Type 5 diabetes: fifth pillar or fifth column

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Abstract

This opinion piece reviews the history of malnutrition related, or malnutrition modulated diabetes mellitus (MMDM). It reviews various terms used to describe this condition, and analyzes current efforts at renaming it as type 5 diabetes. It provides a simple, yet effective diagnostic checklist, based upon Ahuja's diagnostic criteria, for MMDM. While research is certainly required to define and describe this entity, renaming it will create confusion and chaos, rather than comprehension or clarity.

keywords: Diabetes, malnutrition, MMDM, MRDM, pancreatic diabetes, PDDM, PDPM, tropical diabetes

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Introduction

Type 5 diabetes has recently been "recognized" as a distinct entity by the International Diabetes Federation (IDF).[1] This is an important decision, as it highlights the unique needs and necessities of the estimated 20-25 million people who live with this type of diabetes. However, this move must be studied in the context of the diabetes care ecosystem both past and present. At the same time, the potential strengths and spin-offs of this neologism must be analyzed in a balanced manner.

Historical Context

The IDF release suggests that type 5 diabetes is a newly recognized variant of the syndrome. This statement does not take into account the path-breaking work done in India, and other countries, decades ago. The first mention of malnutrition and diabetes comes from the Ayurvedic text Charaka Samhita, which describes various types of 'prameha', including ten 'kapha', six 'pitta' and four 'vata' subtypes. The vata subtypes- vassameha, majjameha, hastimeha and madhumeha-may be associated with undernutrition and debilitation.[2] Malnutrition, whether as a causative, confounding or consequent factor, has therefore been recognized as a part of the diabetes syndrome.[3]

In modern times, Hugh Jones (1959) was perhaps the first to highlight a malnutrition-related diabetic condition.[3] The phenotype he described came to be known as J (Jamaica) type diabetes. Later, this condition was reported from across the world, including India. Amongst others, Tripathi and Kar described a cohort of young persons with a distinct type of diabetes.[4] These persons did not fit in the classic insulin dependent (IDDM) or non-insulin dependent (NIDDM) varieties of diabetes mellitus, as used at that time. Thomas et al have renewed interest in this atypical form of diabetes.[5]

Onomastic Overview

Multiple terminologies were therefore proposed to describe this type of diabetes. Tropical diabetes, M(malnutrition) type diabetes, and insulin requiring diabetes mellitus are some of these. The term ketosis resistant diabetes of young (KRDY) was developed at the All India Institute of Medical Sciences, New Delhi, India.[6] This was apt as it described the unique clinical presentation as well as the treatment strategy of the disease.

In 1985, the World Health Organization recognized malnutrition related diabetes mellitus (MRDM) as a distinct type of diabetes. This was classified into two variants fibro calculous, or fibrocalcific pancreatic diabetes (FCPD), and protein deficient pancreatic diabetes (PDPD). Based on insightful discussion and dialogue, MRDM was later changed to malnutrition modulated diabetes mellitus (MMDM), and PDPD to protein deficient diabetes mellitus (PDDM).[7]

Phenotype

Pioneers such as Ahuja et al proposed robust diagnostic criteria, based on clinico-phenotypic assessment, to help in the diagnosis of FCPD and PDDM. These were later modified to discriminate between the two conditions. Table showcases an edited version of these criteria, written to aid understanding and usage. It must be noted that genomic and metabolomic studies were not available at that time. Hence, diagnostic parameters were based only on clinical observations, and could not incorporate geno-phenotypic relationships.

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Table: Diagnostic criteria for malnutrition modulated diabetes mellitus (MMDM).

History
• Swift onset (10-30 years age)
• Social deprivation
• Sylvan (rural) residence
• h/o Starvation (malnutrition)
Clinical features
• Slim built (BMI <16kgm2)
• Stigmata of malnutrition (skin, hair, mucous membranes, nails)
• Severe hyperglycaemia
• Safe from ketosis
• Sky high insulin requirement (>2 U/kg/day)
Investigation
• Sonography-pancreatic calculi, ductal dilatation in FCPD

Key: BMI= Body mass index; FCPD= fibro calculous pancreatic diabetes

Pathophysiology

MDDM was found to have both insulin secretory defect and insulin resistance. Some authors felt that PDDM was an initial stage of FCPD, or of IDDM. Others opined that these were variants of poorly treated type 2 diabetes. Newer research on insulin resistance in kwashiorkor, and on the in-utero origins of human disease, supported the role of malnutrition in modulating glucose homeostasis, in crafting a distinct phenotype of dysglycaemia.[8] Limited genetic studies were conducted, with varied results. Some overlap was noted in the genotype of MDDM and other types of diabetes.[9]

Number Game

Current discourse on type 5 diabetes suffers from what may be termed as 'medical myopia' or 'academic astigmatism'. The focus on the number five begets a question- what are type 1 to 4? While type 1 and type 2 diabetes are a part of globally accepted diagnostic labels, type 3 and type 4 are not listed in standard lexicon. Type 3 diabetes is used to describe Alzheimer's disease occurring in conjunction with diabetes, while type 3c is sometimes used as a synonym for pancreatic diabetes. Type 4 is a recent entrant to academic circles, and is thought to denote a state of dysglycaemia caused by insulin resistance in elderly individuals. The confusion is compounded by the use of these numbers as suffixes for variants of maturity onset diabetes of the young (MODY).

Adding a fifth type of diabetes, to a numerical quagmire, may complicate, rather than clarify things. Instead of acting as a fifth pillar, or support, for diabetes care, it may work as a fifth column, or saboteur of health. This confusion is already apparent across social media, as commentators of various backgrounds describe the "new diabetes" in differing manners.

Neologism: Necessity Or Nefariousness

Existing terms such as MDDM can easily suffice to describe the 'type 5' phenotype of diabetes. A newer term 'severe insulin-deficient diabetes' (SIDD) is an equally apt label for the same.[10] SIDD can be differentiated from severe autoimmune, severe insulin-resistant, mild obesity-related, and mild age-related diabetes. The cluster-based taxonomy, based upon pathophysiology, also helps in guiding preventive and therapeutic strategies.

Proposing a new name will not create clarity-or consensus; rather, it will cause confusion and chaos. It adds no value either from numerical, a pathophysiologic or pharmacological perspective. Some experts opine that the distinct identify of type 5 diabetes is based on genetic studies. This statement is open to debate. Multinational, multicentric research must be carried out to validate this hypothesis. There is no correlation between genotype and treatment, either. The management of MDDM or SIDD was, and continues to be, high dose insulin. We suggest, therefore, that more research be done. This may include not only genetic markers but microbiome studies as well.

Fifth Wave

Diabetes care has evolved a lot over the past century. The discovery of insulin, the understanding of insulin resistance, and then incretin biology, and the link between obesity and diabetes: these may be listed as the four waves of diabetes science. The fifth wave is now underway: a revisiting of severely insulin deficient diabetes, modulated by malnutrition.

While we welcome global focus on this neglected form of dysglycaemia, we advocate for emphasis on pathophysiology and pharmacology, rather than paedantic posturing.

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