SYNOPSIS

Diabetes Mellitus is a constellation of clinical manifestations, characterized by disorder of intermediary metabolism, and diagnosed on the basis 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.

Type 2 diabetes mellitus (T2DM) is therefore a consequence of the reinforcing effects of insulin resistance which manifests early, is associated with hyperinsulinemia to maintain normoglycemia in the early phase which may last for several years, and followed by hyperglycemia in a subset of patients due to β-cell dysfunction. 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 lifestyle 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 or the prediabetic state.

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. The recognition of a prolonged prediabetic phase (prediabetes) makes it possible to explore new therapeutic avenues which primarily aim at restoration of the β-cell and retarding the progression of prediabetes to overt clinical diabetes. It seems 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.

PREAMBLE

The Diabetes Atlas¹ 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”. 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). From the present estimate of 344 million persons, the number is projected to increase to 472 million by the year 2030. Finally, the recognition of Impaired Fasting Glycemia (IFG) adds to the magnitude of the problem. Thus, it would pose a tremendous challenge to human and material resources for health to deal with more than 1 billion persons with varying degree of glucose intolerance within the next two decades. (Terminology by JSB)

Diabetes figures prominently amongst the non-communicable diseases which constitute 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 heart disease, diabetes and stroke over the period 2005-2015 was $237 billion for India and $30 billion for Pakistan. 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. Finally, in India, diabetes-related mortality constitutes 12-14%, of all deaths in the age group of 40-59 years, being higher amongst women. The IDF estimates that in 2010 diabetes accounts for 1 in 7 deaths among 50-59 years-old persons in the South-East Asia region. These facts emphasize the need to initiate evidence-based intervention strategies for prevention, for early recognition (prediabetes phase 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

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 $\beta$-cells, 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 $\beta$-cell.

In addition to type 1 and type 2, there are other specific types of diabetes which include genetic defects of $\beta$-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 2 diabetes mellitus (T2DM) is now being increasingly recognized in the younger, adolescent and even paediatric age groups where it is generally associated with childhood obesity. This form of diabetes 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.

PREDIABETES: A PERSONAL PERSPECTIVE

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 dealing with Diagnosis of Prediabetic State. A few publications available at that time provided conflicting, and at times, contradictory definition of this entity. Research was mostly concerned with the diagnosis of prediabetes by Cortisone glucose tolerance test. Reviewing the literature at that time, the definition provided by Conn (1958) seemed most satisfying. Pleading 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. I am convinced that this definition is as valid today as it was more than fifty years ago.

My doctoral thesis was completed by the end of 1961 and submitted in February, 1962. 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.

Credit must be given to WP Jackson who extended the concept of prediabetes further by his intuitive foresight, and stated: "the individual who is genetically predisposed to diabetes by inheriting a faulty pancreas, has also probably inherited a faulty vasculature, particularly in certain sites (retina, kidney), though it may equally well be that the subclinical pancreatic defect has itself a deleterious effect on blood vessel walls, long before diabetes becomes manifest." Once again, the presence of retinopathy in IGT is a recognition of the validity, albeit partial, of Jackson’s premise.

Another relevant issue that emerged from the publications at that time, and seems to have been forgotten long since, was the controversy regarding role of obesity in diabetes. German (1958) studied a group of 80 individuals, 40 of them being obese and other half being of normal weight. None had a family history of diabetes. Cortisone glucose tolerance test was performed in the hope that the group of obese persons will definitely show a higher incidence of positive cortisone glucose tolerance test than the non-obese group. However, there was no statistically significant difference in the results obtained from these two groups. He, therefore, suggested that possibly some of the diabetics belonging to middle age obese type, have got a type of carbohydrate tolerance quite different from that seen in true diabetes mellitus. Fajans and Conn (1961) commenting on this particular study of German argued that obesity perse does not predispose to diabetes. However, if the individual has got a family history of diabetes, i.e. he is genetically predisposed to develop impairment of carbohydrate metabolism, then the stress produced by obesity precipitates the disease. As the group of obese people studied by German did not have any family history of diabetes, they were probably not expected to yield positive results on the cortisone glucose tolerance test. Recent data tend to reinforce and support this argument.

