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Diagnostic Criteria and Classification of Type 2 Diabetes including Prediabetes

Pathophysiological Basis for Preventive and Therapeutic Interventions aimed at β-cell Resurrection

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Abstract

Diabetes Mellitus belongs to a group of disorders of intermediatory metabolism, and its diagnosis is essentially based on recognition of ***hyperglycemia*** resulting from *defects in insulin secretion, or in insulin action, or both.* The vast majority of cases of diabetes fall into two broad categories: type 1 characterized by absolute deficiency of insulin secretion, generally due to an immune destruction of pancreatic β-cells; and type 2 where the underlying cause is a combination of insulin resistance and an inadequate compensatory response by β cells.

Since the discovery of insulin, therapeutic interventions have essentially included administration of insulin or its modified versions, insulin analogues, and insulin secretagogues as well as the modalities aimed at lowering insulin resistance through life style modifications, biguanides, or thiazolidinediones. However, *preserving, reviving, or rejuvenating the β-cell to enhance its function has remained elusive as have been the measures to stop progressive deterioration in β-cell dysfunction. An essential prerequisite to achieve this objective is to recognize at the earliest the prediabetic phase.*

As a result of the information based on contemporary science regarding the concept of 'robust' viz-a-viz 'susceptible' β-cell, and a better understanding of mechanisms of impaired β-cell function and reduced β-cell mass, a rational basis for new preventive and therapeutic paradigm namely, restoration of β-cell function and possibly maintenance of β-cell mass, seems to be within the realm of reality.

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The recognition of a prolonged early prediabetic phase makes it possible to explore new therapeutic avenues which primarily aim at restoration of the β-cell and retarding the progression to overt clinical diabetes. Future therapeutic strategies will not only aim at metabolic normalization but may also endeavour to restore, rejuvenate and resurrect the β-cell in the prediabetic phase, and in early T2DM.

Situation Analysis

The *Diabetes Atlas* (1) painstakingly compiled by the International Diabetes Federation (IDF) and the WHO, was released at the 20th World Diabetes Congress, held at Montreal, Canada from 18-21 October, 2009. It is estimated that in 2010, **285 million** persons worldwide have diabetes: of these, 51 million (50.76 million) people aged 20-79 with diabetes were in India. The total number is expected to increase worldwide to **472 million** by 2030; 87 million of whom shall be in India. India heads the table of G10 countries (*G10: the most glycemic countries worldwide), and shall continue to exhibit this dubious distinction till 2030, and possibly later also. The exponential increase in the prevalence of diabetes over the last three decades is easily discernable on the perusal of the report of WHO Expert Committee on Diabetes Mellitus held from September 25-October 1, 1979 in Geneva, and which I had the privilege to Co-chair with Prof. Harry Keen (UK). The report concluded by stating: "*Diabetes mellitus is a major public health problem known to affect more than **30 million** people. In many it remains undiagnosed. It contributes significantly to premature death and prolonged ill-health*"(2). Precisely 30 years later, Diabetes Atlas released in October 2009, puts the figure of persons with diabetes at **284 million** worldwide. A ten-fold increase! This number is projected to further increase to **438 million** by 2030. An equally, and perhaps more disturbing feature, is the number of persons worldwide with Impaired Glucose Tolerance (IGT), described and defined for the first time by the WHO Expert Committee in 1979.

From the present estimate of 344 million persons with IGT, the number is projected to increase to 472 million by the year 2030. Recent recognition of Impaired Fasting Glycemia (IFG) adds to the magnitude of the problem. Diabetes is a challenge for the health sector, which shall have to deal with

**Terminology by JSB*

more than ***1 billion*** persons worldwide with varying degree of glucose intolerance within the next two decades!

