The Diabetes Annual/6
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4 Diabetes in tropical developing countries

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Introduction

Since the publication of *The Diabetes Annual/5*, many new papers have been published on different aspects of diabetes in tropical and developing countries. Most of the papers are in the field of 'malnutrition-related diabetes mellitus' (MRDM) and non-insulin-dependent diabetes mellitus (NIDDM). This chapter is therefore devoted to these two varieties of diabetes in tropical developing countries.

Malnutrition-related diabetes mellitus (MRDM)

Epidemiology and classification

Although the WHO Study Group (1985) (1) succeeded in focusing attention on varieties of diabetes peculiar to tropical developing countries, there is as yet no consensus amongst different workers on the existence of MRDM as an aetiologically distinct entity. The confusion about overlap with 'primary' varieties of diabetes persists, partly because the criteria for diagnosis of MRDM are 'soft', but also owing to many difficulties in clinical distinction between the two 'primary' varieties (IDDM and NIDDM) themselves. Clinical, biochemical and genetic – immunologic studies are appearing from different tropical developing countries, which should ultimately help resolve the controversy. Most of the studies usually apply subtle modifications to the most-quoted (Ahuja's) criteria of MRDM (2). Mohan et al. continue to expose the inadequacies of rigid, arbitrary phenotypic criteria, this time reporting 'FCPD' (fibro-calculous pancreatic diabetes) in elderly (3) as well as overweight (4) subjects, thus challenging the two major aspects (age and body weight) of the original definition. The situation is reminiscent of the all-too-familiar debate necessitating the change of terminology from 'juvenile-onset diabetes' to 'insulin-dependent diabetes'.

Akanji (5) analysed clinical features at diagnosis of young patients in a Nigerian clinic to diagnose those fulfilling the criteria of MRDM. Only 6% of patients were diagnosed before 30 years of age. Their mean BMI was low (19.0 ± 2.8 kg/m^2) and ~ 30% had presented with ketoacidosis. Socioeconomic status of these patients is not discussed but all ate cassava regularly. Only two patients fulfilled both Ahuja's (MRDM) (2) and Mohan's (FCPD) criteria (*The Diabetes Annual/4*). Five patients showed pancreatic calculi on a plain radiograph of the abdomen (FCPD); their mean BMI was 19.8 ± 1.5 kg/m^2, higher than Ahuja's cutoff point of 19.0 kg/m^2. He argues that 'classic' MRDM appears to be rare in a population in which it would be expected to occur commonly, and that the criteria for MRDM may have to be modified appropriately. Thus, despite his own evidence, he assumes that MRDM is more common than would appear to be the case from his own data!

A 'new' set of criteria 'suitable for field study' have been proposed (Surabaya – Kobe criteria) (6) to diagnose 'MRDM' but the association with 'malnutrition' is not favoured! Many previous criteria 'suggestive' of MRDM (relative body weight < 80%, ketosis resistance, insulin resistance and young age at onset) have been retained but it is suggested that 'definite' MRDM be diagnosed only if BT-PABA excretion in urine (a test of exocrine pancreatic function) is < 60% and that further 'classification' into PDPD and FCPD be based on absence or presence of pancreatic calcification seen radiographically. Attention has thus been focused on exocrine pancreatic deficiency as the pathognomonic feature of MRDM at the expense of 'malnutrition'. Furthermore, there is no guarantee that it will define a homogeneous entity distinct from the 'primary' varieties of diabetes because of the exocrine pancreatic involvement in IDDM as well as NIDDM (7 – 9). It is curious that the original term, PDPD (Protein-Deficient *Pancreatic* Diabetes), was unceremoniously changed to PDDM (Protein-Deficient Diabetes Mellitus) without any new data (10). The apparently surprising statements in a paper from a centre collaborating with the proponents of new criteria, 'Our present criteria for MRDM did not mention malnutrition . . ., because our MRDM patients did not show these symptoms. Our patients had recently contracted MRDM and were not malnourished . . .' (11) have to be viewed in this perspective. These reflect an alternative view of the presumed sequence of events in the natural history leading to the clinical picture at presentation (diabetes-related malnutrition rather than malnutrition-related diabetes). Lester (12) constructed the natural history of body weights of diabetic patients attending her clinic in Ethiopia. She could not find any evidence of undernutrition preceding diabetic symptoms, and weight loss appeared to be a result of uncontrolled diabetes. There are few prospective follow-up studies of young malnourished subjects in the tropics

that document the natural history of their clinical, biochemical and exocrine—endocrine pancreatic features.

