# DIABETES IN THE TROPICS: DIFFERENCES FROM DIABETES IN THE WEST

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The importance of the study of diabetes in the tropics was first realized at the beginning of this century after a 1907 symposium on diabetes in the tropics which was published in the British Medical Journal[12]. TULLOCH's[38] book on diabetes in the tropics remains a classic to this day and helped focus attention on several aspects of the disease in tropical countries. The late Professor Kelly West also realized the importance of the study of diabetes in the tropics which he said provided 'some lessons for western diabetology'[44]. The purpose of the present article is to review the present state of the art and the gaps in our knowledge regarding diabetes in tropical countries. The recent WHO study group classification of diabetes[45] includes malnutrition-related diabetes mellitus (MRDM) as an entity separate from insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) forms of diabetes. While MRDM is unique in the strict limitation of its occurrence to the tropical belt, it is not the commonest form of diabetes in most of these countries.

In agreement with WEST[44] we use the term tropical diabetes to designate all forms of diabetes seen in tropical countries and not to any single disease[25]. Thus MRDM constitutes one type of diabetes under the broad category of tropical diabetes. In this review we shall first deal with the variations in IDDM and NIDDM in the tropics and then discuss the MRDM forms of diabetes.

## IDDM IN THE TROPICS

Several reports have shown that the classical insulin-dependent, ketosis-prone form of diabetes is uncommon in tropical countries[25,30,44]. It is difficult

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to exclude the possibility that early death or undiscovered diabetes account for all or some of this low prevalence of IDDM in tropical countries. There are few well conducted epidemiological studies on IDDM in the tropics. However, the fact that Japan (where health care is comparable to that in western countries) has a low prevalence of IDDM[6] suggests that there could be true differences in the occurrence of IDDM in different parts of the world. Recent research also provides evidence for differences in genetically linked susceptibility to IDDM in different populations.

*Studies on HLA and properdin (Bf) system*

In European populations the occurrence of IDDM is strongly linked to the histocompatibility leucocyte (HLA) antigens $DR_4$ and $DR_3$ and over 90% of patients have one or both of these antigens[4]. Recent reports from Taiwan[17], South Africa[28], and India[5] suggest that HLA $DR_4$ is absent in at least two populations: the Chinese and the Asian Indians. More interestingly it has also been shown that differences in genetic susceptibility to IDDM exist not only between Indians and Europeans, but also between North Indians and South Indians[15,16]. Tab. 1 summarizes the HLA and properdin system associations with IDDM in Europeans and other ethnic groups.

There are few data on viral, auto-immune or nutritional factors in the etiopathogenesis of IDDM in tropical countries.

## NIDDM IN THE TROPICS

NIDDM is the commonest form of diabetes in developing countries. At the Diabetes Research Centre, Madras, India, more than 90% of all diabetic patients have NIDDM as defined by the National Diabetes Data Group (NDDG) classification[27]. NIDDM shows several differences in its clinical presentation in tropical countries and these are summarized below:

a) *Reversal of sex ratio* - In affluent countries in the temperate zone the prevalence rates for NIDDM tend to be higher in females than in males and the ratio is usually 1.5:1[44]. In most tropical countries male predominance is more common. Interpretation of this is difficult because of the fact that in some societies women are less likely to seek medical attention than men.

| race | HLA | properdin (Bf) system |
|---|---|---|
| Europeans | B 8<br>B 15<br>B 18<br>DR 3<br>DR 4 | Bf S |
| North Indians | Bw 21<br>DR 3 | Bf S1 |
| South Indians | B 8 | Bf F |
| Chinese | DR 3 | ? |

Tab. 1 - HLA and properdin system associations with IDDM.

However, epidemiological studies[1] do suggest that this could be a true difference. Of further interest is the fact that men are often less fat than women in these societies.

b) *Lower prevalence of obesity* - In Europe and U.S.A., 80% of all patients with NIDDM are obese[43]. In tropical countries, obesity is not very common. On the other hand, a significant proportion of patients tend to be lean[43]. This suggests that the link with obesity and NIDDM might be different in populations across the world.