It is important to remember that not only is there an increasing prevalence of diabetes in India, there is also a shift in the age of onset to younger people, thus affecting economic growth during most productive years of life due to diabetes-related morbidity. Moreover, in India, diabetes-related mortality constitutes 12-14% of all deaths in the age group of 40-59 years, being higher amongst women (1). Diabetes figures prominently amongst the non-communicable diseases which therefore constitutes an impediment to economic growth through reducing the productivity of workforce and by increasing expenditure in health care thereby diverting it from essential investments for economic growth (3). A WHO study projected that the national income foregone due to diabetes, heart disease, and stroke over the period 2005-2015 was $ 237 billion for India. These facts emphasize the need to initiate evidence-based intervention strategies for prevention, for early recognition (especially during early phase of the natural history i.e. IFG and IGT as well as metabolic syndrome), and for close monitoring and appropriate management of diabetes and its complications.

Classification of Diabetes Mellitus:

Diabetes Mellitus is a constellation of clinical manifestations, characterized by disorder of intermediatory metabolism, and diagnosed on the basis of ***hyperglycemia*** resulting from *defects in insulin secretion, or in insulin action, or both*. Based on differential pathogenesis, the vast majority of patients of diabetes mellitus fall into two broad categories: type 1 and type 2. While type 1 Diabetes Mellitus is characterized by absolute deficiency of insulin secretion, generally due to an immune-mediated inflammatory destruction of pancreatic β-cells, although in some cases it may be idiopathic, the underlying cause in T2DM is a combination of insulin resistance at multiple sites, most prominently the muscle, adipose tissue and the liver, *and* an inadequate compensatory response by the β-cell.

In addition to type 1 and type 2, there are other specific types of diabetes (4) which include genetic defects of β-cell function and of insulin action as well as diseases of exocrine pancreas, endocrinopathies, drugs or chemical induced diabetes, and several genetic syndromes. Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition

during pregnancy. Diabetes in pregnancy may be associated with complications such as abortion, miscarriage, or macrosomia.

Type 1 diabetes generally accounts for ~ 5% of all cases of diabetes mellitus encountered in clinical practice. The onset is generally before the age of 30 years, most often in childhood or adolescence, although it may occur at any age. The disease usually has an abrupt onset with increased thirst, increased appetite, and excessive urination and weight loss. Occasionally, it may be diagnosed when the patient presents for the first time in ketoacidosis or coma, especially during an intercurrent illness or surgery. Diabetic ketoacidosis is a serious complication, and if left untreated, often a fatal one. The patients usually are not obese and may even be wasted and underweight. These are the patients in whom the secretion of insulin is extremely low or nil, generally due to an immune-mediated destruction of pancreatic β-cells, and in whom life can be sustained only with supplementation of insulin from external sources (hence the previous terminology of insulin dependent diabetes mellitus or IDDM).

Hyperglycemia and ketonemia constitute the most important sequelae of insulin deficiency in type 1 DM. While hyperglycemia is essentially due to varying combination of lack of glucose utilization and hepatic overproduction of glucose through accelerated gluconeogenesis, ketonemia is a resultant of impaired lipogenesis and enhanced lipolysis leading to a release of free fatty acids (FFA) into the circulation. With a reduced synthesis of triglycerides from FFA in liver due to reduced activity of malonyl CoA, and increased activity of carnitine acyltransferase which facilitates entry of FFA in mitochondria, large amounts of ketones are generated through β-oxidation of FFA, resulting in ketonemia.

Classically, the patients with Type 2 Diabetes Mellitus (T2DM) are obese (80-85%), but may occasionally be normal (10-15%) or at times even underweight (<5%). This provides the basis for a sub classification into obese type 2, and non-obese type 2 DM. Susceptibility to recurrent infections-bacterial, mycotic, or mycobacterial-may be associated with persistent hyperglycemia.

T2DM is now being increasingly recognized in the younger, adolescent and even paediatric age groups where it is generally associated with childhood obesity (5). In adults, T2DM frequently

remains undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications which may, at times, be the presenting feature. Indeed, in the United Kingdom Prospective Study (UKPDS), the prevalence of complications in *newly* diagnosed persons with T2DM was high : of a total of 5102 patients recruited in the study, 39% of men and 35% of the women had some form of retinopathy at the initial presentation (6).