Islet function and ketosis resistance

Resistance to the development of ketosis in adverse conditions is one of the major diagnostic criteria of MRDM (1,2). This metabolic feature is very probably multifactorial. Residual B-cell function (13), concomitant A-cell dysfunction (14), abnormal lipolytic responses of adipose tissue (15,16) and other factors (17) have been implicated.

Abdulkadir et al. (18) from Ethiopia measured serum C-peptide and glucagon in newly diagnosed (within 2–3 weeks of starting insulin treatment) PDPD patients. Serum C-peptide levels were available in 22/56 and glucagon in 14/56 subjects. Serum C-peptide concentrations in PDPD subjects were scattered but somewhat higher than those in IDDM (although statistically not different); serum glucagon concentrations were similar to those in IDDM subjects. Twenty-four patients were treated in hospital with a nutritious diet and insulin for 8 weeks; they increased their body weight by 1.1–5.4 kg/m^2. Treatment improved signs of nutritional deficiency, reversed liver dysfunction and normalised elevated stool-fat excretion. Withdrawal of insulin treatment at this stage revealed that three patients responded adequately to oral sulphonylureas, six became ketotic (approximately within a week of stopping insulin), while others remained free of ketosis for up to 15 days, although substantially hyperglycaemic. The majority of 'control' IDDM patients had become ketotic within 3 days of stopping insulin, although one did not do so for 30 days! Age and weight gain were no different in those patients with or without ketosis. Information on islet function, subcutaneous fat depots and plasma non-esterified fatty acid (NEFA) levels after insulin withdrawal would have been invaluable. Ketosis in these 'MRDM' subjects could be attributable to improved hepatic function (ketogenesis), improved pancreatic exocrine function (with improved absorption of dietary constituents), and increased supply of NEFA (from the expanded subcutaneous fat depots). Nutritional and glycaemic improvement, on the other hand, would be expected to improve B-cell function, making them more ketosis resistant. This study highlights the metabolic heterogeneity in PDPD and also the fallibility of the most important metabolic criterion used in the diagnosis of MRDM, i.e. lack of ketosis.

A study from Indonesia measured plasma C-peptide response in PDPD and FCPD subjects some years after diagnosis (11). Both groups showed substantial B-cell deficiency, FCPD subjects showing a much lower C-peptide reserve than those with PDPD, although no comparison with IDDM has been made. We have measured plasma C-peptide concentrations in

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FCPD subjects at presentation and after treatment (19,20). Although B-cell function was variable, ~ 75% of FCPD subjects at presentation showed severely diminished plasma C-peptide concentrations, indistinguishable from matched IDDM subjects; it is of note that even those subjects were not ketotic, despite diabetic symptoms of long duration. After treatment and improvement in nutrition and glycaemia there was a significant improvement in B-cell function of FCPD subjects, more so than that in IDDM subjects. A report from Uganda (patients treated for at least one year by insulin) showed that plasma C-peptide concentrations in FCPD subjects were lower than those in IDDM subjects during an IVGTT but no information on the tendency to ketosis was provided (21). It appears that there is more to ketosis resistance in MRDM than the mere contribution of residual B-cell function.

A-cell function (plasma glucagon) in PDPD was reported first by Rao et al. (14), who demonstrated normal fasting levels which fell after oral glucose. Recently, Mohan et al. (22) reported plasma glucagon levels in FCPD subjects who were selected on the grounds of not requiring insulin treatment; their B-cell function was comparable to that of NIDDM subjects. Fasting plasma glucagon concentrations were similar to those in NIDDM subjects but, after oral glucose, NIDDM subjects showed the expected paradoxical rise in glucagon levels whereas in FCPD these remained static. This interesting observation may possibly be explained by the intra-islet cellular interaction (23). The authors' contention, that this difference in A-cell response could be a factor in ketosis resistance in FCPD, is attractive but debatable because of the selection of subjects who would be ketosis resistant anyway. We found that plasma pancreatic glucagon levels in FCPD subjects with very severely diminished B-cell function were comparable to those in newly diagnosed IDDM and NIDDM subjects, and showed a paradoxical rise after oral glucose as in the other two groups. These observations raise intriguing possibilities about the selectivity of pancreatic islet-cell damage/dysfunction in FCPD. Other tests of islet function (e.g. arginine infusion) might shed more light on this subject.

