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4 Diabetes in tropical developing countries

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Introduction

Diabetes in tropical developing countries continues to attract epidemiologists, clinicians and basic scientists alike, because of the prospects it offers of not only improving patient care but also its contribution to the general understanding of diabetes itself. The major type of diabetes in the tropics remains non-insulin-dependent diabetes (NIDDM), the insulin-dependent (IDDM) type being relatively rare. The most fascinating type however, is so-called malnutrition-related diabetes (MRDM) to which most attention is devoted below.

Insulin-dependent diabetes mellitus (IDDM)

IDDM is relatively rare in tropical countries. The reason for this is unclear. Both genetic and environmental factors have been implicated. Haphazard organisation of medical services makes prevalence data extremely difficult to obtain in tropical countries. However, data from a large centre suggests a low prevalence of less than two percent in one Indian clinic population (1). More reliable population estimates are available in migrant Asians. Odugbesan and Barnett (2) from Birmingham, U.K. estimated that 4% of Asian and 18% of white diabetics attending their clinic were true IDDM subjects. Samanta et al (3) from Leicester (the 'Bombay' of the U.K.) challenged the view that Asians have a much lower prevalence of IDDM compared to Europeans (0.54/1000 for Asians and 0.99/1000 for white Caucasians, $P > 0.05$). Bodansky (4) reported a prevalence of 0.36/1000 for Asian children from West Yorkshire in the U.K. It appears that the prevalence of IDDM in Asians who have migrated to European countries is higher than that in native Asians. An international study has demonstrated an inverse association between average yearly temperature of the environment and the

incidence of IDDM (5). This could, in part, explain the higher prevalence rates of IDDM in Asians who are resident in the U.K., as well as stressing the importance of environmental factors.

HLA associations in indigenous as well as migrant Asian IDDM patients (6–13) have been reported. It appears that unlike the white Caucasians in whom DR-4 shows a stronger association with IDDM, Asians show the converse: a stronger association with DR-3 and a weaker association with DR-4. This observation, coupled with the fact that DR-4 is less common in Asians in general might offer part of the explanation for the relative rarity of IDDM in Asians from the Indian subcontinent. Recent studies have demonstrated that DQ- β is a primary site for predisposition to IDDM. Asians and white Caucasians have both shown similar associations in this region. Future fine structure analysis by techniques using, for example, oligonucleotide probes (14) should further resolve the question of genetic differences and/or similarities in Asian and white Caucasian IDDMs. Segall (15) has, none-the-less, stressed the importance of studying haplotypes in addition to individual genes, and raised the possibility that different haplotypes may be associated with different pathogenetic mechanisms and clinical-metabolic features. It would be of interest to study whether some of the distinctive features of IDDM in the tropics, such as later age at onset and relative resistance to ketosis, might be explained by haplotype differences.

On the other hand a number of environmental factors, including the effects of malnutrition and parasitic infections on immune response (16), deficient dietary protein (17) and prolonged breast feeding (18) (a common practice in developing countries) might also confer some protection against IDDM.

A previous claim (19) that pancreatic islet cell antibodies (PICA) are seen only transiently in Asian IDDMs is challenged by a recent study in migrant Indian IDDM subjects in the U.K. (20). Immune mechanisms, however, might be modified by the change in environment associated with migration.

Non-insulin dependent diabetes mellitus (NIDDM)

Epidemiology

Methods Akanji et al (21) have demonstrated the effect of ambient temperature on venous plasma glucose concentrations. Higher room temperature (33°C vs 23°C) led to elevation of 2 h plasma glucose (OGTT or a standard meal) by approximately 1 mmol/l. We have confirmed these observations in subjects in the tropics (unpublished data). The reasons for

this appear twofold: first, the 'arterialisation' of venous blood, and second, the possibility that metabolic differences could also contribute. It is intriguing to speculate how much this factor would contribute artefactually to the relatively high prevalence of hyperglycemia in tropical environments.