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\textsuperscript{11}. In the context of present focus on pre-diabetes, the Expert Committee’s observations on this issue are reproduced verbatim:

\textit{Potential diabetes}:

These are persons in whom diabetes may be prognosticated with reasonable reliability. They respond normally to a glucose tolerance test (GTT), but there is a clear risk of their developing diabetes. Potential diabetes include:

1. The identical twin of a diabetic;  
2. A person with both parents diabetic;  
3. A person with one diabetic parent whose other, non-diabetic, parent has or had a diabetic parent, sibling, or offspring, or a sibling with a diabetic child;  
4. A woman who has given birth to a live or stillborn child weighing 4.5 kg. or more at birth, or to a stillborn child showing hyperplasia of the pancreatic islets not due to rheasus incompatibility.

Latent diabetes:

1. A person in whom the GTT has produced a normal result but who is known to have been diabetic according to the GTT at sometime during pregnancy, during infection, when under some other stress, or when obese.  
2. A person who has abnormal blood-glucose responses (similar to those found in diabetes mellitus) to provocative tests, such as the cortisone-augmented GTT (The Committee considered that these tests should at present be largely confined to research).

Asymptomatic (sometimes referred to as subclinical or chemical) diabetics

1. A person with a diabetic response to the GTT whose fasting true blood-sugar is below 130 mg/100 ml (capillary) or 125 mg/ 100 ml (venous).  
2. As above, but with fasting true blood-sugars above the stated values.

The Expert Committee categorically stated its considered position regarding pre-diabetes and potential diabetes as follows:

\textit{Pre-diabetes}:

‘This 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. It is well known that in the pre-diabetic stage increased levels of insulin and/or insulin antagonists may be found in the blood, some vascular changes may be present or it may be found that women have given birth to babies of high birth weight. However, \textit{pre-diabetes should exclude impairment of glucose tolerance by definition}. The last statement is a complete negation of contemporary consensus. It was also pointed out by the Committee that certain persons were potential diabetics from the moment of conception, so that any steps that might be taken, such as control of maternal diabetes during pregnancy, to alleviate or reduce the chances of the early development of diabetes should be strongly recommended on preventive grounds.(\textsuperscript{4} italicized by the author for emphasis)

Since the publication of the report by WHO Expert Committee in 1965, a substantial amount of data had been generated during the following 10 years, primarily due to availability of methods of measurement of insulin in clinical settings\textsuperscript{19,15,16} and also due to monumental epidemiological data collated, synthesized and analyzed by Kelly West. My own intensive involvement in diabetes research continued, both at the AIIMS and in the UK, with several publications. Stage was set for exchange of views at the 9th IDF Congress in New Delhi (Oct. 31 – Nov. 5, 1976). John Butterfield initiated the efforts to request WHO to reconvene Expert Committee on Diabetes to review the position in the light of data generated and presented at the IDF Congress. The final trigger was provided by the publication of Kelly West’s voluminous compendium.

\textit{Epidemiology of Diabetes and its Vascular Lesions}, with over 2300 references, published by Elsevier\textsuperscript{27}. Both National Diabetes Data Group of the USA\textsuperscript{28} and the WHO organized meetings to internalize the new information and formulate appropriate recommendations. Accordingly, 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 pre-diabetes and potential diabetes. These were grouped together under a new category designated \textit{statistical risk classes} (subjects with normal glucose tolerance but substantially increased risk of developing diabetes)\textsuperscript{2}. There was a further subclassification as:

\textit{Previous abnormality of glucose tolerance (PrevAGT)}

\textit{Potential abnormality of glucose tolerance (PotAGT)}

The major reason for using the new terminology of \textit{statistical risk classes} was the fact that this terminology only indicated \textit{enhanced risk} without assigning any clinical disease connotation. In contrast, terms such as latent diabetes, potential diabetes or pre-diabetes, by virtue of incorporating ‘diabetes’ tended to suggest, howsoever unintended, a disease perspective. Furthermore, in uninformed but sensitive public mind, these terms incorporating ‘diabetes’ may have possibly caused an undue apprehension, and even social stigma.

