The Genetics of Non Insulin Dependent Diabetes Mellitus (NIDDM) in Africa

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NIDDM as a genetic disorder

NIDDM is one of the commonest metabolic disorders encountered in clinical practice, affecting an estimated 3% of the population of the Western World [1]. Prevalence data from Africa have recently been reviewed [2] and it appears that NIDDM has a prevalence in South Africa comparable to that found in developed countries, with a similar rate in rural and urban populations. In the northern part of South Africa, the available data indicates a low prevalence rate in both rural and urban populations in most areas studied [3]. However, in some countries, such as Tunisia, the prevalence in urban communities is similar to that of the Western World [4].

The pathogenesis of NIDDM is not known, but it is widely believed that the disorder has a significant genetic component which acts together with environmental factors such as obesity in determining the clinical expression of the disease. The evidence for the existence of the hypothetical genotype is derived primarily from epidemiological data from three main sources; population studies, twin studies and family studies.

(a) Population Studies

The prevalence of NIDDM varies widely from <3% in some developing countries to 50% in Pima Indians [5] and there is evidence to suggest that the effect is partly accounted for by genetic factors [6]. The influence of population genetics on the prevalence of NIDDM was clearly demonstrated in a study of the Micronesian population of Nauru in 1982 [7]. HLA typing was used as a means of identifying the degree of foreign genetic admixture in this relatively isolated population, and it was shown that full-blooded Nauruans had a significantly greater prevalence of NIDDM than those with foreign genetic admixture in whom the putative diabetic genotype had presumably been diluted. Similar findings have been reported from studies in Mexican Americans [8].

Migrant Asian Indian populations have a higher prevalence of NIDDM than both the population of India and the population in the country of settlement, suggesting a founder gene effect with concentration by generations of inbreeding [9]. In South Africa, the Indian population has an age-adjusted prevalence of NIDDM of 13%, which is higher than any other population group in the country [10].

Studies of the Pima Indians have provided further evidence for a genetic component in that population, with a bimodal distribution of glucose tolerance suggesting a single major gene determining diabetes susceptibility [1].

(b) Twin Studies

Prevalence studies in monozygotic and dizygotic twins with IDDM and NIDDM have added to the thesis that the genetic influence in NIDDM is significant. Barnett et al studied 200 pairs of British monozygotic twin and found 48 of 53 pairs (90.6%) concordant for NIDDM, while only 80 of 147 pairs (54.4%) concordant for IDDM [12]. Newman et al studied American male monozygotic and dizygotic twins and found a 58% concordance rate for NIDDM in monozygotic twins, with 65% of the non-diabetic monozygotic twins demonstrating abnormal glucose tolerance [13]. Problems with follow-up precluded direct comparison with the dizygotic twins.

(c) Family Studies

It has long been noted that NIDDM tends to cluster in families [14] with a risk of 50% for the development of NIDDM in the offspring of two affected parents [15]. Furthermore, numerous studies have shown that non-diabetic first-degree relatives of NIDDM probands have abnormalities in glucose metabolism. Eriksson et al studied 26 first degree relatives of NIDDM patients, 19 patients with NIDDM and 14 healthy controls and found impaired non-oxidative glucose metabolism in normal controls, with impairment in first-phase insulin secretion additionally present in relatives with impaired glucose tolerance [16]. Similar findings have been reported by others [17, 18] and the subject has been recently reviewed in relation to the pathogenesis of NIDDM [19].

Thus, the collective evidence argues strongly for a major genetic component in the pathogenesis of NIDDM, although the nature of the defect remains unknown. Furthermore, the role of environmental factors, including diet, physical activity and obesity play an undefined role in enhancing expression of the genotype.
Methods of searching for the diabetes genes have used traditional linkage analysis and with the advent of new biotechnology, direct molecular screening of candidate genes for mutations. Despite these techniques, the genetic defect remains undefined in majority of patients with NIDDM.