Population studies A number of prevalence studies have been published. Ramchandran et al (22) performed an OGTT (WHO criteria) in an iron ore factory hospital (Kudremukh) in South India. The overall prevalence of diabetes was high at 5% and in those above 40 years it was a staggering 21%. Higher socio-economic status and obesity were associated with increased risk. As with the Daryaganj survey (23) this study emphasises the very high prevalence of diabetes in Indians in Asia. After all it may not be necessary to migrate to the U.K. to get diabetes! The difference from the Indian Council of Medical Research study (24) which quoted a prevalence of only about 2% is not easy to explain. It could be a real increase over a decade, but methodological differences could also contribute.

Omar et al (25) studied the prevalence of diabetes (OGTT) and hypertension in South African Indians, and also reported a high prevalence of diabetes (9%). Half the diabetic subjects also had hypertension. Simmons et al (26) studied the prevalence of known as well as undiagnosed diabetes (OGTT) in Coventry, U.K. In a preliminary analysis 11.2% of Asian men and 8.9% of Asian women were found to have diabetes; by contrast diabetes was found in only 2.8% Caucasian men and 4.3% Caucasian women. Unlike these reports, a study from Israel (27) showed that Israelis originating in Africa and Asia had a smaller prevalence of diabetes than those originating in America, Europe or Israel itself. It thus appears that Asians are genetically more susceptible to develop NIDDM either at home or abroad. Indeed, Ramchandran et al (28) have demonstrated a very high risk of diabetes in the South Indian families with only one diabetic parent. Native Africans, on the other hand seem less prone to develop NIDDM. A study in rural Mali (29) found only 0.92% of the population with fasting glucose > 7.0 mmol/l; Caucasians and Fulanis were more susceptible than Negroes.

Complications

The WHO Multinational Study (30) reported a widely different prevalence of macro- and micro-vascular disease in NIDDM subjects from different countries. Reports have now appeared from Africa, the continent not represented in the WHO Study. Lester and Keen (31) found low rates of macro-vascular disease (peripheral as well as coronary and cerebral arteries) in Ethiopian diabetic patients from Addis Ababa, as did Rolfe (32-35) in

Zambian Africans. Hypertension ($> 160/95$ mmHg) was fairly common in both these populations (20% and 40%, respectively) and did show an association with the macro-vascular disease. Other risk factors, such as elevated blood lipids, smoking and obesity, were relatively uncommon. Both studies noted a moderate prevalence of background retinopathy, peripheral neuropathy and proteinuria. Proliferative retinopathy was rare. The main cause of visual loss was cataracts. Micro-vascular disease was associated with hypertension but not with HbA_{1c} concentrations. Dietary habits have been described in an Ethiopian study. Low calorie intake and a high PUFA/SFA ratio seem to have favourably affected blood lipids and atherogenesis.

By contrast, migrant Indian Asians show very high rates of morbidity and mortality from coronary artery disease (36–38). At least part of this seems to be related to the high prevalence of diabetes in these populations. Bangladeshis in East London (36) have three times the prevalence of diabetes, and higher plasma triglyceride and insulin concentrations than found in Caucasians. The authors hypothesize that insulin resistance may be the basic metabolic abnormality in Indian Asians, leading to hyperinsulinaemia, diabetes and abnormalities of lipoprotein metabolism, culminating in atherosclerotic coronary artery disease. Hyperinsulinaemia in Asians may have a genetic-racial basis as reported in the past (39–42), and as confirmed by Scholfield et al (43) recently. In the latter study, Asians showed higher glucose and higher insulin concentrations in the plasma than those in matched American vegetarians during an OGTT. Erythrocyte insulin receptor number was lower and affinity diminished in Asians compared to the Americans. This could partly reflect higher circulating insulin concentrations. The importance of this study is that vegetarian Americans have been compared, thus reducing the contribution of dietary factors. Decreased erythrocyte insulin receptor number and affinity have been reported by Ramchandran et al (44) in the offspring of conjugal diabetics. More studies are urgently needed amongst Asians in Asia where diabetes and coronary artery disease are both assuming increasing proportions.

