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Ethnic comparisons in diabetes and insulin levels

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The prevalence of non insulin dependent diabetes mellitus (NIDDM) is increasing exponentially. While the genetic causes of NIDDM remain unclear, the differences in prevalence of NIDDM over time, between and within different ethnic groups highlight the importance of environmental factors in the development of NIDDM in any given individual. Besides the classical risk factors for NIDDM such as obesity and indolence, the role of intra-uterine over-exposure or deficit of nutrients is increasingly felt to be of importance in the aetiology of NIDDM. Indeed, ethnic differences in hyperinsulinaemia, can be detected at birth in some populations. *In utero* exposure to increased fuel supply may be of particular importance in Polynesian and American Indian populations. If this is so, efforts to control NIDDM will take several generations to be successful.

Lessons from the epidemiology of non-insulin dependent diabetes

Advances in molecular biology are revealing increasing numbers of genes associated with non-insulin dependent diabetes (NIDDM). So far, these have collectively been shown to account for under 10% of NIDDM in a variety of ethnic groups[1]. The recent introduction of the glutamic acid decarboxylase antibody assay has suggested that up to 22% of NIDDM in Europeans may actually be following a slow or incomplete insulin dependent diabetes (IDDM) type process[2]. However, the aetiology of NIDDM in the vast majority of patients, particularly non-Europeans, remains unknown.

Different ethnic groups have different prevalences of NIDDM[3]. Any hypotheses purporting to account for the mechanisms behind NIDDM, must therefore be able to explain differences in the prevalence of NIDDM between and within ethnic groups. For this reason, epidemiological studies of NIDDM are useful in providing both direction and validation for ongoing research into the aetiology of NIDDM. However, these differences in prevalence are associated with different levels and ranges of the two major risk factors for NIDDM (besides age): obesity and fitness[4].

The standardisation of the oral glucose tolerance test in 1979 has permitted a rapid growth in the number of comparable prevalence studies world-wide. These have revealed a massive difference in the age standardised prevalence of NIDDM. Among those aged 30-64 years, the prevalence of NIDDM ranges from 1.2% in Rural Tunisia and rural Tanzania to 50.3% in the Pima Indians of North America and 41.3% in Nauruans[3]. Comparisons of the same ethnic group in different locations, with similar standardisation, have shown significant differences which may indicate potential growth in the prevalence of NIDDM. For example, among Indian Asians, the prevalence ranges from 2.7% in rural Indians to 22.0% in Fijian Indians and among Chinese, the prevalence ranges from 1.6% in rural China to 13.1% in Mauritius.

This potential for growth in the prevalence of NIDDM is now being confirmed in studies comparing the prevalence of NIDDM over time. Prospective studies among Mauritians[5], Polynesians[6], Japanese[7] and other populations suggest a 50-100% increase in the age adjusted prevalence of NIDDM over the next 10-20 years. While the thrifty genotype hypothesis may explain aspects of the epidemiology of NIDDM, and an inherited predisposition to NIDDM may be a prerequisite to NIDDM, these geographical and temporal differences in prevalence within the same ethnic group indicate that other mechanisms are also of importance. To what extent lifestyle factors, such as obesity and inactivity, account for these mechanisms is unclear.

Thrifty genotype, thrifty phenotype and/or fuel mediated teratogenesis

One of the major pieces of evidence supporting the thrifty genotype hypothesis and a major role for genetic susceptibility to NIDDM were studies among monozygotic and dizygotic twins. However, recent studies suggest that only 40% of second monozygotic twins develop NIDDM rather than the >90% previously reported[8]. Such twins not only share their genomic sequences, but also share their intra-uterine life, although this may differ somewhat between twins. Investigations into this *in utero* environment have generated two major hypotheses that compete with, or complement, the thrifty genotype hypothesis. These are the thrifty phenotype[9] and the fuel mediated teratogenesis hypotheses[10].

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The thrifty phenotype hypothesis proposes that poor fetal and early post-natal nutrition impose mechanisms of nutritional thriftiness upon the growing individual and thereby predispose to NIDDM[9]. The hypothesis suggests that such undernutrition impairs the development of the endocrine pancreas, resulting in reduced β cell mass and a greater likelihood of NIDDM when exposed to environmental risk factors such as obesity, inactivity and ageing. In a number of European populations, the risk of NIDDM has been shown to increase as the birthweight decreases. Asian Indians, an ethnic group with a low birthweight have a high prevalence of NIDDM[11]. Furthermore, hypo-insulinaemia among those with NIDDM in European cohorts has been shown using a new (IRMA) assay[12].

