Malnutrition and Diabetes in the Tropics

REPORT OF THE INTERNATIONAL WORKSHOP ON TYPES OF DIABETES PECULIAR TO THE TROPICS

The International Workshop on types of Diabetes Peculiar to the Tropics was held in Cuttack, India, 17–19 October 1995. The workshop was attended by 60 delegates, most from four developing countries (India, Bangladesh, China, and Ethiopia), with observers from Europe and the U.S. It is now well recognized that diabetes in tropical regions and in some developing countries presents clinically differently from IDDM and NIDDM in the Western world and developed countries. The World Health Organization (WHO) acknowledged this in 1985 by recognizing a third class of diabetes, designated malnutrition-related diabetes mellitus (MRDM) and subdivided into fibrocalculous pancreatic diabetes (FCPD) and protein-deficient pancreatic diabetes (PDPD) (subsequently often called protein-deficient diabetes mellitus [PDDM]). Since then, information has been collected about diabetes in tropical regions. Such knowledge was presented and discussed at the workshop to serve as a stimulus to the further research that is necessary into the etiologic, epidemiological, and clinical aspects of this class of diabetes.

Another category of diabetes was also discussed: NIDDM in subjects of low body weight (also referred to as "lean NIDDM"). All cases of diabetes can be divided into IDDM and NIDDM according to the patient's current clinical and metabolic state. It was the consensus of the workshop that although it has served a valuable purpose, the term MRDM now be supplanted by the following: *1)* malnutrition-modulated diabetes mellitus (MMDM), to replace PDPD; *2)* FCPD, to be considered as a specific form of diabetes, clinically either NIDDM or, less frequently, IDDM; *3)* the low–body weight end (BMI $\leq$18.5 kg/m^2) of the spectrum of NIDDM, to replace the term lean NIDDM.

From our discussions, the following three consensus statements were advanced:

PDPD, PDDM

There is a clinical syndrome of diabetes that occurs in young malnourished individuals in developing countries. These patients' clinical features differ from the usual clinical presentations of IDDM or NIDDM as described in developed countries and from that of FCPD. These patients are insulin-requiring but not ketosis-prone. The designation recommended for this group is MMDM. This term replaces all other nomenclatures, such as MRDM, PDPD, and PDDM. The clinical characteristics of MMDM include:

1. having early onset of diabetes, usually before 30 years of age;
2. requiring insulin (to obtain adequate glycemic control);
3. not being prone to ketosis;
4. having an absence of imaging evidence of pancreatic calculi or ductal dilation;
5. having low BMI (usually <17), with other clinical features of malnutrition and often growth retardation.

FCPD

1. FCPD is a form of diabetes with a high prevalence in tropical and developing countries.
2. FCPD is due to chronic calculous pancreatopathy not to chronic alcoholism or other recognized ascribable causes such as hyperparathyroidism.
3. It is usually seen in young and malnourished individuals but also occurs in others.
4. Diabetes and pancreatic calculi and/or ductal dilatation are essential features. Recurrent abdominal pain and steatorrhoea are other important features, but absence of these latter does not preclude the diagnosis.
5. The clinical profile of diabetes shows a spectrum of hyperglycemia varying from severe to mild. Ketosis is uncommon.
6. Pancreatic calculi are usually large multiple and intraductal. Marked ductal dilatation and fibrosis are usual; inflammatory changes are uncommon.
7. Abnormal exocrine pancreatic function is invariably present but is often demonstrable only following investigation.
8. FCPD is associated with an increased risk of pancreatic carcinoma.
9. Management of FCPD includes treatment of diabetes, oral enzyme replacement, and relief of pain. Surgery may be required for severe intractable pain and for other indications.
10. The etiology of FCPD is uncertain. The roles of nutritional, environmental, and genetic factors need further investigation.

NIDDM in lean subjects

This group supports the WHO classification of NIDDM into obese and nonobese subclasses. In some developing countries, nonobese patients constitute the more common category, and a proportion of them have BMI of <18.5. There are many factors that are not well understood in these subjects with NIDDM and low body weight; further research is required in this group.

