An Update on the pathogenesis of Diabetes Mellitus

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Introduction

The term "Diabetes mellitus" encompasses a heterogeneous group of disorders characterized by insulin hyposecretion and/or insensitivity. Type 1 (insulin-dependent) diabetes mellitus is thought to have an autosomal recessive inheritance and an autoimmune pathogenesis, exhibited by lymphocytic insulitis. The latter may be triggered by viruses or chemical agents. Type 2 (non-insulin-dependent) diabetes mellitus has a stronger genetic association. It is associated with obesity. Hyalinization and fibrosis are seen in the pancreatic islets of Langerhans, and the peripheral target cells are deficient in insulin receptors. This paper summarizes current knowledge regarding pathology and pathophysiology of both types of primary diabetes mellitus.

Pathogenesis of type I diabetes mellitus (type 1 DM)

Type 1 DM is a chronic autoimmune disease associated with selective destruction of insulin-producing pancreatic β-cells. The onset of clinical disease represents the end stage of β-cell destruction leading to type 1 DM. Several features characterize type 1 DM as an autoimmune disease: [a] presence of immuno-competent and accessory cells in infiltrated pancreatic islets; [b] association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA); [c] presence of islet cell specific autoantibodies; [d] alterations of T cell mediated immunoregulation, in particular in CD4+ T cell compartment; [e] the involvement of monokines and TH1 cells producing interleukins in the disease process; [f] response to immunotherapy; and [g] frequent occurrence of other organ specific autoimmune diseases in affected individuals or in their family members. The mechanisms that cause the immune system to mount a response to this small population of highly specialized cells have been intensively studied. We shall summarize the recent evidence obtained in the clinical and experimental studies on immunogenetics and immunopathogenesis of type 1 DM. These new findings will justify the statement made by Shields Warren in 1930 "The pancreas in diabetes is not simply the scarred field of an old battle-ground, but is the actual field of conflict. It does not submit without a struggle to injury. This conception explains the gradual development of the disease through slow but progressive destruction of the islands and the failure of regeneration to make good the losses."

Immunogenetic determinants:

A variety of gene loci have been studied to determine their association with type 1 DM. The early studies suggested that the B8 and B15 of HLA class I antigens were increased in frequency in the diabetics compared to the control group. However, more recently the focus has shifted to the class II HLA-DR locus. It was found that DR3 and DR4 were more prevalent than HLA-B in type 1
DM than HLA-B. Finally alleles of HLA DQ locus have been implicated in disease susceptibility. Restriction fragment length polymorphism (RFLP) analysis and direct sequencing, using the polymerase chain reaction (PCR) to amplify specific DNA sequences, have improved our understanding of the HLA complex and of the involvement of HLA alleles in disease susceptibility. Evidence was put forward indicating that the ability to confer susceptibility or resistance to type 1 DM resides within a single amino acid residue of the HLA-DQ β-chain. The use of locus-specific oligonucleotide probes derived from HLA DQ β-chain sequences has helped also to clarify the relationship between DR4 subtypes and type IDM associated DQ alleles. It was found that only those DR4-positive haplotypes which carry the DQW8 allele at the HLA DQ locus are associated with type 1 DM. Comparison of DQβ-chain sequences from type 1 DM probands and controls showed that haplotypes which were positively associated with the disease differ from those which are negatively associated by the amino acid of position 57 in the first domain of HLA-DQ β-chain. The positively associated haplotypes, have alanine, valine or serine at position 57. In nonsusceptibility haplotypes aspartic acid was found at position 57.4 However, several observations do not support the “position 57” hypothesis. Most important is definitely the findings that specificities DQW4 and DQW9 have an aspartic acid in position 57; in Japanese patients type 1 DM is highly associated with DQW4 and DQW9.3 This indicates that other mechanisms must be involved to account for the susceptibility to type 1 DM in some groups. The observed association between type 1 DM and HLA has been interpreted as a consequence of a functional involvement of HLA class II molecules in type 1 DM. The involvement of the DQ β-chain itself or the DQαβ heterodimer could indicate that the antigen presentation function of class II molecules is relevant for type 1 DM susceptibility.