Exocrine function

This is reported in two of the studies mentioned above. Both studies showed exocrine deficiency in PDPD. In the Ethiopian study (18), elevated stool-fat excretion returned to normal levels after nutritional rehabilitation and insulin treatment. In two patients autopsy showed severe pancreatic acinar atrophy and fibrosis but no calculi, a finding similar to those reported in kwashiorkor (24). In the Indonesian study (11), pancreatic isoamylase showed a substantial diminution in PDPD, but not as severe as that in FCPD. However, the effect of nutritional and glycaemic improvement has not been

described. These studies are some of the very few that have reported exocrine pancreatic function in PDPD. A previous study had failed to demonstrate pancreatic deficiency in PDPD (25). More studies are needed to clarify the exocrine–endocrine pancreatic interactions in tropical varieties of diabetes.

We have expanded our studies of the exocrine pancreatic marker serum immunoreactive trypsin (IRT), faecal chymotrypsin (FCT) and pancreatic isoamylase in different groups of diabetic subjects in India (PDPD was not diagnosed in subjects studied by us) (7,8,19). More than 90% of FCPD subjects showed severe diminution in all exocrine pancreatic markers; about 30% of IDDM and ~ 15% of NIDDM subjects showed diminution but never as severe as in FCPD. In the earlier stages of tropical calcific pancreatitis (TCP) (non-diabetic or IGT) there was evidence of active pancreatitis (elevated IRT) in some. There was a progressive and parallel decline in exocrine (IRT and FCT) and endocrine (plasma C-peptide) markers with deterioration of glucose tolerance, lending support to the idea that diabetes in FCPD is secondary to chronic pancreatitis.

Aetiology and pathogenesis

A study in children with varying degrees of protein-energy malnutrition (PEM) showed glucose intolerance in more severe cases, associated with a diminished immunoreactive insulin response to oral glucose (26). Serum growth hormone concentrations showed higher basal levels, not completely suppressed after oral glucose. All these factors are diabetogenic, as has been reported in many studies in the past. Major prospective studies are needed to understand the long-term implications of such observations.

As already mentioned briefly in *The Diabetes Annual/5*, familial aggregation of FCPD in south India was first reported anecdotally by Pitchumoni (27) and by Geevarghese (28). Mohan et al. (29) systematically studied families of FCPD patients in Madras (OGTT, plain abdominal radiograph, ultrasonography and FCT). Approximately 10% of patients had an additional member in the family with either pancreatic calculi or other evidence of exocrine pancreatic pathology. There was also a very high prevalence of glucose tolerance abnormalities, either with or without exocrine pancreatic involvement. Interestingly, consanguinity was present in all three families depicted, with strong familial aggregation. This is perhaps the strongest evidence so far for a possible genetic basis for FCPD in south India. However, as the authors stress, the familial aggregation could be attributable to either genetic or environmental factors. Previously, they have reported on the prevalence of various 'diabetic' genetic markers in FCPD (30) and are studying these in the family members. We have not as yet found

any familial clustering of TCP in our patients from central India. Familial occurrence of diabetes (and possibly TCP) in south India is possibly related to very high consanguinity and/or strong environmental agent(s). In the absence of a specific genetic marker, it is perhaps premature to draw any conclusions about the genetics of FCPD.

In a very interesting paper, Abdulkadir et al. (31) demonstrate an increased frequency of HLA DR-3 with a relative risk of ~ 7 in their PDPD patients, but DR-4 did not differ from controls. Previous demonstration that DR-3 may be associated with a relatively milder variety of IDDM, including later age at onset and relative preservation of B-cell function compared with DR-4-associated disease, supports the hypothesis that PDPD could be a milder variety of IDDM, possibly further influenced by associated malnutrition. It is also possible that DR-4-related severely affected patients might die in the community before diagnosis. The same authors have also shown that ketosis resistance in PDPD is not always a permanent feature (18), providing further support for the theory that PDPD may be a subtype of IDDM rather than an aetiologically separate entity.