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COMMENTARY: TIME TO RETHINK MALNUTRITION AND DIABETES IN THE TROPICS

The last 3 decades have seen a fascinating evolution in concepts regarding the role of nutrition in the etiopathogenesis of diabetes in tropical countries. The pendulum has swung from one extreme ("The evidence that malnutrition protects adult populations from diabetes seems unassailable." [1]) to the other ("Malnutrition is probably a major determinant of diabe-

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FCPD, fibrocalculous pancreatic diabetes; MMDM, malnutrition-modulated diabetes mellitus; MRDM, malnutrition-related diabetes mellitus; PDPD, protein-deficient pancreatic diabetes; PDDM, protein-deficient diabetes mellitus; WHO, World Health Organization.

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tes." [2]). The turnaround has been so complete that the WHO has recognized MRDM as a form of diabetes that is distinct from classical IDDM and NIDDM (3). The umbrella term MRDM highlights the association (frequent but not invariable) of malnutrition with certain clinical diabetic syndromes in the tropics and has some utility because these syndromes have features that set them apart from both IDDM and NIDDM. Unfortunately, the creation of a third major form of diabetes that is neither insulin-dependent nor non-insulin-dependent presents major problems. In particular, the implication of etiologic distinctness conveyed by the term MRDM obfuscates the relationship of the tropical syndromes to the international nomenclature (i.e., IDDM versus NIDDM). The internationally accepted classification is based on clinical patterns not on etiology, and there appears to be little justification for such a radical departure from it.

In the decade since the publication of the WHO report, fresh evidence has become available regarding the interaction of malnutrition and diabetes in the tropics. It has recently been argued that the truth probably lies somewhere between the two extremes of either indicting malnutrition as the proximate cause for the peculiar diabetic syndromes described in the tropics or rejecting a role for it entirely (4). This centrist position has been affirmed in the above statement, leading to a recommendation that the nomenclature for the tropical diabetic syndromes be changed in a manner that reflects current thinking. The recommended changes may be summarized as follows:

1. The term MRDM is inappropriate, and the continued use of this terminology is inadvisable for the following reasons: it carries the implication of a uniform etiopathogenetic mechanism for several diverse clinical syndromes; epidemiological studies have failed to show an invariable association between malnutrition and these forms of diabetes; and its diagnosis relies exclusively on a low BMI being present at diagnosis of diabetes. The problem with this heavy reliance on a low BMI has to do with the fact that subjects with these syndromes of diabetes belong to the lower socioeconomic groups and are hence thin even before the onset of diabetes. Moreover, a history of prolonged neglect of symptoms can almost invariably be elicited in patients from a rural background. Thus, a significant component of the low BMI at diagnosis may be attributable to diabetes-related malnutrition, and its clinical use as an invariable marker of malnutrition-related diabetes may not be entirely justified.

2. FCPD, one of the two clinical syndromes incorporated under the umbrella term MRDM in the WHO classification, is often associated with malnutrition as a consequence of severe exocrine and endocrine pancreatic deficiency, which usually has remained untreated for an extended period before diagnosis. Since several studies show a frequent association between this syndrome and a low socioeconomic status, malnutrition may play a permissive role in its pathogenesis. However, compelling evidence for such a postulation is lacking, and there is a general agreement that this is a (secondary) form of pancreatic diabetes of uncertain etiology seen in tropical countries. Its relationship to nonalcoholic variants of pancreatic diabetes seen in temperate zones has not been determined.

3. There is no evidence implicating either protein deficiency or a pancreatopathy in the causation of so-called PDPD, the second of the two clinical syndromes that comprise MRDM. Thus, this term is erroneous and should be discarded. Experimental and clinical data support the contention that malnutrition can both play a permissive role in the pathogenesis of diabetes in a number of situations and modify the clinical picture of coexistent diabetes to give rise to "unique" features, such as insulin resistance and ketosis resistance. Thus, the entity that was formerly called PDPD is more appropriately termed malnutrition-modulated diabetes mellitus (MMDM).