Following "epitope selection" approach to explain autoimmune phenomena Nepons have suggested a model wherein HLA class II alleles affect IDDM susceptibility as follows: a) the array of class II dimers encoded by any individual's HLA complex, vary in their affinities for a specific peptide that can induce autoimmunity to β-cells; b) only certain class II dimers, the products of "susceptibility genes," actually promote autoimmunity to β-cells after binding that peptide, c) an individual is susceptible if the product of a susceptibility gene binds the peptide more strongly than the products of the nonsusceptibility genes present in that individual. Thus, in this model the products of certain HLA alleles are associated with type 1 DM because they bind and present specific peptides so as to induce an immune response to pancreatic β-cells. Sheeny had recently argued an alternative model in which immunological tolerance is the primary determinant of type 1 DM susceptibility. He suggested that the HLA alleles negatively associated with type 1 DM (e.g. DR2, DQW1) code products with high affinity for certain β-cell peptide or peptides needed to establish and maintain tolerance to β-cells, whereas the alleles that are common in IDDM (e.g. DR3, DR4 and DQW8) produce products that have low affinity for the tolerogenic peptide(s) or that bind the peptide(s) in the wrong orientation or configuration for establishing tolerance. Thus, the susceptible HLA genotypes would be those that "tolerize" ineffectively because of weak or otherwise ineffective binding of tolerogen. To this it may be added that HLA related differences in the production of inflammatory and down-regulatory cytokines may play a role in susceptibility to type 1 DM as recently argued in the regulation of autoaggression in the central nervous system.
β-Cell specific autoantigens:

The nature of autoantigen(s) responsible for the induction of type 1 DM is unknown. However, two recent lines of evidence are relevant to this issue. In an animal model of type 1 DM, multiple low dose streptozotocin (MLD-STZ)-induced diabetes, Herold and colleagues have shown that transplantation of isolated islets into the thymuses of adult mice will induce immunologic tolerance to the subsequent induction of autoimmune diabetes. These findings suggest that the non-responsiveness to induced autoimmune diabetes was due to T cell maturation in the presence of islet antigens. This assumption is supported by the findings that autoimmune diabetes may be prevented, in an animal model of spontaneous type 1 DM, diabetes prone Bio Breeding (BB) rats, by intrathymic transplantation of islet. Thus, islet antigen-reactive T cells have been either depleted or inactivated in the thymuses with grafted islets. Failure to delete these T cells during normal development may reflect the inaccessibility of islet antigens for antigen presentation by MHC class II positive accessory cells because antigens are not shed or are present in low concentration. It was already proposed that tolerance to islet cell autoantigens is maintained simply by lack of efficient autoantigens presentation. It was also demonstrated that the inactivation of different antigen specific T cell subsets depends on self antigen concentration in the circulation. Antigens involved in type 1 DM include 64kD antigen, glutamic acid decarboxylase (GAD) and cytoplasmic islet cell antigens. Cytoplasmic islet cell antibodies (ICA), bind cytoplasmic islet cell components on sections of human pancreas and the 64kDa antibodies precipitate a 64kDa protein from islet cell extract. Whereas 64kDa antibodies were shown to be β-cell specific within the islet, some ICA-positive sera have been described to react with all islet cells. The target antigen of the 64kDa antibodies was identified as the enzyme GAD. In order to analyze the fine specificities of ICA peripheral blood lymphocyte from prediabetic individuals and patients with newly diagnosed type 1 DM have been immortalized by EBV transformation. Islet cell specific b-cell line producing IgG antibodies that bound to cytoplasmic islet cell antigen(s) were established. Surprisingly all (six) monoclonal antibodies produced by these lines, recognized GAD as target autoantigen. Thus, GAD may be a major target antigen in type 1 DM. It was recently documented that antibodies to GAD are sensitive markers for diabetes development but may also be present in genetically susceptible individuals who are unlikely to develop disease. Limited trypsin diagestion of the islet 64,000-M antigen yields three major poly-peptide products. It appeared that the presence of antibodies to 37,000M fragments were the best markers for diabetes development in genetically susceptible twins. Antibodies reacting with insulin can be also detected in the clinically latent prediabetic period. However, it appears that insulin autoantibodies have a lower sensitivity as a marker for diabetes development than GAD antibodies or ICA. The relative contributions of the above mentioned autoantigens to the induction and/or perpetuation of disease remains to be clarified. It is clear, however, that the identification of autoantigens in type 1 DM is essential both for diagnostic purposes and for potential immunotherapeutic intervention in the disease process.

