Children with type 1 diabetes who do not have islet-cell or other autoantibodies at presentation have a similar degree of metabolic decompensation as do children who have these antibodies, although those with more of the different types of antibodies appear to have the most accelerated islet destruction and a higher requirement for exogenous insulin during the second year of clinical disease [51]. A few patients without obvious evidence of islet autoimmunity have been described in whom the onset of hyperglycemia was abrupt, glycosylated hemoglobin values were normal, and serum pancreatic enzyme concentrations were high [52].

Autoantibodies to biochemically characterized beta-cell autoantigens: Insulin Autoantibodies (IAA), Auto-antibodies to the tyrosine phosphatases IA-2, Glutamic Acid Decarboxylase Autoantibodies (GADA), and zinc transporter 8 autoantibody (ZnT8A) [53] help to define type 1 diabetes a, if measured prior to or shortly after initiation of insulin therapy. IAA are masked by antibodies induced by exogenous insulin and become very hard to measure after just 10 to 14 days of insulin therapy. ZnT8A tend to disappear quickly after diagnosis of diabetes, while GADA and IA-2A tend to persist longer, but are rarely seen more than 5 years after diagnosis. Testing for at least two of these autoantibodies at diagnosis is now considered standard of care in type 1 diabetes. Good commercial assays exist for IA-2A, GADA, and ZnT8A, with the former two recently harmonized [54]. IAA are low-affinity antibodies and harder to measure; however, high-quality non-radioactive assays for IAA are close to being commercially available [55]. The search for additional islet autoantibodies and assay that would reliably detect autoreactive T-lymphocytes are active areas of research.

6. Complications

The management of type 1 diabetes and modalities for prevention of complications has evolved, such that the majority of patients with excellent care and education should avoid major microvascular complications. The finding from the Diabetes Control and Complications Trial (DCCT) follow-up study of “metabolic memory”, namely long term benefit from early intensive glucose management is very encouraging [56]. Intensive management and strict guidelines for lipid lowering and early introduction of renoprotective medications are the

norm. Laser therapy for advanced retinal disease is also the norm and "anti- Vascular endothelial growth factor (VEGF)" ocular therapy for macular edema is being extensively studied. Effective prevention of microvascular complications requires detection of early lesions, including determination of lipids, blood pressure, microalbuminuria, retinal exams. Preventative foot care and cardiovascular evaluation are also essential, with macrovascular disease a major problem for patients with long-term diabetes. Patients with type 1 diabetes have more severe progressive coronary artery atherosclerosis for any level of Low-density lipoprotein (LDL) cholesterol (57-586-57). Neuropathy remains difficult to treat [59] despite introduction of several newer medications.

Patients with diabetes and renal failure have a particularly poor prognosis when on dialysis. Every effort should be directed toward "early" renal transplantation in patients with type 1 diabetes and renal failure.

Genetic factors and key gene mutations have been implicated in the pathogenesis of diabetes. However, increasing evidence suggests that complex interactions between genes and the environment may play a major role in many common human diseases such as diabetes and its complications [39, 59-73]. Furthermore, the increased risk for both type 1 diabetes and type 2 diabetes can be controlled through medications, changes in dietary habits and increased exercise; subjects with diabetes continue to be plagued with numerous life-threatening complications. This continued development of diabetic complications even after achieving glucose control suggests a metabolic memory of prior glycemic exposure and indicates a missing link in diabetes etiology which recent studies have suggested may be attributed to epigenetic changes in target cells without alterations in gene coding sequences. Exploring a role for epigenetics in diabetic complications could allow for new insights clarifying the interplay between the environment and gene regulation and identify much needed new therapeutic targets.

Diabetic microvascular complications have been reported to be encountered with impairment in the olfactory system. Recently we have shown that polymorphism in the olfactory receptor, OR14J1C, may lead to an olfactory impairment that could be due to presence of microvascular diseases or other complication directly related to type 1 diabetes. The genetic alteration in the OR14J1 gene, A to C, could be linked to epigenetic processes [39].

6.1. What are common consequences of diabetes?

Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves.

- Diabetes increases the risk of heart disease and stroke. 50% of people with diabetes die of cardiovascular disease (primarily heart disease and stroke).
- Combined with reduced blood flow, neuropathy in the feet increases the chance of foot ulcers and eventual limb amputation.
- Diabetic retinopathy is an important cause of blindness, and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. After 15 years of diabetes, approximately 2% of people become blind, and about 10% develop severe visual impairment.

- Diabetes is among the leading causes of kidney failure. 10-20% of people with diabetes die of kidney failure.
- Diabetic neuropathy is damage to the nerves as a result of diabetes, and affects up to 50% of people with diabetes. Although many different problems can occur as a result of diabetic neuropathy, common symptoms are tingling, pain, numbness, or weakness in the feet and hands.
- The overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes.

7. Conclusion

Type 1 diabetes has become perhaps the most intensively studied autoimmune illness results from autoimmune destruction of the insulin-producing ß-cells in the islets of Langerhans. This process occurs in genetically susceptible subjects, is probably triggered by one or more environmental agents, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic. This long latent period is a reflection of the large number of functioning β-cells that must be lost before hyperglycemia occurs.

Polymorphisms in MHC genes and Non-MHC genes account for genetic susceptibility of the diseases. Genes in both the MHC and elsewhere in the genome have influence risk, but only HLA alleles have a large effect.

There are a number of autoantigens within the pancreatic ß-cells that may play important roles in the initiation or progression of autoimmune islet injury and its autoimmunity which might be a good prediction factor. Environmental factors that may affect risk include pregnancy-related and perinatal influences, viruses, and ingestion of cows' milk and cereals.

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