4. NIDDM in malnourished individuals may represent one end of a spectrum of body weights associated with NIDDM; thus, lean NIDDM in tropical countries may not be an etiologically distinct entity. However, this syndrome occurs even in relatively affluent patients, and responsiveness to oral hypoglycemic agents is often preserved for prolonged periods after diagnosis. These features suggest that it may not be correct to dismiss it simply as a nutritionally modified variant of classic heredofamilial NIDDM. Further research is necessary to elucidate its etiopathogenesis and natural history.

The recommended changes in nomenclature reflect a major shift in emphasis, which is rooted in three concepts. The first and most fundamental of these concepts is that malnutrition may not be the primary cause of diabetes in the tropics. The reasons for such a reevaluation may be found in the existing literature, exhaustively reviewed elsewhere (4–7a). The preponderance of evidence indicates that in the majority of individuals with coincident malnutrition and diabetes, malnutrition cannot be indicted as the sole causative factor for diabetes. In particular, there is no evidence, experimental or human, to support the contention that "continued protein deprivation would ultimately result in irreparable damage to beta cells" (2) of a severity sufficient to cause diabetes in and of itself. Thus, it is clear that, notwithstanding the WHO classification of MRDM (and PDDM) as an etiologically distinct syndrome of diabetes, malnutrition is not the primary or even the most proximate cause of diabetic syndromes peculiar to the tropics. In the case of the syndrome of FCPD, the association is even more tenuous because it also occurs in well-nourished subjects and malnutrition can be excluded as the primary etiologic factor in such patients (8–10). Thus, at the present time, FCPD is best considered as a secondary form of diabetes. However, the conclusion that malnutrition does not play a primary role in the etiology of diabetes in the tropics does not mean that malnutrition plays no role whatsoever in the causation of diabetes in the tropics. Thus, a deficiency of antioxidants in the diet could set up unmitigated oxidative damage in the pancreas from xenobiotics abundantly present in the tropical environment, thereby contributing to the pathogenesis of FCPD (11).

A second concept important to understanding the interaction between malnutrition and diabetes in the tropics is that malnutrition could have an indirect role in the etiopathogenesis of diabetes in the tropics. Experimental data indicate that malnutrition might well play what has been termed a secondary role, whereby it unmasks or amplifies the effects of a primary diabetogenic influence that in itself might not be operating to its full effect (4). Recent epidemiological studies from the U.K. show a strong association between early (fetal and neonatal) malnutrition and the risk of diabetes and syndrome X in later life (12–14). The ar-

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guments that the authors of those studies make in support of this proposed link (15) are very similar to those advanced by one of us previously in relation to diabetes in the tropics (5,6), i.e., that the increased risk of diabetes is a consequence of fetal malnutrition (possibly due to maternal nutritional deprivation). According to these arguments, on the one hand, impaired development of β-cells during a critical period of intrauterine and early neonatal life results in an irreversible diminution in β-cell number and mass. On the other, resistance develops to the actions of growth-promoting factors, such as insulin, growth hormone, and IGF-I, in tissues and persists into postnatal life (16,17). These two processes may interact with each other or with other diabetogenic influences (genetic or environmental) to increase susceptibility to the future development of diabetes. Hales and Barker (15) have called this concept "the thrifty phenotype hypothesis," a term that carries the teleological implication of a long-term price that has to be paid to ensure the short-term survival and growth of the developing organism. The most obvious feature of the thrifty phenotype is a low birth weight, but low ponderal index, short length, and small head and waist circumferences at birth have been associated with adult diabetes or other cardiovascular risk factors in adult life. Similar reports of the association of low birth weight with adult diabetes and insulin resistance are available from the U.S. and Sweden (18–20). The thrifty phenotype concept is relevant to the causation of diabetes in the developing countries of the tropics. Malnutrition in pregnant mothers and fetal malnutrition are common: a third of all babies born in India have a low birth weight, predominantly because of intrauterine growth retardation (21). Studies from both India and the U.K. link fetal malnutrition with an insulin-resistant state in adult life, characterized by diabetes and coronary artery disease (14,22). Early life malnutrition coupled with overnutrition later in life seems to constitute a particularly deleterious combination of factors, suggesting an ongoing interaction between the two ends of the spectrum of dysnutrition in the pathogenesis of adult diabetes (23). Thus, the concept of a thrifty phenotype that is rendered detrimental by subsequent overnutrition provides insight into some of the well-known peculiarities of diabetes in developing countries in the tropics, such as India. As might be predicted from the thrifty phenotype concept, subjects in these countries develop diabetes at a an earlier age and with a relatively lower BMI, characterized by marked central obesity and more severe insulin resistance than in individuals in developed countries and display several other cardiovascular risk factors, despite being thin (24–26). Thus, early malnutrition followed by predominantly central weight gain could lead to the insulin-resistance syndrome, supporting the secondary hypothesis for the role of malnutrition in diabetes (5). This framework also provides an explanation for the high prevalence of diabetes in migrant Indians (first generation), who have a higher BMI than native Indians and greater central obesity than indigenous populations (27). Some have argued that such observations indicate that the thrifty phenotype actually represents a selective survival manifestation of the "thrifty genotype" (19). However, this interesting variation on the overall theme must remain in the realm of speculation until definitive studies on genetic markers are carried out.