c) *High prevalence of NIDDM in migrant populations* - In certain populations within the tropical belt, high prevalence rates for diabetes are found. These include Micronesians and the people of the Mabuaig Islands in the Torres Strait[44]. Asian Indians are an interesting group from an epidemiological point of view. The prevalence of diabetes in Indians in India is not unduly high and varies from 1.5 to 2%[1]. However, the prevalence of diabetes in migrant Indians is very high and often exceeds that of the local host population two- to three-fold[37]. This finding has been confirmed in Indians in Trinidad[31], Fiji[46], South Africa[18] and recently in the U.K.[19]. These differences in prevalence rates between the host populations and the Asian Indians cannot be explained by differences in body weight or other environmental factors. This suggests that there could be differences in the genetic susceptibility to NIDDM between Asian Indians and Europeans. The evidence for this is reviewed below. On the other hand the fact that the prevalence of diabetes is higher in the migrant Indians compared to Indians in India points to the role of environmental factors as well. It is likely that a combination of genetic and environmental factors is responsible for the high prevalence of diabetes in migrant Asian Indians[24].

d) *Genetic factors in NIDDM in the tropics* - Recent studies have shown that there are differences in genetic influences in the etiopathogenesis of NIDDM in at least one ethnic group in tropical countries, the Asian Indians.

(1) *Studies on offspring of conjugal diabetic parents* - Offspring of conjugal diabetic parents (OCDP) are a high risk group for development of diabetes because of the strong genetic background. Earlier studies in Europeans had shown that the prevalence of diabetes in OCDP is low and varies from 3-12%[35]. A recent study from Madras based on a large series of OCDP showed that 50% have overt diabetes and 12% impaired glucose tolerance (IGT) according to the NDDG criteria[41]. Thus 62% have abnormal carbohydrate tolerance and this is considerably higher than that reported in any European series.

(2) *Prevalence of MODY and younger age at onset of NIDDM* - The form of diabetes known as MODY (maturity onset diabetes of the young) was first described by TATTERSALL and FAJANS[36]. The characteristics of this form of diabetes include onset at a young age, absence of ketosis and autosomal dominant inheritance[34]. Among Europeans, this type of diabetes is uncommon[29]. On the other hand reports from India[23] and South Africa[3] have shown that MODY is common among Asian Indians. In most tropical countries, e.g. Ethiopia and India, there is a shift to the left of the age at diagnosis of diabetes with the peak prevalence occurring at least a decade earlier than in western

countries[4,44]. The reason for this is not known but it may be related to the younger age structure of the populations of these countries.

(3) *Studies on C-peptide responses to glucose load in 'prediabetics'* - Pancreatic B-cell responses to glucose load were assessed in two groups of 'prediabetic' subjects namely the offspring of MODY[26] and in OCDP[33]. In both groups it was found that decreased pancreatic B-cell reserve could be demonstrated years before the onset of diabetes. Studying a similar group of European OCDP, BONORA et al.[7] were unable to find evidence of B-cell dysfunction in their study subjects. This again probably points to differences in genetic susceptibility to diabetes in different ethnic groups.

e) *Vascular complications in NIDDM* - The WHO multinational study of vascular complications[45] has provided valuable data on vascular complications in different countries. It was seen that while there were some differences in the prevalence rates of microvascular complications in different countries, no consistent pattern of presence or absence of these complications was seen among patients in tropical countries. The prevalence of peripheral vascular disease has been reported to be less common in tropical countries[14,22], but this needs to be confirmed. There is obviously need for further studies on the epidemiology of vascular complications in tropical countries.

## MALNUTRITION RELATED DIABETES MELLITUS (MRDM)

In tropical countries special forms of diabetes associated with protein-calorie malnutrition have been reported. The recent classification of the WHO study group includes MRDM as a separate entity and this emphasizes the need for more knowledge about these forms of diabetes.

In 1955, HUGH-JONES[13] described a form of diabetes with certain unique features that he called the 'J type' diabetes because it was reported from Jamaica. The characteristics of this type of diabetes are: (a) onset in youth (usually between the ages of 15-40 years); (b) insulin resistance as shown by requirements of large doses of insulin (over 2 U/kg body weight); (c) ketosis resistance, i.e. absence of ketoacidosis even when insulin injections are withdrawn for long periods of time; and (d) extreme leanness with a history of undernutrition in infancy or childhood. The WHO study group has defined this type of diabetes as protein deficient pancreatic diabetes (PDPD).

The second form of MRDM has most of the above features but there are three additional ones: (1) history of recurrent abdominal pain from childhood; (2) pancreatic calcification and/or fibrosis of the gland; and (3) evidence of exocrine pancreatic insufficiency. The study group has called this form of diabetes, fibro-calculous pancreatic diabetes (FCPD).