Environmental factors:
Despite strong evidence for an association with genetic factors, the concordance rate for type 1 DM is surprisingly low in identical twins. This observation suggests that susceptibility to the disease, rather than the expressed disease, is inherited. The lack of 100% concordance in identical twins for type I DM has contributed to a search for environmental factors associated with the disease. The only clearly defined environmental factor increasing the risk for developing type 1 diabetes is congenital rubella infection, where up to 20% of such children later in life develop diabetes. This observation, in addition to the findings that an aminoacid sequence of DQ-bchain is also present in the E1 envelope protein of rubella virus would support viral antigen mimicry as an etiological factor in type I DM. The role of environmental factors is also suggested by an analysis of immune responses to cow's milk proteins. Nearly all type 1 DM patients have antibodies to a peptide of bovine serum albumin and demonstrate a T-cell response to it, compared to only about 2% of control.

**Immunopathogenesis:**

The pathogenesis of selective b-cell destruction within the islet in type 1 DM is difficult to follow due to marked heterogeneity of the pancreatic lesions. At the onset of overt hyperglycemia a mixture of pseudoatrophic islets with cells producing glycogen (a cells), somatostatin (d cells) and pancreatic poly-peptide (PP cells), normal islets, and islets containing both b-cells and infiltrating lymphocytes and monocytes may be seen. It should be noted that lymphocytic infiltration is found only in the islet containing residual b-cells. It is likely that the chronicity with which type 1 DM develops reflects this heterogeneity of islet lesions. In contrast to this chronicity in the natural history of the disease, b-cells are rapidly destroyed when pancreas is transplanted from identical twin donors into their long-term diabetic twin mates in the absence of immunosuppression. In these cases massive insulitis develops rapidly with infiltrating T lymphocytes indicating an anamnestic autoimmune reaction. In addition this observation also indicates that the chronic time course in type 1 DM (but not in a transplanted pancreases) is a consequence of down regulatory phenomena taking part in immunopathogenesis of the disease. These down regulatory mechanisms have been analysed in the animal models of type 1 DM. The existence of three animal models for type 1 DM, the BB rat, NOD mouse and MLD-STZ-induced diabetic mouse, has improved ability to understand the processes leading to b cell destruction. However, since all conclusions drawn from animal models are based on the assumption of an analogy with human disease, the analogy needs detailed validation. Activation of islet antigen specific CD4+ T cells appear to be absolute prerequisite for the development of diabetes in all animal models of type 1 DM. CD4+ islet specific T-cell clones derived from diabetic NOD mice, when injected into prediabetic or nondiabetesprone Fl mice, induce insulitis and diabetes. It was also reported that CD4+ T cells are sufficient to induce insulitis while CD8+ T cells contribute to the severity of the damage. These findings together with the evidence that insulitis in chronic graft versus host disease may occur in the absence of CD8+ T cells suggest that CD4+ T cells may be the only immunocompetent cells required in the disease process. However, it seems that only one subset of CD4+ T cells is responsible for disease induction. CD4+ T cell bearing
alloantigen RT6 are absent in diabetes prone BB rats and appear to protect AO rats from MLD-STZ induced diabetes.\textsuperscript{19,20} Down-regulation of diabetogenic autoimmune response by the spleen cells derived from animals treated with adjuvants could also be explained by CD4+ T cell subsets interplay.\textsuperscript{21} Preliminary results by Lafferty's group (to be published) indicate that pretreatment with adjuvant does not block the autoimmune response \textit{per se}, but rather may deviate the response from TH-1 type to TH-2 type cytokine profile. Indeed, high level of TH1 type cytokines IL-2 and interferon g are found to correlate or/and to enhance induction of autoimmune diabetes in experimental models.\textsuperscript{22-24} The TH-1 type cells, and in particular their product IFN-g, activate macrophages. In animal models of type 1 DM electron microscopic studies of pancreata showed that macrophages are the first cell type invading the islets.\textsuperscript{25} In vitro studies and studies on perfused pancreas suggest that Interleukin 1 (IL-1) and tumor necrosis factor (TNFa), two cytokines mainly produced by macrophages, induce structural changes of b-cells and suppression of their insulin releasing capacity.\textsuperscript{26,27} However, it seems that IL-1 and TNF do not contribute appreciably to the cytotoxic activity of macrophages.\textsuperscript{28} Interferon g is also a powerful activator of macrophages for nitric oxide synthesis. Recently, evidence has been provided indicating that NO synthase activity is involved in diabetes development.\textsuperscript{29} These data indicated, for the first time, that nitric oxide may be a pathogenic factor in autoimmunity and suggested a possibility that a new class of immunopharmacological agents, capable of modulating nitric oxide secretion may be tested in the prevention of type 1 DM development.\textsuperscript{30}