Braganza hypothesised that her 'oxidant stress' hypothesis for non-alcoholic pancreatitis could be expanded to include TCP (32). Initial studies in Madras, India, have revealed that the clearance rate of theophylline (used as a marker for cytochrome P-450 function, presumably reflecting 'oxidant stress') was elevated in subjects with FCPD compared with non-diabetic controls (33). Theophylline clearance was (disappointingly) lower in Madras subjects than in Caucasians, which the authors ascribe to lower dietary protein. Urinary excretion of D-glucaric acid (used as a marker for activity of 'detoxifying' pathways) was similar in patients and controls, implying a relatively defective detoxification of free radicals in patients in view of the increased oxidant stress. Patients gave a history of increased exposure (either past or present) to various 'xenobiotics' including alcohol and cigarettes as well as to dietary cyanogens (source not specified) and unsaturated fatty acids, besides a number of polycyclic aromatic hydrocarbons (petroleum products). The authors suggest that various xenobiotics had induced cytochrome P-450I and that (relative) deficiency of antioxidants could set the stage for free radical damage to the pancreas. However, selection of 'laboratory controls' as well as an interviewer bias could have influenced conclusions about xenobiotic exposure. In addition, the influence of hyperglycaemia on these mechanisms needs to be more formally approached, in view of the claims that free-radical damage is involved in diabetic complications (34). In similar studies Adithan et al. (35,36) showed that theophylline clearance was elevated in IDDM but not in NIDDM patients from Pondicherry in south India but he did not study TCP. It is, perhaps, too early to draw any conclusions about the possible aetiopathological role

of oxidant stress in TCP, although it certainly is an attractive proposal, particularly from the viewpoint of therapeutic intervention.

Non-insulin-dependent diabetes (NIDDM)

Epidemiology

Asia New data on the very high prevalence of NIDDM in Asian Indians has been reported. A house-to-house survey of 'known diabetes' was carried out in Eluru (south India) (37) using methods similar to those used in the Southall survey (38). Prevalence was 6.1% in subjects > 40 years of age and 13.3% in the group aged 50–59 years. Despite the poor socioeconomic background, these rates are comparable to those in relatively affluent subjects in Delhi (39) as well as in migrant Asians in the UK (38). The authors have stressed the need for formal prevalence studies (OGTT and WHO criteria) in India. Against this background, a report from a north Indian hospital inpatient population is slightly surprising (1.2% diabetic, 2% IGT) (40). The author ascribes the low prevalence to the habitual consumption of a high-fibre diet but neither data on obesity nor the age-adjusted prevalence are provided.

Africa and Afro-Caribbeans A number of important studies have been reported from Africa. McLarty and colleagues reported an age-adjusted prevalence of 1.1% NIDDM and 8.4% IGT (WHO criteria) in native Africans from six Tanzanian villages (41). Almost one-half of the population was underweight (BMI < 20 kg/m^2) and only 6% were overweight (BMI > 25 kg/m^2). There was no appreciable deterioration of glucose tolerance with age. Very few diabetic subjects were symptomatic. Fasting and 2 h blood glucose levels were inversely related to BMI and haemoglobin concentrations, although the actual distribution curve of blood glucose in relation to BMI was U-shaped. There was no association of diabetes with alcohol intake.

Many previous studies have also reported low rates of diabetes in native Africans (42–44). However, a study in Nigeria (45), based on fasting plasma glucose (WHO criteria) and 75 g OGTT only, in a selected subpopulation gave a diabetes prevalence of 1.4%, which is higher than the prevalence previously reported from the same country (46). In addition, the use of fasting plasma glucose levels for screening must have underestimated the prevalence. In general, native Africans do not seem to be much affected by NIDDM today but the rates could be rising. In the Nigerian study, there was an association of diabetes with alcohol intake in male subjects which

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could be a significant risk factor in some areas. Information on exocrine pancreatic function in these patients would be of interest. Although formal prevalence rates according to modern criteria are not available for the Caribbean islands, migrant Afro-Caribbeans in the USA (47) and UK (48) have shown higher prevalence rates of NIDDM compared with the native White populations, suggesting that migration could precipitate NIDDM in groups traditionally believed to be less susceptible.