Genetic factors in NIDDM

Hitman et al (45) studied diabetic Punjabi Sikh (Aryans) from the U.K. and South Indian Dravidian NIDDMs from India (46). They were unable to find any significant associations with genetic markers, including the insulin gene 5' hypervariable locus, the insulin receptor gene and class II HLA genes, in Punjabi Sikhs. South Indian Dravidians, however, showed an association with the class 3 allele of the insulin gene, but not with the other two markers. Interestingly, a weak association with HLA Bw61 (but not DR) has been

described in South African (47, 48) and Fijian Indians (49) with NIDDM. Similarly, a class-I allele association of the 5'-hypervariable region of insulin gene, usually seen in IDDM in white Caucasians, is described in a South African Indian family with NIDDM (50). Thus, there is a genetic heterogeneity in different subpopulations of Asian diabetics and findings from one study need not be applicable to other populations. The peculiar overlap with some 'IDDM markers' may have some relevance to the unusual metabolic features and the difficulties in classifying the young insulin requiring Asian diabetics.

Gestational diabetes (GDM)

If NIDDM (and MODY) are very common in Asians it is not unreasonable to expect a high prevalence of GDM in young Asian women. Two recent reports (51, 52) from the U.K. have stressed the much higher prevalence of GDM in migrant Asian women compared to white Caucasian women. Unfortunately, very little data is as yet available in native Asians. Ruiz et al (53) found a high prevalence of GDM in hospital population in Argentina. In our preliminary screening programme (unpublished data) we have found a very high prevalence of GDM in high risk pregnancies. Early diagnosis and prompt treatment (usually diet) have led to a normal outcome in the majority. A bad obstetric history may suggest undiagnosed GDM. Large scale population studies are, therefore, required to evaluate the prevalence and foetal/maternal risk of GDM, particularly in rural areas and poor communities (54). If MRDM really exists (!) it should not be unreasonable to expect high rates of 'gestational-MRDM'. Interestingly, it has been shown in Pima Indians (55) that future risk of NIDDM was higher in the offspring of mothers showing diabetes during pregnancy. High rates of GDM in Asian women may be a risk factor in the future development of diabetes in the offspring.

Malnutrition related diabetes mellitus (MRDM)

'What's in a name? That which we call a rose by any other name would smell as sweet'

This 'new' class of diabetes has been in the forefront since a WHO study group (56) thought it necessary to recognise it as a major class of diabetes worldwide. The *Diabetes Annual* /4 has highlighted the controversy surrounding the definition of protein-deficient diabetes (PDDM) and also suggested a new set of criteria for fibro-calculeous-pancreatic diabetes (FCPD).

The original concept implied that childhood protein malnutrition somehow led to development of diabetes in later life, but this has been challenged (57, 58). The concept of 'malnutrition' can be broadened to include micronutrients, toxins etc. The debate, therefore, about the definition of MRDM continues and is unlikely to have a more meaningful outcome unless aetiological relationships are clarified. Until such time only descriptive studies (59) are worthwhile.

The many ways in which 'malnutrition' could affect the pathogenesis, clinical and metabolic features, complications, outcome and treatment of diabetic syndrome are eloquently reviewed by Rao (60). Such a framework could provide a useful basis for future research. We may still have an interesting outcome to this 'fruitful metabolism of error' (61).