Diagnosis of Diabetes Mellitus:

Clinical diagnosis of type 1 and type 2 diabetes mellitus has been summarized above. Laboratory diagnosis of diabetes is generally based on measurements of blood glucose. Normal fasting plasma glucose (FPG) after a minimum of 8 hrs. fast is < 100 mg/dl (< 5.6 mmol/l). Plasma glucose of < 140 mg/dl (< 7.8 mmol/l), two hours after challenge with 75 gm. glucose, is considered normal. There is a continuous spectrum of glucose levels between those considered normal and those that are considered diagnostic for diabetes (fasting ≥ 126 mg/dl or 7 mmol/l and 2-hr. post glucose challenge ≥ 200 mg/dl or 11.1 mmol/l).

Impaired fasting glucose (IFG) is defined as fasting plasma glucose (FPG) levels ≥ 100 mg/dl (5.6 mmol/l) but < 126 mg/dl (7.0 mmol/l). **Impaired glucose tolerance (IGT)** is diagnosed when 2-h value in the oral glucose tolerance test (OGTT) is ≥ 140 mg/dl (7.8 mmol/l) but < 200 mg/dl (11.1 mmol/l). IFG and IGT constitute early phase in the natural history of the disease, and are sometimes designated as ***Prediabetes.***

Prediabetes

Almost to-date, 50 years ago, I got interested in the subject of Prediabetes and started work at the All-India Institute of Medical Sciences under late Prof. K.L. Wig for my MD Thesis: the subject of thesis was *Diagnosis of Prediabetic State*. Reviewing the literature at that time, the definition provided by Conn (1958) (7) seemed most appropriate. Suggesting that prediabetic state must be defined in terms of both *time* and *objective* manifestation, Conn believed that in an individual ***destined*** *to become* ***diabetic****, the prediabetic state must be regarded as existing from the time of conception to the time that a definitive diagnosis can be made by present method of testing.*

My doctoral thesis was completed by the end of 1961 and submitted in February, 1962 (8). Describing my conceptual understanding of prediabetes, I stated: "the prediabetic state becomes a target which will continue to move towards the goal of ***eventual*** understanding. What may be regarded as prediabetes today, may later be shown to be a clear manifestation of the fact that the disease is present." Fifty years later, I firmly believe that the statement holds true even today.

WHO Expert Committee on Diabetes Mellitus, which met in Geneva on 24-30 November, 1964, was the first substantive international effort by the WHO to provide global perspective of the diagnosis and classification of diabetes (9). In the context of present focus on prediabetes, the Expert Committee's observations on this issue are relevant and are reproduced *verbatim*:

'***Pre-diabetes*** is a term that can be used *retrospectively* when reviewing a case. The definitions above differ slightly from those adopted by many physicians, who would classify as pre-diabetes the identical twin of a diabetic, and the children of two diabetic parents. **However, it is recommended that the term "pre-diabetes" should be reserved for the period of time from conception to the diagnosis of an episode of diabetes (of any defined severity), and that it should be used in research rather than in clinical situations. However, pre-diabetes should exclude impairment of glucose tolerance by definition.'*

Subsequently, WHO Expert Committee on Diabetes Mellitus, referred to earlier, met in Geneva, 25 September-1 October, 1979, and supported the formulation of a new classification. A major recommendation was made with respect of terms *prediabetes* and *potential diabetes*. These were grouped together under a new category designated *statistical risk classes (subjects with normal glucose tolerance but substantially increased risk of developing diabetes)* (2). There was a further subclassification into *Previous abnormality of glucose tolerance (PrevAGT) and Potential abnormality of glucose tolerance (PotAGT)*. The major reason for using the new terminology of *statistical risk classes* was the fact that this terminology indicated only *enhanced risk* without assigning any clinical disease connotation.

**Italicized by the author for emphasis*

PREDIABETES: *Reincarnation or Renaissance*:

The term prediabetes which was nearly abandoned during the last three decades, at least in the clinical context, following the NDDG and WHO Expert Committee reports and the general acceptance of these reports by the international community, has now emerged in its new incarnation. This has been mainly due to three developments: (i) introduction of the term impaired fasting glycemia (also called impaired fasting glucose by ADA) to define a fasting plasma glucose ≥ 100 mg /dl or ≥ 5.6 mMol/L (5.6 mMol/L – 6.9 mMol/L); (ii) definition and continuing redefinition of Metabolic Syndrome; and (iii) elucidation and better comprehension of natural history of T2DM especially in the context of the pathophysiology of its early phase.