However, the hypothesis is not consistent with the data from Pima Indians, where, a "U" shaped curve has been shown between birth weight and the risk of NIDDM[13]. That is, both small and large babies are at increased risk of future NIDDM. The Pima data has recently been used to suggest that the association between low birth weight and NIDDM has been through selective survival of those low weight infants genetically predisposed to insulin resistance ie this is expression of a "thrifty" genotype rather than "thrifty" phenotype.

The thrifty phenotype hypothesis also fails to explain how ethnic groups with high mean birthweights (eg Pima Indians, Polynesians) can have a high prevalence of NIDDM. The association between maternal diabetes and macrosomia and the high prevalence of NIDDM in the offspring of diabetic parents has led to the fuel mediated teratogenesis hypothesis[10]. This hypothesis proposes that exposure to glucose and other fuels causes β cell hyperplasia (as can be shown in the macrosomic fetus) and subsequent predisposition to future NIDDM. Evidence in humans comes from a 24 year follow up among Pima Indians[14]. While 5.7% of the offspring of women with a 2 hour glucose concentration <5.6 mmol/l had abnormal glucose tolerance, 50% of the offspring of women with a 2 hour glucose ≥7.8 mmol/l had abnormal glucose tolerance. The development of diabetes was more common in the offspring of women who developed diabetes during rather than after pregnancy. This observational study, while suggestive, can not absolutely separate genetic and *in utero* contributions to the development of NIDDM.

Evidence that *in utero* exposure to hyperglycaemia can lead to NIDDM in non-genetically prone subjects has, however, come from experiments in the rat[15,16]. *In utero* exposure to mild maternal hyperglycaemia results in macrosomia and eventual diabetes in the offspring. These findings have been shown whether hyperglycaemia has been induced by pre-gestational streptozocin[15] or partial pancreatectomy[16]. This diabetes then continues in the next 4 generations (when the experiment was terminated), in spite of the absence of any inherited predisposition.

If NIDDM was indeed due to *in utero* exposure to under- or over-nutrition, it would be expected that a maternal (rather than paternal) history of diabetes would be of the greatest importance *vis a vis* the development of NIDDM in the offspring. A number of studies in many ethnic groups have now shown that the probability of a diabetic individual having a diabetic mother rather than diabetic father is indeed much increased (2-3:1 respectively)[17]. As mitochondrial mutations only account for <2% of NIDDM in the populations studied to date[18], other means for inheriting/ acquiring NIDDM must be operating. Recent data collected during a door to door survey in South Auckland suggest that European, Maori and Pacific Islands women with NIDDM and previous diabetes in pregnancy have an increased risk of having a diabetic offspring over and above the usual maternal risk[19]. Although problems with reporting and ascertainment may exist in all such historical data, if true, there may be at least 3 mechanisms operating: a true genetic mechanism, *in utero* exposure to hyperglycaemia and perhaps a maternal inheritance mechanism (although this may be comprised of the previous mechanisms and ascertainment/ reporting problems). The thrifty phenotype hypothesis is also not excluded.

One clue to the mechanisms involved may come from addressing the question "when does hyperinsulinaemia commence?". All ethnic groups studied to date at high risk of NIDDM are hyperinsulinaemic when compared with Europeans[20]. In Asian Indians, Australian Aborigines and others this hyperinsulinaemia is present by early adult life[21]. However, a recent study of the umbilical cord blood in the offspring of women without diabetes suggested that when compared with Europeans, Asian Indians (who have low birth weights) had low insulin concentrations while Polynesians (who have a high birth weight) had higher insulin concentrations[22]. The "normal" Polynesian mothers were relatively more obese and hyperglycaemic when compared with the other subjects, and the neonates were similar to the offspring of women who had had gestational diabetes.

Conclusions

The data so far seem to suggest a more complex interaction of mechanisms than previously considered: a mix of "thrifty" genotype, "thrifty" phenotype and fuel mediated teratogenesis. Such complexity would help explain the difficulties in finding the genes responsible for NIDDM and the importance of clinical epidemiological techniques. These studies are of particular importance in view of the current pandemic of NIDDM. It is unclear to what extent the age adjusted increase in the prevalence of NIDDM is due directly to the growing prevalence of the traditional risk factors for NIDDM: obesity and inactivity. However, the growing prevalence of obesity among fertile women needs to be considered as a potential contributor to this pandemic through associated minor degrees of glucose intolerance in pregnancy and subsequent subtle damage to the fetal β cell *in utero*.

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