2) Studies of Candidate Genes

a) The insulin gene

The insulin gene is located on the short arm of chromosome 11[20] and is composed of 1430 base pairs with three exon and two introns. The gene is flanked by the tyrosine hydroxylase gene on the 5’ end [21] and by the insulin-like growth factor gene on the 3’ end [22]. Inherited defects in the coding regions of the insulin gene have been described, but these are rare and comprise a minority of the diabetic population. Studies of the insulin gene using restriction fragment length polymorphisms (RFLP’s) have failed to demonstrate a significant role for the insulin gene in NIDDM using different models of inheritance [23, 24].

More recently, application of the polymerase chain reaction (PCR) and single stranded conformational polymorphism (SSCP) as a mutation screening method, identified an abnormal insulin promoter in American Blacks with NIDDM [25]. It was estimated that this abnormality contributed to diabetes in approximately 5% of this population with NIDDM.

Therefore, from the evidence to date, the conclusion is that insulin gene defects contribute to a minority of patients with NIDDM.

b) The Insulin receptor (INSR) gene

The INSR gene is composed of 22 exons and 21 introns and is located on the distal end of the short arm of chromosome 19 [26]. Metabolic studies have indicated that insulin resistance forms an integral stages of NIDDM and hence the INSR gene is a logical candidate gene to study. Mutations in the INSR gene using restriction fragment length polymorphisms (RFLP’s) have failed to demonstrate a significant role for the insulin gene in NIDDM using different models of inheritance [23, 24].

Using PCR-SSCP, however, no significant abnormalities of this part of the INSR gene have been identified in patients with NIDDM [31]. More recently, attention has been directed towards analysis of genes encoding proteins involved in the post-receptor signal transduction cascade such as insulin receptor substrate-1 [32] to further explore the mechanisms of insulin resistance in patients with NIDDM.

c) The glucokinase gene

Glucokinase (GK) is one of a family of hexokinases that is expressed in the pancreatic b-cell and the liver. In the b-cell, GK appears to act as a "glucose sensor", providing the cell with information of the prevailing blood glucose concentration and thereby regulating insulin secretion [33]. The GK gene, on chromosome 7, has been one of the most informative loci yet examined, yielding evidence of pathogenetic role in maturity-onset-diabetes of the young (MODY) subgroup of NIDDM. This disorder is inherited in an autosomal dominant fashion and has a typical clinical expression with early onset of hyperglycemia, due to a b-cell defect and slow progression [34]. The heterogeneity exists with a number of different mutations described in French and British pedigrees with MODY [35, 36]. The genetic diversity is further emphasized by the finding that mutations of the GK gene are not invariably found in pedigrees with MODY [34]. Nonetheless, this group of patients represent the largest subgroup of diabetics in whom the genetic defect is characterized.

Analysis of the GK gene in typical NIDDM has been informative [37]. The mutations described in some pedigrees have been associated with a clinical phenotype resembling MODY and thus may represent MODY diagnosed later in life [38]. It has been estimated that glucokinase gene abnormalities probably account for < 1% of cases of typical NIDDM [39].

d) Glucose transporter genes

The family of glucose transporters comprise of six facilitative glucose transport molecules with different sites of expression and physico-chemical properties [40]. Glucose transporter 2 (GLUT 2) is expressed in the liver and pancreatic islet and GLUT 4 is expressed in muscle and fat [40]. With the important roles these tissues play in glucose homeostasis, the GLUT 4 genes were considered excellent candidate genes to study in patients with NIDDM.
Evidence for GLUT 2 being important in the pathogenesis of NIDDM was provided by studies in diabetic rats which showed a significant reduction in pancreatic β-cell GLUT 2 immunostaining in diabetic rats as compared to controls which was shown to be unrelated to the effect of chronic hyperglycemia [41]. The postulates of the role of GLUT 2 dysfunction included that of chronic sub-optimal β-cell glucose transport relaying inaccurate information regarding the prevailing blood glucose concentration, consequently resulting in an inappropriately low insulin secretory response [41]. A second postulate was that GLUT 2 is lost in the development of NIDDM and is replaced by a low Km transporter (e.g. GLUT 1), thus producing the hypothetical β-cell "exhaustion" [42].

Linkage studies with GLUT 2 gene polymorphisms have not shown a significant association with NIDDM [43, 44] and direct molecular scanning has identified a missense mutation in exon 3 of the gene in Pima Indians, but is of uncertain significance [45]. Similarly, analysis of the GLUT 4 gene by linkage studies and direct molecular approaches have failed to demonstrate a significant role for this locus in the pathogenesis of NIDDM [46, 47] and it appears unlikely that mutations of glucose transporter genes will account for more than a minority of cases of NIDDM.