\textit{Pathogenesis of type 2(non-insulin-depenenO diabetes mellitus (type 2 DM)}

Type 2 DM has a greater genetic association than type 1 DM. The 100\% concordance rate in identical twins is thought to be overestimated, due to a selection or reporting bias. A population based twin study in Finland has shown a concordance rate of 40\%. Environmental effect may be a possible reason for the higher concordance rate for type 2 DM than for type 1 DM.\textsuperscript{31} Type 2 DM affects 1-2\% of caucasians,\textsuperscript{32} but it is much higher in some ethnic groups such as Pima Indians\textsuperscript{33} and Arabs,\textsuperscript{34} an approaches 50\% in South India. This indicates that genetic factors are more important than environmental factors. Except for maturity onset diabetes of the young (MODY), the mode of inheritance for type 2 DM is unclear.

MODY, inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome 7p. Glucokinase is a key enzyme of glucose metabolism in beta cells and the liver.\textsuperscript{35,36} MODY is defined as hyperglycemia diagnosed before the age of twenty-five years and treatable for over five years without insulin in cases where islet cell antibodies (ICA) are negative and HLA-DR3 and DR4 are heterozygous. MODY is rare in Caucasians, less than 1 \%, and more common in blacks and Indians, more than 10\% of diabetics. Chronic complications in MODY were thought to be uncommon but later were found to be more common, indicating its heterogeneity. Considering MODY as a separate entity may masquerade its association with specific genetic diseases; and without a definite genetic marker, it should be treated as type 1 DM.\textsuperscript{37} Identification of a nonsense mutation in the glucokinase gene and its linkage with
MODY was reported for the first time in a French family, implicating a mutation in a gene involved in glucose metabolism in the pathogenesis of type 2 DM. Later, sixteen mutations were identified in 18 MODY families. They included 10 mutations that resulted in an amino acid substitution, 3 that resulted in the synthesis of truncated protein, and 3 that affected RNA processing. Hyperglycemia in these families was usually mild and began in childhood, whereas the hyperglycemia of MODY families without glucokinase mutations usually appeared after puberty.

Molecular genetic studies in type 2 DM, with the exception of MODY, have not been as successful as in type 1 DM. Mutations in the insulin gene lead to the synthesis and secretion of abnormal gene products, leading to what are called insulinopathies. Most of the patients with insulinopathies have hyperinsulinemia, inherited in autosomal fashion, heterozygous for normal and mutant alleles, and normally respond to exogenous insulin administration. Most insulin gene mutations lead to (a) abnormal insulins, such as insulins Chicago and Wakayama where the mutation leads to an amino acid replacement at an important site for receptor interaction; or (b) the mutation may interfere in the proinsulin processing to insulin. The association of the polymorphic (hypervariable) 5' flanking region of the human insulin gene and type 2 DM is lacking in some population groups, indicating that it may be one of many factors in a multifactorial disease. Even MODY patients have shown no association with this region. It was mentioned earlier that there is a strong association between HLA-DR3/4 and type 1 DM. It was also reported that such an association is present with type 2 DM, rendering HLA-DR3/4 markers for beta cell destruction in these patients.