The third concept underlying the changed emphasis reflected in the consensus statement is that malnutrition modifies the clinical picture of diabetes when the two conditions occur coincidentally. This has been referred to as the "tertiary" role (5). Thus, in both humans and experimental animals, malnutrition is associated with insulinopenia, insulin resistance, and an absence of ketosis, three "unique" features of the clinical syndrome that was formerly called PDPD (4–6,28). Furthermore, experimental data indicate that the insulin resistance and insulin deficiency of malnutrition can be expressed in the context of coexisting diabetes (29–32). These observations indicate that it is probable that the clinical picture of human diabetes can be modified by coexisting malnutrition. Thus, the interaction between malnutrition and diabetes may have nothing to do with etiology and everything to do with the clinical presentation. A shift in emphasis from etiology to clinical patterns would also make it easier to determine the proper placement of the clinical syndromes of diabetes in the tropics within the internationally accepted clinical classification. Thus, instead of the etiologically derived and hence inappropriate terminology espoused by the WHO (PDPD), it has been suggested that t term MMDM (malnutrition-modulat diabetes mellitus) be used. The new te tacitly acknowledges that the clinical sy drome may mask the underlying form diabetes. It also implies that it is an inhe ently heterogeneous entity, made up diverse syndromes that may be clinical similar but etiologically different. In oth words, MMDM may occur over a templa of either IDDM or NIDDM. This simpl concept takes into account the contradic tory observations reported by differen authors in studies of patients with th same clinical syndrome. For instance, nu tritional rehabilitation of these subject can uncover an underlying pattern of ei ther NIDDM or IDDM (33,34). Similarly some reports indicate that these subjects are islet cell antibody positive (35) and have partial HLA identity with classical IDDM (36), whereas others show quite the opposite (37,38). Thus, MMDM may be thought of as a mixed bag: it includes nutritionally modified forms of both classical types of diabetes, the basic features of the underlying syndrome being masked by the clinical and metabolic features of malnutrition. The new concepts discussed above thus provide an internally consistent framework within which are incorporated all of the sometimes contradictory observations regarding the interaction between malnutrition and diabetes. The framework is based on the two hypotheses for which there is some evidence, the secondary and the tertiary hypotheses described earlier (5), and accords with the available data, both clinical and experimental, regarding the interaction. Therefore, at the present time, it seems reasonable to conclude that malnutrition plays an important role in precipitating or modifying diabetes in developing countries, but that it is neither the sole nor even the proximate cause of the syndromes that are peculiarly seen in malnourished populations. However, it is important to recognize that the last word on the subject has not been written. At a time when our understanding of this interaction continues to evolve, it is vital to keep an open mind on this fascinating subject. Any connection between malnutrition and diabetes may appear esoteric and remote to diabetologists used to seeing obese patients in the developed world, but the field has nonetheless provided a wholly unexpected insight into the pathogenesis of diabetes itself, based on the ep-

idemiological evidence that is at the heart of the thrifty phenotype hypothesis.

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