(e) The mitochondrial genome

The mitochondrial genome is a small double-stranded circular structure composed of 16,569 base pairs with no intron sequences [48]. The genome contains 37 genes which encode 13 proteins involved in the respiratory chain as well as molecules involved in protein synthesis [48]. The mitochondrial genome is entirely maternally derived and evidence has been presented that the inheritance of NIDDM has a maternal predominance [47, 49, 50]. This observation, coupled with the fact that oxidative metabolism in the β-cell is important in the regulation of insulin production [51] has led to analysis of the mitochondrial genome in NIDDM.

Mitochondrial cytopathies are recognized causes of disease and abnormalities in mitochondrial DNA have been described in association with the Kearns-Sayre syndrome, Pearson syndrome, Leber hereditary optic neuropathy, myoclonic epilepsy with ragged red fibres (MERRF), mitochondrial myopathy, lactic acidosis and stroke-like episodes (MELAS) and others [48].

Recently, Reardon et al [52] described a family with diabetes, sensorineural deafness and cardiomyopathy associated with the same mutation in mitochondrial DNA previously described by Goto et al in the MELAS syndrome [53]. This mutation was a point mutation at position 3243 of the t-RNA (leu) mitochondrial gene and has subsequently been found in other pedigrees in whom diabetes forms part of a variable syndrome including deafness and other neurological disorders (54, 55).

A second mitochondrial genetic abnormality associated with diabetes and deafness has been described in a family without evidence of neurological disease. This abnormality was 10.4 kb deletion of mitochondrial DNA [56].

Studies of the mitochondrial genome in diabetes are ongoing and additional defects may well be found. These will account for a subgroup of diabetics in defined as that of maternally inherited late onset insulinopaenic diabetes variably associated with deafness and other neurological disorders [57].

(f) Other candidate loci

Other genetic loci examined in relation to NIDDM include, amongst others, the glycogen synthase gene [58], insulin receptor substrate-1 gene [32], the hexokinase II gene [59] and HLA loci [60].

Taken together, the results of analysis of candidate genetic loci provide evidence of specific genetic susceptibility only for and estimated 5% of the cases of NIDDM. Thus, the nature of the putative loci conferring disease susceptibility in majority of the cases of NIDDM remain unknown, albeit the subject of earnest research.

The genetics of NIDDM in Africa

The contribution of genetic factors to NIDDM susceptibility in Africa is unknown and, indeed, the question as to whether diabetes in Africa is the same disease as that found in the developed world is unanswered.

A limited role for genetic factors in NIDDM in Africa was suggested by McLarty et al in a review of diabetes in Africa, with the finding that a positive family history of diabetes was reported in most published studies, although in the majority, was less than 10% [3]. Apart from the information provided by these studies, there is little further detail regarding inheritance patterns of NIDDM in the various countries of Africa.

Malnutrition is common in Africa and other developing countries, yet malnutrition-related diabetes (MRD) is uncommon as a recognized disease entity [61]. Apartment MRD, there may be a role for
malnutrition in the intrauterine and early post-natal life in the genesis of typical adult NIDDM. It is possible that the "inheritance" of NIDDM in Africa is related to pre and post-natal malnutrition with consequent impairment of normal pancreatic islet development. This would manifest as NIDDM in adults as the development of obesity or other factors induce insulin resistance, in a manner analogous to the thrifty phenotype hypothesis proposed by Hales and Barker [62].

These mechanisms have been suggested by Joffe et al in South African Blacks living in the Johannesburg region [63] with support provided by earlier studies showing that insulin secretary capacity is reduced in obese non-diabetic Blacks as compared to obese non-diabetic Whites [64].

Conclusion

The genetic contribution to NIDDM in the developed world is widely accepted with much supportive evidence, but the situation in Africa is at present unclear with insufficient data on which to base such an assumption. Clearly, there is a need for well-planned epidemiological surveys complemented by research into the pathogenetic mechanisms of NIDDM specific to Africa.

REFERENCES