Pancreatic abnormalities in islet secretory cells in type 2 DM are noted in beta, alpha and delta cells of the islets. Defects involving insulin secretion include relative decrease in basal secretion, decreased first and second phases of insulin response, glucose insensitivity and amino acid hypersensitivity of insulin release. Number and volume of beta cells are usually decreased to half of the normal, and, the alpha cell mass is increased leading to hyperglucagonemia. The islets exhibit hyalinization and amyloid deposition, containing islet amyloid polypeptide (IAPP) or amylin. This is a minor secretory peptide of the beta cells, released along with insulin and C-peptide, but its role in the pathogenesis of type 2 DM is not well understood. This amylin is thought to produce insulin resistance. IAAP is reduced with progression of type 2 DM. Intimate contact between beta cells and amyloid deposit in type 2 DM is noted by electron microscopy. Away from the islets in the exocrine pancreas, fatty infiltration and diffuse fibrosis are evident. Defective islet cell function is the primary event which may be due to an autoimmune reaction producing hyperglycemia in type 2 DM.

The insulin receptor gene is located on chromosome 19 and it encodes a protein having alpha and beta subunits including the transmembrane domain and the tyrosine kinase domain. Mutations affecting the insulin receptor gene have been identified and their association with type 2 DM and type A insulin resistance is recognized. Type A insulin resistance is hereditary and type B is an autoimmune disorder. Restriction fragment length polymorphism (RFLP) analysis of the insulin receptor gene, erythrocyte glucose
transporter gene and HLA genes were not found useful as genetic markers for type 2 DM.

Insulin resistance is insufficient to cause overt glucose intolerance, but may play a significant role in cases of obesity where there is known impairment of insulin action. Insulin resistance per se may be a secondary event in type 2 DM, since it is also found in non-diabetic obese individuals. Insulin secretion defect may be the primary event, presenting as impaired pulsatile secretion of insulin. Hence, hyperglycemia is an inducer as well as a consequence of impaired islet cell function and insulin resistance. Many factors contribute to the insulin insensitivity, including obesity and its duration, age, lack of exercise, increased dietary fat and decreased fibres, and genetic factors. Fish oil is found to prevent insulin resistance in animals, but not in humans. It has a protective effect against thrombosis and vasospasm in type 2 DM.

Insulin resistance in type 2 DM is not totally clear, it may involve reduced insulin receptor number, it may be secondary to hyperinsulinemia and hyperglycemia, or it may result from reduced tyrosine kinase activity or even abnormalities distal to the receptor involving glucose transporter proteins through a family of glucose transporter genes. The GLUT2 gene, expressed in liver and pancreatic beta cells, and GLUT4, expressed in skeletal muscle and adipocytes, are strong candidate genes for the genetic susceptibility to type 2 DM (reviewed in 48a). Analysis of these two glucose transporter genes, in addition to GLUT1, encoding for the brain/erythrocyte glucose transporter, has yielded, in Caucasians, no association of any RFLP marker on haplotype with either type 2 DM or obesity.

Obesity has genetic as well as environmental causes. It has a strong effect on the development of type 2 DM, as it is found in western countries and some ethnic groups such as Pima Indians. Obesity is more than just a risk factor, it has a causal effect in the development of type 2 DM against a genetic background. The evolution from obesity to type DM results from a succession of pathophysiological events: (a) augmentation of the adipose tissue mass, leading to increased lipid oxidation; (b) insulin resistance noted early in obesity, revealed by euglycemic clamp, as a resistance to insulin-mediated glucose storage and oxidation, blocking the function of the glycogen cycle; (c) despite maintained insulin secretion, unused glycogen prevents further glucose storage leading to type 2 DM; (d) complete b-cell exhaustion appears later.

Type 2 DM patients have a characteristic shoulder, girdle-truncal obesity. When compared with the gynoid, peripheral type obesity, patients who have android, central-type of obesity, show a higher rate of insulin resistance, type 2 DM, hyperlipidaemia, hypertension and premature mortality. Furthermore, the fat cells in shoulder-girdle-truncal obesity expand and shrink in response to calorie intake; but in pelvic-girdle obesity, the fat cells do not show such a response.

Nutrient composition has also been found to be a risk factor for developing type 2 DM, where increased fat and decreased carbohydrate consumption have contributed to
hyperinsulinemia of obesity. Dietary fibres, both soluble and insoluble, improve type 2 DM. It is also found that simple sugars do not directly cause diabetes. Deficiency of micronutrients, such as chromium and copper, is found to be an important cause of type 2 DM in a minority of cases.