Experimental studies

Swenne, Crace and colleagues have studied the effects of a limited period (3 weeks) of childhood protein-energy malnutrition (PEM) on 'adult' (12 weeks) rats (62). PEM led to lower body weight, a temporary (only at 6 weeks) high 30 minute plasma glucose concentration during a GTT (not diabetic by WHO criteria!), and a persistent low insulin response (venous blood) despite normal glucose levels at 12 weeks. Islets from such rats, *in vitro*, (63) showed a diminished insulin response to glucose and non-glucose stimuli. Glucose tolerance deteriorated after 12 weeks and at 48 weeks there was no difference between the study and control groups (64). The insulin secretory response recovered in the study group to some extent, and was similar to that of the control group at 48 weeks, the latter having deteriorated. Despite the fact that C-peptide levels were not reported in these experiments, B-cell secretion appears to be diminished. Increased insulin sensitivity (65) could be responsible for the persistent low insulin response beyond the period of food deprivation. The exact significance of glucose 'intolerance' during food deprivation is not clear. Measurement of other fuels, such as NEFA and ketone bodies, would have helped to assess their contribution to glucose intolerance through the 'glucose - fatty acid cycle' (66). The relevance of such experimental models to 'human MRDM' is not yet established. These recent studies have however, revived the interest in animal models. It would be useful to assess B-cell function more intensively, *in vivo*, and also to see if the diabetogenic agents prove more detrimental in the study group.

Aetiology and pathogenesis

Autoimmunity A paper from Indonesia (67) has reported the presence of

islet cell antibodies in a case of 'MRDM' (sub-type not mentioned). This study highlights the difficulties of classifying young insulin requiring diabetic subjects in the tropics. The case in question may be a C-peptide 'positive' IDDM from a poor socio-economic background. There appears to be a substantial diabetes-related malnutrition, worsened by exocrine pancreatic deficiency. The only other study to report ICA positivity (68) in 'MRDM' showed similar rates to IDDM! HLA typing, and clinical and biochemical follow-up of all such patients would be very rewarding. At a MRDM meeting in London Ahuja reported an association with HLA DR-3 in his 'MRDM' (PDDM) patients. It would support the hypothesis that 'MRDM' (PDDM) is a *forme fruste* of IDDM (69), at least in a subset of patients.

Genetic factors Familial occurrence of FCPD has been described from South India (70, 71) where FCPD has the highest reported prevalence. The contribution of genetic and environmental factors to familial transmission is not known. A recent report (46) is perhaps the first to study the available genetic markers in FCPD. Surprisingly, both HLA DQ-B and the class 3 allele of insulin gene were increased in FCPD. This blurs the boundaries between the two major types of diabetes. Twenty percent of FCPD patients compared to one percent of control subjects possessed both the markers. It appears that FCPD in South India is genetically heterogeneous. The effect of the very high prevalence of NIDDM in South India is difficult to eliminate. The authors conclude that FCPD occurs in individuals genetically susceptible to either type of diabetes, who also have pancreatitis. Such a hypothesis could be challenged if we believe that diabetes in chronic pancreatitis (in this case TCP) is *secondary* to progressive exocrine damage reducing the B-cell mass below a critical level (72). The majority of TCP individuals would then be expected to become diabetic with increasing duration of pancreatitis. A study of TCP subjects who have not developed diabetes after many years of pancreatitis might provide useful information.

Environment and exocrine pancreas The search for environmental factors in the pathogenesis of FCPD continues. 'Malnutrition' and cyano-glucoside toxicity are the prime contenders. Due to increased awareness FCPD is now reported from an increasing number of places in India (73). Factors other than cassava in the diet may operate in these places. Many of our patients consume jawar (74) which is said to be high in cyanide content. A comparative study (75) from Trivandrum, South India and Marseille, France, compared dietary intake and exocrine pancreatic function in controls and subjects with chronic calcifying pancreatitis [Tropical Calcific Pancreatitis (TCP) in India, alcoholic pancreatitis in France]. Socio-economic status,