Impaired Fasting Glycemia & Impaired Glucose Tolerance:

Although the ADA defined IFG as a fasting plasma glucose (FPG) level of 5.6 – 6.9 mmol/L, there is growing concern, justifiable on scientific evidence, that such a low threshold level of FPG may lead to a loss of specificity and positive predictive value as a risk factor for diabetes (10). With this perspective in view, to include IFG in the definition of prediabetes, alongwith IGT defined on the basis of well substantiated WHO criteria based on a standard OGTT using 75 gm. glucose load, needs critical reappraisal. In addition, as has been rightly argued, even with the ranges of plasma glucose proposed for IFG and IGT, there is no substantive evidence that such glycemic thresholds definitively enhance the risk of prospective diabetes, cardiovascular disease, or all-cause mortality. Although risk factors for prediabetes, as defined by ADA and accepted by several others, may well reflect those for T2DM also, there is no dataset generated as a result of well designed prospective studies which have conclusively provided a profile of identified risk factors for the development of prediabetes. Indeed, no prospective data are available to determine whether screening for the presence of prediabetes gives long-term health benefits.

In most population studies, the rates of progression for IFG and IGT to overt diabetes are nearly similar, with IGT having greater sensitivity but less specificity. Furthermore, the whole concept of 'progression' becomes questionable if some of the long-term studies are subjected to a critical review.

For example, in an 11-year follow-up well designed study based on the diagnosis of IGT (WHO criteria) in adult subjects in Mauritius (with a substantial population of Indian origin), 46% developed diabetes, 28% continued to exhibit IGT, 4% developed IFG, *but most importantly*, glucose levels ***normalized*** in 24%. Using the criterion of IFG (6.1 – 7.0 mMol/L)* in the same population subset, follow-up showed 38% developed diabetes, 7% continued to show IFG, 17% developed IGT, and glucose levels ***normalized*** in 38% (11). Putting together, it is obvious that after a long follow-up, only about 50% of subjects with IGT or IFG develop overt diabetes.

How is it then justifiable to 'designate' 50% of subjects as 'Prediabetic' when indeed they are not likely to develop diabetes even after a prolonged follow-up? Driving on American highways, the concept of a 'U' turn seemed to have completely alluded the enthusiastic investigators. As a result of intensive debate, American Diabetes Association (12) in January, 2010 have revised the earlier definition and stated: "IFG and IGT should not be viewed as clinical entities in their own right but *rather risk factors for diabetes as well as cardiovascular disease.*" This position is entirely in congruence with the earlier WHO classification where these abnormalities were termed as *statistical risk classes (subjects with normal glucose tolerance but substantially increased risk of developing diabetes)*(2). However, addition of increased risk of cardiovascular disease alongwith diabetes by the ADA makes it more meaningful in the clinical context.

Prediabetes and Metabolic Syndrome:

In a recent review (13), we have highlighted the inherent contradictions not only regarding the diagnostic criteria of Metabolic Syndrome (MetS), but the adversary positions adopted by reputable international professional organizations led by eminent epidemiologists, as well as clinical and biomedical scientists. A new ***interim*** joint statement (2009) by the IDF, National Heart, Lung, and Blood Institute (NHBLI), the International Atherosclerosis Society, the American Heart Association (AHA), and the World Heart Federation, ***with the notable exception of ADA and European Association for the Study of Diabetes (EASD),*** has tried to harmonise the different definitions of MetS (14). It has proposed that presence of three or more