Stress has also been thought to induce type 2 DM. Electroconvulsive therapy has been tried, inconclusively, to improve the disease in depressed patients. Actually, obesity and over-availability of food rather than stress, are the contributing factors to type 2 DM. Therefore, when permanent change in dietary habits is established, some people should be allowed to escape the "life-long" diagnosis of type 2DM.

In conclusion, it is said that both types 1 and 2 DM have a genetic background; however, we are unable to define the genetic lesion and the mode of inheritance of this disease. Type 1 DM has a high discordance in identical twins, indicating that the nuclear genetic component per se is not sufficient for full penetrance; therefore it is most likely due to environmental changes. Type 2 DM exhibits several features of a degenerative disorder and can thus possibly be attributed to a variety of degenerative processes associated with defects in oxidative phosphorylation. Hence, the possibility that environmental factors could preferentially affect the second human genome, the mitochondrial DNA, thus leading to metabolic, immunologic, genetic and phylogenetic alterations.

Acknowledgements

This paper was presented in part by one of us (MFH) at the 1992 meeting on 'Update in Diabetes', Abu Dhabi, UAE. We thank Dr. M. Agarwal for the critical review of the manuscript, and M. Channon and P.K. Ratnayaka for the secretarial assistance.

References

4 TODD JA, ACHA-ORBEA H, BELL JI.; A molecular basis for MHC class II-associated autoimmunity. Science, 1988; 240: 1003-1009.
5 NEPON GT.; A unified hypothesis for the complex genetics of HLA associations with IDDM. Diabetes, 1990; 39: 1153-1157.
16 GILL RG and HASKINS K.; Molecular mechanisms underlying diabetes and other autoimmune diseases. Immunology Today. 1993; M: 49-51.
20 PRAVICA V, EJDUS Z, MOSTARICA M, STOSIC S and LUKIC ML.; Resistance to multiple low-dose streptozotocin-induced diabetes in rats: Dependence on RT6 + T cells. (in press).
31 KAPRIO J, TUOMILEHTO J, KOSKENVUO M et al.; Concordance for Type I (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes mellitus in population based cohort of twins in Finland. Diabetologia, 1992; 35: 1060-1067.
34 RICHENS ER, ABDELLA N, JAYYAB AK, ALSAFFAR M and BEHBEHANI K.; Type 2 Diabetes in Arab patients in Kuwait. Diabetic Medicine, 1988; 5:231-234.
51 EVEPHART JE, PETTITT DJ, BENNETT PH and KNOWLER WC.; Duration of obesity increases the incidence of NIDDM. Diabetes, 1992; 41: 235-240.
HAFFNER SM, MITCHELL BD, STERN MP, HAZUDA HP and PATTERTSON JK.;
Public health significance of upper body adiposity for non-insulin dependent diabetes in

National Diabetes Data Group; Classification and diagnosis of diabetes mellitus and other

WILSON PW, MCGHEE DL and KANNEL WB.; Obesity, very low density lipoproteins
and glucose intolerance over fourteen years: the Framingham study. Am. J. Epidemiol,

KNOWLER WC, PETTITT DJ, SAAD MF et al.; Obesity in the Pima Indians: its

MCKEIGNE PM, PIERPOINT T, FERRIE VE and MARMOT MG.; Relationship of
glucose intolerance and hyperinsulinaemia to body fat pattern in south Asians and

JOFFE BI, PANZ VR, WING JR, RAAL FJ and SEFTEL HC.; Pathogenesis of non-
insulin-dependent diabetes mellitus in the black population of southern Africa. Lancet.

KNOWLER WC, NELSON RG, SAAD MF. BENNETT PH and PETTITT DJ.;

FELBER JP.; From obesity to diabetes: pathophysiological considerations. International

SCHMIDT MI, DUNCAN BB, CANANI LH, KAROHL C and CHAMBLESS L.;
Association of waist-hip ratio with diabetes mellitus. Strength and possible modifiers.

FAKHRI 0, FADHLI AA, EL KAWI RM.; Effect of electro-convulsive therapy on diabetes

AKINMOKUN A, HARRIS P, HOME PD and ALBERTI KGMM.; Is diabetes always

GERBITZ KD.; Does the mitochondrial DNA play a role in the pathogenesis of diabetes?