duration and severity of symptoms, and previous treatment with oral pancreatic enzymes were not discussed. Indian subjects tended to eat less calories particularly from fats and proteins. The source and quality of protein and the type of fats consumed may make a significant contribution to 'qualitative' malnutrition but are not discussed. It is not clear if the dietary evaluation refers to the intake prior to diagnosis or after treatment was instituted. The authors conclude that low fat intake may be aetiologically important in TCP. Exocrine function tests revealed reduced output of fat and protein digesting enzymes with increased output of amylase in Indian controls, particularly children. Significantly, calcium and lactoferrin concentrations in pancreatic juice were increased in Indians (patients as well as controls) and in TCP patients compared to controls (both populations). Increased calcium excretion is thought to be a non-specific marker for pancreatic lesions and lactoferrin is a natural antioxidant. Increased excretion of these two in the pancreatic juice suggests a subclinical pancreatopathy in Indian subjects.

It is of note that non-alcoholic chronic pancreatitis in the West is thought to result from heightened 'oxidative detoxification reactions' mediated by the cytochrome P-450 family (76). Cyanide or the non-nitrile portion of the cyanogenic glycosides could cause cellular toxicity by depleting natural antioxidants. Limited dietary availability of natural antioxidants (selenium, vitamin C, vitamin E) could predispose to possible oxidative damage at lower doses of the 'toxins'. Similar mechanisms are invoked to explain some of the clinical manifestations of kwashiorkor (M. Golden, in the London MRDM meeting, in press). The 'oxidant stress' hypothesis would bring together 'malnutrition', dietary 'toxins' and other factors in the aetiology of FCPD, or indeed 'MRDM' in general. Pitchumoni and his colleagues (77) have suggested a unifying hypothesis for alcoholic and tropical pancreatitis. They propose that alcoholic pancreatitis results from simultaneous exposure to cyanide in cigarette smoke, while tropical pancreatitis may result from dietary cyanide in malnourished children.

Exocrine pancreatic function Faecal chymotrypsin (FCT) is a simple, cheap and non-invasive test of pancreatic function. Its value in the diagnosis of pancreatic disease has been established (78, 79). Mohan et al (80) found subnormal FCT in over 85% of FCPD, $\approx 25\%$ of IDDM and $\approx 5\%$ of NIDDM subjects from South India. Serum amylase was similar in the three groups but lipase was decreased in FCPD.

We have investigated (81) serum immunoreactive trypsin (IRT) in diabetic subjects. Subnormal IRT concentrations were found in over 90% of FCPD subjects, $\approx 30\%$ of IDDM and $\approx 15\%$ of NIDDM subjects. Diminished exocrine function is a feature of primary varieties of diabetes even from the

West (82–84) and is thought to be due to diminished local trophic effects of insulin on the surrounding acini (85). It is not clear if IDDM and NIDDM patients in the tropics also have subclinical pancreatopathy of the type seen in FCPD. It is noteworthy that Balakrishnan et al (75) found evidence of 'pancreatitis' (elevated calcium and lactoferrin in the pancreatic juice); and elevated IRT concentrations have been reported (81, and unpublished data) in asymptomatic non-diabetic controls as well as IDDM and NIDDM subjects from India. Such results would substantiate an existence of a subclinical pancreatopathy in tropics, possibly related to increased environmental oxidant stress. Thus, FCPD would represent an extreme end of the spectrum, and subclinical pancreatopathy could also influence the clinical course and metabolic behaviour of the 'primary' varieties of diabetes in the tropics.

Contribution of insulin resistance Insulin resistance [either primary or secondary to insulin deficiency (86) and metabolic changes (87–89)] could worsen the effects of insulin deficiency, and contribute to the pathogenesis of hyperglycaemia in FCPD. Mohan et al (90) performed insulin tolerance tests in 12 FCPD (previously diagnosed, insulin treated; mean insulin dose 36 U/day), 10 NIDDM (newly diagnosed; untreated; normal BMI but significantly more obese than the FCPD group) and 12 control subjects. K_{ITT} (the rate constant for glucose decrement) was lower in FCPD and NIDDM subjects compared to controls, and there was no significant difference between the diabetic groups. K_{ITT} was widely scattered in FCPD, some were normal; K_{ITT} was inversely related to fasting plasma glucose but not to C-peptide concentrations. The authors conclude that FCPD patients show evidence of insulin resistance, similar to that found in NIDDM patients.