* This has now been further lowered by the ADA to 5.6 – 6.9 mMol/L (Author)

of the following five criteria which include: (i) elevated waist circumference (cut-off points to be based on population – and country-specific definition); (ii) elevated triglycerides (≥ 150 mg/dl); reduced HDL Cholesterol (< 40 mg/dl for males and < 50 mg/dl for females); elevated blood pressure (Systolic ≥ 130 mmHg and / or diastolic ≥ 85 mmHg); and elevated fasting glucose (≥ 100 mg/dl), in drug naïve subjects (drug treatment for elevated triglycerides *or* drug treatment for reduced HDL *or* drug treatment for elevated blood pressure serve as alternate indicator), should be considered diagnostic of MetS. In this cacophony of arguments between protagonists and opponents of MetS, there is the solitary sane voice of Gerald Reaven, the high priest who originally described Syndrome X, which subsequently was named as MetS. In his recent masterly review, Revean concluded (15): '(i) health care providers should avoid labeling patients with the term metabolic syndrome ; (ii) adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors; and (iii) all CVD risk factors should be individually and aggressively treated. If these goals are achieved, there is no longer a need for a diagnosis of metabolic syndrome, nor a controversy about the best definition of the metabolic syndrome, or any confusion as to the clinical approach to patients who, although they are at greater risk of CVD, do not qualify for a diagnosis of metabolic syndrome.'

Be as it may, in the context of present discussion of prediabetes, it is best to surmise that the subjects with MetS may have about a twofold increased risk of developing diabetes and atherosclerotic cardiovascular disease. Whether the terms prediabetes, and /or MetS best define diabetes and cardiovascular risk remains to be established.

NATURAL HISTORY OF T2DM:

pathophysiology of early phase:

The role of insulin resistance in the pathogenesis of T2DM is well recognized. During the last few decades, extensive work has shown liver, muscle and adipose tissue as key sites, among others, where insulin resistance is exhibited. In liver, there is overproduction of glucose during basal state (fasting hyperglycemia); in muscle, there is impaired glucose uptake following ingestion of a carbohydrate meal (postprandial hyperglycemia); in the adipocyte, there is impaired lipogenesis and increased lipolysis with day-long elevation in FFA concentrations. It has also been shown that elevation in plasma FFA impairs insulin stimulated glucose uptake in liver

thereby increasing hepatic glucose production. Likewise, FFA impairs glucose uptake in muscle. Finally, elevated plasma FFA inhibit insulin secretion (lipotoxcity). Compensatory response by β-cells includes *both* an increase in β-cell mass, as well as an increase in insulin secretion. Thus hyperinsulinemia compensates for increased insulin resistance thereby ensuring continued normoglycemia as long as possible. Indeed, this may continue over life-time in the presence of 'robust' β-cells.

Role of Progressive β-cell dysfunction:

In contrast, in susceptible subjects, in due course β-cell function begins to decline even when insulin resistance continues to be stable, though severe. This is the harbinger of changes in blood glucose: initially postprandial hyperglycemia, and subsequently fasting hyperglycemia, both tending to increase in severity overtime. There is evidence to suggest that most obese subjects have robust β-cells which provide adequate compensation, both in terms of increased β-cell function and increased β-cell mass, to counter insulin resistance due to obesity, surfeit of nutritional factors and sedentary life style. However, 15-20% subjects, due to genetic predisposition because of *susceptible* β-cells, are unable to achieve adequate compensation and go through different phases of IFG and IGT, and finally may develop overt T2DM.

Early indicators of β-cell Dysfunction:

Failure to achieve adequate compensatory functional increment of β-cell as measured by diminished first phase insulin secretory response to glucose, occurs early during IGT phase (16). Subsequently, there is a progressive decline in β-cell function exhibited by diminished or lack of first phase, and a decreased second phase of insulin response to glucose. There is a close correlation between fasting plasma glucose and first phase insulin response. Higher the FPG, lower the acute insulin response. It is noteworthy that *rate* of progressive decline of β-cell function differs from individual to individual. In the UKPDS which included subjects with newly diagnosed T2DM, it was shown that β-cell function was low at onset (diagnosis), and continued to decline with deterioration in glycemic control, with increasing duration of diabetes. This was observed irrespective of the type of therapy administered to study subjects (17).