The low prevalence rates of diabetes in native Africans are in sharp contrast to the high rates in migrant Asians settled in Africa, emphasising the ethnic susceptibility of Asians to NIDDM, although an additional effect of migration is likely. Muslim (49) as well as Hindu (50) Asians in Tanzania showed an age-adjusted rate of ~ 7% for diabetes and ~ 20% for IGT. The relative importance of genetic and environmental factors cannot be studied in the absence of comparable data in native Asians. Interestingly, a follow-up after one year in the Hindu community showed an improvement in glucose tolerance in 80% of IGT and in 20% of diabetic subjects without any change in body weight or blood lipids. Similar improvement in IGT has been reported within 5 days of the first test in native Africans (41). The significance of this important finding remains to be established but should caution us against overinterpretation of single point prevalence studies. A large survey in Mauritius demonstrated very high rates of diabetes (> 10%) and IGT (> 15%) equally distributed in different communities, i.e. Hindus, Muslims, Creole and Chinese (51). This 'global' high prevalence points towards the powerful influence of environmental factors in the pathogenesis of NIDDM in Mauritius, especially because of the low rates expected in the Chinese. It is rather surprising that the Asians were not more severely affected!

The importance of environmental factors in the pathogenesis of NIDDM is again highlighted in an urban – rural survey of diabetes in Tunisia, where the urban population showed thrice the prevalence of diabetes found in the rural population (52). Interestingly, a history of diabetes in parents was found more in those who had been resident in urban areas for long periods than in those who had migrated from rural areas in the recent past, although diabetes rates in the two groups were similar. This observation highlights the 'environmental input' in the familial clustering of NIDDM. Family histories of NIDDM in African diabetic subjects are in general found less [~ 25% in Ethiopia (53) and Libya (54), ~ 15% in Tanzania (55)] than the usual figure of > 50% in Asians. Again, in the absence of genetic marker(s) it is not possible to be sure whether familial aggregation represents genetic or environmental risk. Thus, Asians could possess an excess of 'susceptibility gene(s)' or could have been exposed to a diabetogenic environment a generation or two earlier, arguably in the absence of any 'genetic' predisposition.

Clinical characteristics at presentation have been described in a prospective study of diabetic subjects newly diagnosed since 1981, from a large referral centre in Tanzania (55 – 57). Swai et al. found that ~ 15% of their patients were 'insulin-requiring', ~ 65% were non-insulin-requiring and the remainder could not be classified precisely for a variety of reasons. The majority (88%) were symptomatic. There was a seasonality of presentation, the numbers first attending the diabetic clinic being maximum during the months of August to November, irrespective of insulin requirement. Insulin-requiring patients were usually < 20 years and non-insulin-requiring > 40 years old. The mean BMI was 19.2 kg/m^2 in insulin-requiring and 25.9 kg/m^2 in non-insulin-requiring patients. Urban dwellers and office workers tended to be more obese than the rural residents and manual workers and also tended to present with diabetes at an earlier age. Four percent of patients died at presentation; ~ 30% of insulin-requiring and ~ 20% of non-insulin-requiring patients were dead within 5 years of diagnosis, usually of metabolic and infectious causes. The authors have stressed the poor prognosis of diabetes in Africa and the need for public awareness, early detection, proper management and follow-up. In Benghazi, Libya approximately 98% of patients attending the clinic were NIDDM, more than 75% presented after 40 years of age and obesity was common (~ 50% of men and ~ 85% of women) (54).

Obesity, B-cell function, insulin (in)sensitivity

Obesity is an accepted risk factor for NIDDM, especially in the developed countries. At the same time, it is well known that the prevalence of NIDDM may be quite high in some relatively non-obese populations. Obel (58) found that the BMI of NIDDM patients in urban Kenya was lower than that of the urban control subjects; rural controls were the thinnest. He concluded that obesity may not be a significant risk factor for NIDDM in the African Black. Information on body weight changes before diagnosis was not available. A similar lack of obesity is also noticed in indigenous Indian NIDDM subjects (59).