According to Harris and Zimmet\textsuperscript{9}, who were not members of the Expert Committee and could offer independent interpretation, the term \textit{Prev AGT} replaced the former terminology of Latent Diabetes. They state: ‘the term is restricted to those persons who now have normal glucose tolerance but who have previously
demonstrated diabetic hyperglycemia or impaired glucose tolerance either spontaneously or in response to an identifiable stimulus. Individuals who have been gestational diabetics and returned to normal glucose tolerance after parturition form an obvious subclass of PrevAGT. Another small but important group of individuals in this class are former obese diabetics whose glucose tolerance has returned to normal after losing weight. Clinical studies have shown that many patients under acute metabolic stress due to trauma or injury experience transient hyperglycemia. Apart from studies of former gestational diabetics, there has been little systematic investigation of the later liability of persons who have exhibited glucose intolerance to develop diabetes. However, it is likely that this is increased and that there is utility in including all those with a history of glucose intolerance, now normal, in this PrevAGT class’.

Likewise, according to these authors, PotAGT replaced the former terminology of prediabetes. ‘This class includes persons who have never exhibited abnormal glucose tolerance but who are at substantially increased risk for the development of diabetes. Individuals who are at increased risk for IDDM include (in decreasing order of risk) : persons with islet cell antibodies; monozygotic twin of an IDDM diabetic; sib of an IDDM diabetic, especially one with identical HLA haplotypes; offspring of an IDDM diabetic. Individuals who are at increased risk for NIDDM include (in decreasing order of risk) : monozygotic twin of an NIDDM diabetic; first-degree relative of an NIDDM diabetic (sib, parent or offspring); mother of a neonate weighing more than 4 kg; obese individuals : members of racial or ethnic groups with a high prevalence of diabetes, eg. a number of American Indian tribes. The degree of risk for many of these circumstances is not well established as yet’.

AWHO Study Group on Diabetes Mellitus met in Geneva in 1984 (I had also the privilege to co-chair the Group) and updated the classification by including malnutrition-related diabetes mellitus as a major class 20. This was based on extensive data on this subject reviewed elsewhere 21. The diagnostic criteria were also revised to ensure closer correspondence with SI units (in 1980 report, 7 mMols was equated with 1.2 G/L which was obviously wrong. In 1985 report 7 mMols or 126 mg/dl became the cut-off point). The 1985 criteria have been mostly upheld till now, although some changes in the classification were incorporated in 1999 22. However, the Consultative meeting in 1999 was never upgraded to the status of WHO Expert Committee or a WHO Study Group but was designated as a report of ‘WHO Consultation’ arranged by the department of non-communicable diseases surveillance. The organization of the meeting was arranged through financial support from Bayer, UK; Bayer, Germany; Novo Nordisk, Copenhagen, Denmark etc.

PREDIABETES

Reincarnation or Renaissance

The term prediabetes which was nearly abandoned, 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 mm/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 23. 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% 24. 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, I think the concept of a ‘U’ turn seems to have completely alluded the enthusiastic investigators.

Prediabetes and Metabolic Syndrome:

In a recent review 25, we have highlighted the inherent contradictions...
not only regarding the diagnostic criteria of 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 (NHBIL), 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. It has proposed that presence of three or more 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, Reave concludes: ‘(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.’ [*This has now been further lowered by the ADA to 5.6 – 6.9 mMol/L (Author)*]

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 determined.

NATURAL HISTORY OF T2DM

Pathophysiology of Early Phase:

The subject was extensively reviewed at APICON 2009. The salient features, however, may be recapitulated. 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 (lipotoxicity). Compensatory response by β-cells includes both an increase in β-cell mass, as well as an increase in insulin secretion. Thus hyperinsulinaemia compensates for increased insulin resistance thereby ensuring 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 who are unable to achieve adequate compensation go through different phases of prediabetes (IFG and IGT), and finally may develop 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. 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.

Another early indicator of β-cell dysfunction is an increased fasting ratio of proinsulin (P1 : 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.

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-aminocid 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 IGT show any amyloid-positive islets while exhibiting a 40% deficit of relative β-cell volume32. 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.

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 prediabetes 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.