Another early indicator of β-cell dysfunction is an increased fasting ratio of proinsulin (PI: long chain precursor of insulin which is processed in the β-cell to produce equimolar amounts of

insulin and C-peptide) to total immunoreactive insulin (IRI). Increased P1 / IRI in the fasting state is due to a decreased processing of proinsulin, correlates with β-cell dysfunction, and is predictive of development of T2DM (18).

Progressive loss of β-cell mass and function: Mechanism(s):

The major factors for continuing progressive loss of β-cell *function* and *mass* include glucotoxicity, lipotoxicity (sometimes combined as glucolipotoxicity), and amylin toxicity. Amylin is a 37-aminoacid β-cell peptide that is co-stored and co-secreted with insulin in response to glucose and other β-cell secretagogues. Deposits of amylin, also called islet amyloid polypeptide (IAPP), have been reported in a majority of subjects with T2DM. Nevertheless, only 10% of those with IFG show any amyloid-positive islets while exhibiting a 40% deficit of relative β-cell volume (19). Amylin increases β-cell apoptosis. Several studies have shown pro-apoptotic effects of human IAPP on β-cells as well as central neurons; the term 'Alzheimer of islets' has been suggested.

Glucolipotoxicity essentially implies the deleterious effects of a combination of increased flux of glucose and free fatty acids (FFA) on β-cell function. The mechanism(s) of such adverse effects on β-cell include: (i) inhibition of adequate / optimal glucose utilization in mitochondria, (ii) enhanced generation of reactive oxygen species (ROS) causing mitochondrial damage, (iii) generation of nitric oxide with damage of cellular metabolism and eventually leading to β-cell death and (iv) effects on the microenvironment of β-cell through changes in cytokines which may alter the ability of β-cell to proliferate.

Epilogue:

Irrespective of the underlying mechanism(s), a general consensus has now emerged that impaired β-cell function and possibly diminished β-cell mass appear to be *reversible* especially in the early phase (IFG and IGT) and even immediately after the onset of clinical T2DM, so long as the limiting threshold of critical β-cell mass had not been surpassed and the β-cell secretory function has not been irreparably damaged. As a result of the information based on contemporary science regarding mechanisms of impaired β-cell function and reduced β-cell mass, a rational basis for new therapeutic paradigm namely, restoration of β-cell function and possibly maintenance of β-cell mass, seems to be within the realm of reality.

With the recognition of novel therapeutic targets, several new drugs are under clinical trials. A large number of molecular targets have been identified in the hope to correct diverse aspects of metabolic dysregulation. Three receptors, i.e. GLP-1R, GPR 119 and GPR40 that are expressed in the β cell have been explored extensively. Drugs that agonize these receptors or enhance endogenous secretion of GLP-1 have been subjected to extensive clinical trials and several have been released for therapeutic use. The subject has been recently reviewed (20). Finally, the therapeutic potential of Glucokinase activators (21), Gluconeogenesis inhibitors i.e. Fructose-1,6 bisphosphatase (FBPase) (22), and sodium glucose transport (SGLT-2) inhibitors (23), amongst others, is also under various phases of clinical trials.

The biomedical scientists, while planning to celebrate the centenary of epoch-making discovery of insulin in 1921, are deeply conscious and concerned that there is as yet a lack of the *ideal* drug(s) for the management of Type 2 Diabetes Mellitus (T2DM). Such a drug, when available, would not only ensure longer and definitive control of hyperglycemia with normalization of postprandial glucose, but would also delay/prevent loss of β-cell function, result in an increase of β-cell mass and function, normalize postprandial glucose, improve metabolic risk factors predisposing to diabetes, and directly minimize or affect the progression of diabetes complications *while* avoiding weight gain and/or increasing cardiovascular risk in any manner. To this wish list, may now be added the lack of mitogenic potential in view of the concern emanating from an increase in the reported occurrence of several malignancies with the use of certain insulins, especially long-acting insulin glargine.

The safest approach therefore is *prevention*: prevention of obesity with efforts initiated during childhood, healthy balanced nutrition at home, school and workplace, and enhanced physical activity irrespective of age.

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