Recent studies have drawn attention to the central ('android') distribution of body fat rather than its mere presence as an important risk factor for metabolic and vascular disruption (60 – 62). Very little data on central obesity have till now been reported from tropical and developing countries. A recent study in obese Kuwaiti Arab women showed a direct correlation between 2 h plasma glucose during an OGTT and waist – hip ratio, but not BMI (63). McKeigue et al. (64) studied central obesity in migrant Asians in the UK and demonstrated a significant association between waist – hip ratio and hyperglycaemia, hyperinsulinaemia, dyslipidaemia and coronary artery

disease (Reaven's 'Syndrome X'). For a given BMI, Asians had a higher waist – hip ratio than did White Caucasians, perhaps explaining the higher risk in Asians of diabetes as well as of coronary artery disease. We have made similar observations in native Indians. In a group of non-diabetic and newly diagnosed IGT and NIDDM subjects, fasting as well as 2 h plasma glucose during an OGTT were directly related to waist – hip ratio but not to BMI. IGT and NIDDM subjects both had a higher waist – hip ratio than did the non-diabetic controls; BMI was highest in IGT subjects but only marginally higher in NIDDM subjects compared with non-diabetic controls. Thus, NIDDM subjects were centrally more obese, even though not by BMI criteria. Similarly, in a study from Mauritius, central obesity has been shown to be a risk factor for diabetes (65). More information is needed on the distribution of obesity in different populations and its relationship with metabolic and vascular morbidity.

Plasma insulin and C-peptide concentrations were measured in a small number of newly diagnosed diabetic patients from a rural tribe in north-western Tanzania (66). There was no difference in plasma insulin and C-peptide concentrations between diabetic patients and non-diabetic controls, demonstrating the existence of both insulin deficiency and insensitivity. A study from Saudi Arabia measured plasma insulin and C-peptide concentrations in newly diagnosed diabetic subjects in the fasting state and after intravenous glucagon injection (67). The authors found a significant endogenous B-cell reserve and propose that insulin insensitivity associated with obesity is the major risk factor for NIDDM in their patients. Similar results have also been reported from Nigeria in diabetic patients of long standing (68). The great variability between different insulin assays makes comparison between studies difficult. The cross-reactivity of proinsulin and its split products in the conventional radioimmunoassays also complicates the interpretation of immunoreactive insulin results (69). Rao (70) demonstrated lower plasma (free) insulin concentrations and an exaggerated rise in glucose levels during an OGTT in underweight NIDDM subjects compared with obese patients (both treated with insulin). He argues that chronic undernutrition might accentuate B-cell dysfunction and aggravate glucose intolerance. Plasma C-peptide would have been a more valid measurement of B-cell function in these insulin-treated patients. More significantly, in the absence of prospective anthropometric and metabolic data from before the time of development of diabetes, the 'chicken and egg' situation in relation to B-cell function and obesity remains unexplained. A reference has already been made to Lester's study from Ethiopia (12), which showed that most of the 'malnutrition' in her patients developed after the onset of diabetes and was possibly attributable to the uncontrolled diabetic state, rather than the other way round.

A reference has already been made in previous volumes of *The Diabetes Annual* to the insulin insensitivity of Asian subjects. Two more studies have reinforced the previous findings: McKeigue's study (64) has already been referred to; Hughes et al. (71) studied survivors of an initial myocardial infarction in Asians and Europeans in London and showed that Asians have higher 2 h plasma insulin and C-peptide levels after an oral glucose load. Thus, hyperinsulinaemia in Asians (presumably secondary to insulin resistance) seems to be associated with coronary heart disease. The methodology of OGTT and interpretation of C-peptide-insulin data in this study have been criticised (72,73). This paper also stimulated a debate on the insulin – atheroma hypothesis (74–76). Although central obesity is not described as one of the primary features of Syndrome X, it was related to hyperinsulinaemia in Asians in both of the above studies, and McKeigue believes it to be of major importance in Asians. It is a common clinical observation that Asians develop central obesity at a relatively early age and even in the absence of generalised obesity, but the pathogenesis of this central obesity remains unexplained.

Complications

Macrovascular The susceptibility of Asians to coronary artery disease and their relative immunity to peripheral vascular disease is well known. The association of coronary artery disease with insulin insensitivity has been mentioned above. Two more papers have highlighted the contribution of diabetes to an increased risk of coronary heart disease in migrant Asians. Thus, diabetes mellitus was present in 78% of Indian women in South Africa suffering myocardial infarction (77). The proportion was similar in younger as well as older groups (below and above 45 years). Obesity, lipid abnormalities and a family history of coronary heart disease were other risk factors, especially in older women. Woods et al. (78) performed a parallel case-control study of the risk of diabetes for myocardial infarction in Asians and Europeans in Leicester, UK: diabetes increased the risk of myocardial infarction ~ 3.3 times in Asians, but in Europeans only by ~ 1.3 times, compared with non-diabetic subjects. Interestingly, there was a preponderance of insulin-treated subjects in Asian diabetic patients suffering myocardial infarction (60% compared with 22% in Europeans), increasing the relative risk to 9.9 in this subgroup, though the numbers were small. Data on glycaemic control preceding the infarction would be very interesting. It is intriguing to speculate whether insulin deficiency or insensitivity contributed more to the problem in this subgroup. The authors point out that the final event leading to myocardial infarction is thrombotic and the risk factors for this could differ from those for the slow process of atherosclerosis (discussed above). There i
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above). There is very little information on the risk factors for thrombosis in Asian subjects. The possible dietary contribution to diabetes and atherosclerosis in Indians is reviewed by Raheja (79). The subject of coronary heart disease in migrant Asians has been reviewed by McKeigue et al. (80).