The study group report mentions that between 20-70% of all diabetic patients in some tropical countries have MRDM forms of diabetes. These figures appear to be rather high. In Jamaica, in HUGH-JONES's[13] original report only 13/215 (6%) patients had PDPD. In a subsequent report it was shown that many of these patients were actually poorly controlled NIDDM patients[39]. In Rhodesia only 1% of all diabetic patients had calcification of the pancreas[10]. In Tanzania only one patient with FCPD type diabetes has been reported in the literature[11] and in South Africa MRDM forms of diabetes are uncommon[32].

MRDM is reported more frequently from India. In North India PDPD, and in South India FCPD seem to be the more common types of MRDM. In AHUJA et al.[2] series from New Delhi, 27% of the patients with age at diagnosis below 40 years had PDPD diabetes but FCPD was seen only in a small group. VAISHNAVA and HAGROO[40] reported that 24% of a series of young diabetics (age at diagnosis below 40 years) had what would now be termed as PDPD but only two of their patients had evidence of pancreatic calcification. It must be emphasized that these figures concern only diabetics below the age of 40 years and not all diabetic patients seen in the clinic.

FCPD has the highest prevalence in South India and in the state of Kerala it is almost an endemic disease. GEEVARGHESE[9] has reported on the largest series of FCPD patients. At Madras, 13% of a group of young diabetics had FCPD[42]. Thus, while in some tropical regions the disease is fairly prevalent the figures do not appear to be as high as those reported by the WHO study group. Obviously proper epidemiological studies have to be done to define more clearly the distribution and prevalence of MRDM in tropical countries.

MCMILLAN and GEEVARGHESE[20] have put forward an interesting hypothesis to explain the occurrence of FCPD. The geographic distribution of FCPD coincided with the areas of consumption of cassava (manioc, tapioca). Cassava is known to contain cyanogenic glycosides, linimarrin and lotaustralin. Ingested cyanide is normally destroyed in the body by conversion to thiocyanate. This detoxification requires sulphur which is derived from sulphur containing amino acids. McMillan and Geevarghese performed animal experiments to see whether cyanide was able to produce pancreatic injury and diabetes. Studies in rats showed that ingestion of cyanide led to transient hyperglycemia. There was also a correlation between the ingestion of protein and the excretion of thiocyanate. They therefore concluded that their findings supported a role for cyanide in the etiopathogenesis of FCPD. The cassava hypothesis might explain the occurrence of MRDM in areas where the plant is consumed. However, it does not explain the occurrence of the disease in other places such as Madras where cassava is not consumed. The possibility of cyanide or other toxic agents in other foodstuffs has not yet been ruled out in these regions.

Recently, we have described heterogeneity with respect to several aspects of FCPD[22].

1) protein calorie malnutrition was seen in only 25% of our patients; however, 71% were lean;

2) cassava ingestion was absent;

3) while the majority of patients were ketosis-resistant a small sub-group were ketosis-prone; yet another sub-group responded to oral agents;

4) studies of C-peptide showed that there was a good correlation between the C-peptide reponses and the pattern of response to treatment;

5) vascular complications hitherto believed to be uncommon in these forms of diabetes were found to occur with the same frequency as in NIDDM. A more recent study[21] has shown that both proliferative retinopathy and maculopathy, the two sight threatening forms of diabetic retinopathy, are seen in patients with FCPD.

*Gaps in knowledge and future needs in studies on diabetes in the tropics*

There are major lacunae in our knowledge regarding the various forms of diabetes seen in tropical countries. It is not known whether differences in

genetic susceptibility to IDDM are present even within tropical regions. Studies on HLA and other genetic markers, viral and auto-immune aspects of the disease as well as data on vascular complications in IDDM in the tropics should provide more data on the profile of IDDM in tropical countries. Studies on NIDDM should focus on genetic mechanisms in other tropical countries. The significance of MODY in tropical countries has to be defined more clearly and future studies should show whether MODY is a separate form of NIDDM or whether it merely represents a continuum of NIDDM presenting at a younger age. The relative roles of genetic and environmental factors for the causation of diabetes and the factors responsible for the high prevalence in migrant populations deserve further study.

Finally, MRDM offers a fascinating area for research. Epidemiological data on the prevalence and clinical variations in the presentation of MRDM should be obtained. The role of malnutrition needs to be studied more closely. A search for cyanide and/or other toxic substances in various foodstuffs might help to plan intervention strategies for the future.

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