It is possible to disagree with the conclusions for a number of reasons. FCPD subjects were insulin treated, hence insulin antibodies could absorb the injected insulin leading to lower free insulin concentrations, and falsely low K_{ITT} values. On the other hand, previous treatment and metabolic control would improve insulin sensitivity, as shown by the inverse relation between K_{ITT} and the fasting plasma glucose. In addition, counter-regulatory hormones, especially glucagon would influence the results. Future studies need to control for such variables. From clinical experience it is well known that FCPD subjects need large doses of insulin at or near diagnosis (91) when they are severely hyperglycemic, underweight and consume large amounts of food. With improvement in glycemic status, weight gain and normalisation of appetite after insulin treatment, requirements fall to more reasonable levels. Ramchandran et al (92) performed serial studies of erythrocyte insulin binding in FCPD subjects. Initially the number and the affinity of

receptors were both significantly diminished. The affinity improved after treatment but the number of receptors apparently remained the same, unlike in NIDDM where it also increased. Such improvement in receptor function in insulin sensitive tissues could improve insulin sensitivity after metabolic control.

Clinical studies Clinical characteristics of TCP have been reported from New Delhi (93), Papua New Guinea (94) and migrants in France (95). Of the 23 TCP subjects from New Delhi, half were diabetic and two developed diabetic ketoacidosis during a pancreatitis episode. Serum proteins were normal and only three had BMI < 15 kg/m². The authors conclude that malnutrition and tapioca are unlikely to be etiologically important. Migrants with TCP (95) showed a peculiar tendency to hyperosmolar-nonketotic coma (unheard of in the subcontinent), goitre in some [absence prompted McMillan (96) to put forth his cyanide hypothesis], and 'special' skin lesions.

Suresh et al (97) have compared the value of ultrasonography and plain X-ray abdomen in the diagnosis of 'FCPD'. While ultrasonography missed a few stones, it demonstrated abnormalities of pancreatic morphology in subjects without calcification but subnormal FCT. These abnormalities (heterogeneous appearance, increased echogenicity) may also be seen in 'NIDDM'. Ductal dilatation (seen only in 2/16 of their non-calcific cases) is possibly a more important criterion. In the absence of any other marker the classification of such individuals as TCP/FCPD is doubtful. It would be interesting to follow up such cases. This study again highlights the subclinical pancreatopathy concept.

Conclusions

Recent studies have extended our knowledge of the peculiarities of diabetes in tropical-developing countries. Besides the much discussed role of childhood malnutrition, a number of other genetic, environmental factors seem to be implicated. Asians (particularly from the Indian subcontinent) at home or abroad seem to have a strong genetic predisposition to NIDDM. Migrant Asians are also prone to develop coronary artery disease. The common link might be the insulin resistance, the cause of which is not clear. Native Africans appear less susceptible to diabetes and macrovascular disease, compared to Asians. Studies of genetic markers in NIDDM have shown different results in different populations. Insulin dependent diabetic subjects in the tropics have shown a primary association with HLA DQ-B, as do white Caucasians, but the differences in haplotypes could be

associated with the different pathogenetic mechanisms, and consequently different clinical-metabolic features.

The original concept of MRDM seems oversimplistic. The concept of 'malnutrition' is rapidly expanding and a variety of different (known and unknown) dietary components (deficiency as well as toxicity) could possibly lead to a number of diverse metabolic effects culminating in hyperglycaemia in susceptible individuals. The exact target for such mechanisms (exocrine/endocrine pancreas, extrapancreatic) is largely unknown. Pancreatopathy appears more prevalent in tropics than hitherto suspected and may lead to diabetes or interact in various ways with primary diabetic syndromes. The aetiology and pathogenesis of this pancreatopathy are not known.

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