Microvascular Ever since migrant NIDDM Asians in the UK were reported to have a higher prevalence of 'microalbuminuria' (81) and also of clinical proteinuria (82) than comparable Europid subjects, reports of diabetic renal involvement in native Asians have been awaited. Two large referral centres in India [Vellore, south India (83,84) and Chandigarh, north India (85)] have reported their experience of clinical diabetic nephropathy in NIDDM subjects. Approximately 500 diabetic subjects were admitted at Vellore with a diagnosis of diabetic nephropathy (24 h urinary protein excretion > 500 mg on two occasions) in the period 1980 – 1985. In 55% of these, the known duration of diabetes was < 10 years; in 20% it was < 5 years; the majority were diagnosed as diabetic before 50 years of age. Men outnumbered women by a ratio of 4 : 1. Coronary heart disease was present in ~ 30% of patients and retinopathy in ~ 75% of patients, whereas cerebrovascular disease and peripheral vascular disease were relatively rare (~ 7% and ~ 5%, respectively). Approximately 10% of patients suffered from tuberculosis (pulmonary or lymphatic). The degree of proteinuria and renal function did not show a consistent pattern in relation to the duration of diabetes. Thirty percent of patients with 'end-stage renal failure' were between 41 and 50 years old. Chugh et al. (85) from Chandigarh described features of 250 NIDDM patients (> 40 years of age at diagnosis) with proteinuria > 150 mg/24 h. In a manner very similar to that of the Vellore data, 20% were proteinuric within 5 years of diagnosis and ~ 55% within 10 years of diagnosis. Renal insufficiency (serum creatinine > 133 μmol/l) occurred 11 ± 8 (mean ± SD) years after the diagnosis of diabetes, and end-stage renal failure (serum creatinine > 707 μmol/l) occurred 12 ± 7 years after diagnosis. Uncontrolled hypertension was associated with a more rapid decline of renal function. Both these studies provide cross-sectional data on diabetic nephropathy in NIDDM patients in India. Direct comparison with data from the West is difficult. Treatment of end-stage renal failure is a nightmare in developing countries because of severe resource limitations, psychosocial prejudices and legislative hindrance to cadaveric transplantation. As prevention is the only rational approach in such a situation, study of the natural history and special risk factors of diabetic renal disease in the tropical developing countries should be a priority.

Gestational diabetes (GDM)

In *The Diabetes Annual/5* data were discussed which emphasised that GDM (WHO criteria, IGT plus diabetes) is more common in migrant Asian women. However, studies correlating the level of maternal (hyper)glycaemia with foetal morbidity and mortality are few. On the basis of experience in many countries, the Pregnancy Study Group of the European Association for Study of Diabetes has increased the 2 h plasma glucose value during a 75 g OGTT to 9 mmol/l for a diagnosis of GDM to be made (86). A considerable number of Asian GDM women are IGT by WHO criteria and many show 2 h plasma glucose $\leq$ 9 mmol/l. Repeatability of an OGTT, especially in the borderline zone, is low [reviewed in (87)]. It is necessary to exclude the possibility that a higher prevalence of 'GDM' in Asian women might be merely a 'chemical' overestimate. Large multicentre studies using a standardised protocol need to be planned to define the levels of maternal glycaemia which will increase the foetal (and maternal) risks during pregnancy in developing countries.

Samanta et al. (88) compared the risks of GDM (WHO criteria) in Asian and White Caucasian women in Leicester, UK. Only 'high risk' women were screened; 1.38% of Asian women and 0.87% of White women showed 'GDM' (2 h plasma glucose $\geq$ 7.8 mmol/l during a 75 g OGTT, $p < 0.01$ for the difference between the two groups); the majority had IGT. In Asian women there was a significant trend towards increasing maternal 'complications' (toxaemia and caesarian section) across the glycaemic bands but this was not the case in White women. Foetal 'complications' (including microsomia – birth weight < 2500 g) were (expectedly) higher in Asian mothers with GDM. In both ethnic groups foetal problems were higher at either end of the maternal glycaemic bands. The small number of 'serious foetal complications' excluded a more detailed analysis of this important aspect. In the absence of information on 'background' frequencies of these problems in pregnancies that were not high risk in both groups, it is difficult to put these results in their proper perspective. The authors have suggested that 'the abnormal glucose tolerance in Asian women does not seem to suggest any major risk in terms of foetal and maternal complications'. However, the risks of 'minor' glucose tolerance abnormalities could be substantially different in developing countries because of the lower standards of medical care and also because of the possible interaction with other risk factors (maternal malnutrition, infections, etc.).

A study from Vellore, south India (89) reported whole-blood glucose concentrations during a 75 g OGTT in 668 unselected pregnant women attending the antenatal clinic at this referral centre. The distribution of blood glucose values is remarkably similar to the cutoff points suggested by WHO (1985).

However, no data on the prevalence of GDM nor of the foetal risks have been reported.

A study of 145 unselected pregnancies in Singapore (90) revealed a very high prevalence of GDM at 13.1% using WHO criteria. The prevalence rate is 10 times higher than that reported in 1985. Prevalence was highest in Indian women (23.5%). Only half of GDM women showed the classic 'high risk' attributes. Again, the outcome in these pregnancies is not reported.

Conclusions

Controversies about the existence and the definition of MRDM continue. The pathogenetic overlap between the two subvarieties of MRDM (PDDM and FCPD), if any, is not clear at present and this is partly responsible for the existing confusion. A 'new' set of diagnostic criteria has been suggested (Surabaya – Kobe) which proposes exocrine pancreatic deficiency as the pathognomonic feature of 'MRDM', rather than malnutrition. Many aspects of the previous definition (age, nutritional status, ketosis resistance) have been challenged, and the thesis that diabetes-related as well as maldigestion-related malnutrition contributes to poor nutritional state at diagnosis in these patients, is gaining ground. IDDM-like HLA associations and the development of ketosis in African PDPD patients after feeding are strong pointers that PDPD is only IDDM in disguise. On the other hand, FCPD appears to be a form of secondary diabetes (related to Tropical Calcific Pancreatitis) and more attention should be paid to understanding the underlying actiopathological mechanisms. Heightened 'oxidant stress' coupled with (relative) deficiency of antioxidants has been proposed as a possible pathogenetic mechanism for FCPD. The metabolic – endocrine basis of 'ketosis resistance' in MRDM appears to be multifactorial and previous explanations based on residual B-cell function can offer only a partial explanation. Glucagon secretion in both varieties of MRDM seems to be preserved to a much greater extent than the B-cell function, not unlike the situation in the early years of IDDM.

High rates of NIDDM have been reported even in rural native Asians, suggesting that ethnic susceptibility makes a significant contribution in this group. The stronger association of diabetes with coronary artery disease in Asians than in White Caucasians has been confirmed in different studies and evidence produced that the link could be through insulin resistance and hyperinsulinaemia. The important association of central obesity with hyperinsulinaemia, diabetes, dyslipidaemia and coronary artery disease (Reaven's Syndrome X) appears to be stronger in Asians than in White Caucasians and warrants further efforts to unravel the metabolic – endocrine basis of this association.

Native Africans seem to be less susceptible to NIDDM than native Asians but the incidence in Africans could be rising. Protection seems to be related to a 'primitive lifestyle' and leanness, migration to an urban environment or to western countries being associated with an increase in NIDDM. Extraordinarily high rates of glucose intolerance (IGT and diabetes) have been found in Mauritius in all ethnic groups, lending strong support to the apparently important role of environment in the pathogenesis of NIDDM on this island.

The foetal and maternal risks of the relatively high prevalence of 'GDM' in Asian women remain unexplained. A major study in the UK failed to show any major risks of GDM in migrant Asian women. Studies in native Asian women (and in women in other developing countries), especially in relation to maternal malnutrition and infections, would be of great importance.

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