**PRINCIPLES AND PRACTICE OF MANAGEMENT**

Community awareness, sensitization, and education aimed at behaviour modification constitute the trilogy underlying principles of management. Early intervention is the key to successful outcome of lifestyle modification. There is a steep rise in the prevalence of obesity among children worldwide which makes them much more prone to chronic diseases as they grow older, thereby curtailing both the longevity as well as quality of life. As Prof. Kate Steinbeck pointed out at the 10th International Congress on Obesity in Sydney, Australia: 'The children in this generation may be the first in history to die before their parents because of health problems related to weight'. This phenomenon is already well recognized in developing countries with high infant mortality due to malnutrition, infections and infestations. Nevertheless, with epidemiological and demographic transition, the world now has more fat people than hungry ones, with more than a billion overweight people compared to 800 million who are undernourished. Developing nations are facing a 'Double Trouble Syndrome', with unhealthy coexistence of both communicable and non-communicable diseases, along with the spectre of HIV looming large on the horizon.

It is therefore timely to give serious thought to preventive aspects especially with regard to childhood obesity. It is being increasingly recognized that the internal environment of the fetus, and the external environment of the infant and the growing child play a significant role in the development of obesity in childhood and adolescence. The warning signs identified for enhancing obesity risk include watching more than eight hours of television a week; sleeping fewer than 10.5 hours each night; above average birth weight; obesity in both parents; excessive weight gain in the first year of life and rapid growth between birth and the age of two years.

In the adult subjects, data from several randomized prospective studies have documented beneficial efforts of lifestyle intervention in preventing T2DM. In the Diabetes Prevention Programme (DPP), 3234 nondiabetic persons, 25 years of age or older, with IGT and fasting glucose levels between 5.27 – 6.94 mmol/L (95 mg – 125 mg/dl), were assigned either to placebo or to a lifestyle intervention programme aimed at least a 7% weight loss and 150 mts. of physical activity/week. The average follow-up was 2.8 years. Compared with the placebo, life style intervention resulted in 58% relative risk reduction in progression to T2DM31. Such lifestyle intervention may also result in a longer lasting behavioural change. At the end of DPP study after 2.8 years, a follow-up showed that an approximately five-fold difference in physical activity levels was largely maintained in the intervention group, although most of the weight lost during the study period had been regained.

In a similar Finnish Diabetes Prevention Study34, 532-persons with IGT were randomized to an intensive life style intervention group or a control group. After 3.2 years of follow-up there was 58% relative risk reduction in progression to T2DM. Those who achieved the greatest number of the five pre-established lifestyle goals in the study (weight reduction > 5%; fat intake < 30% of total energy intake; saturated fat intake < 10% of total energy intake; dietary fibre intake ≥ 15 g/ 1000 kcal; and at least moderate intensity exercise for > 4 hours weekly) showed the lowest rate of progression to diabetes.

Two studies from Asia (Japan and India) provide data similar to that from the USA and Europe. In 458 Japanese men with IGT, the cumulative 4-year incidence of diabetes was 9.3% in the control group, versus 3.0% in the intensive intervention group, with a relative reduction in development of diabetes of 67%35. In the Indian Diabetes Prevention Programme, lifestyle modification in 531 subjects with IGT at enrolment delayed the developed of type 2 diabetes in Asian Indian subjects, with a 3-year cumulative incidence of diabetes of 55% in the control group compared with 39% in the lifestyle intervention group36.

**PHARMACOLOGICAL INTERVENTION (S)**

Considering the beneficial effects of diet and physical exercise (the possibility of beneficial effects of Yoga needs to be explored in well designed studies in the Indian subcontinent), drug therapy cannot
be rationally recommended in preference to lifestyle intervention. The argument is further strengthened if it is reiterated that nearly 50% of subjects with IFG or IGT may show normalization of blood glucose on a long term follow-up. Although in the DPP, administration of 850 mg. metformin twice daily resulted in a 31% risk reduction in progression to diabetes, equally good (and possibly better) results were obtained by lifestyle intervention. In another trial (STOP-NIDDM) acarbose (100 mg. thrice daily) reduced progression to diabetes by nearly 25% after 3.3 years. Thiazolidinediones (Rosiglitazone 8 mg. daily for a median duration of 3 years) reduced the risk of diabetes or death by 60%. The current critique of adverse effects of thiazolidinediones, especially bone fractures, would hardly justify their prolonged use. Equally, it is too early to consider newer approaches aimed at regeneration of β-cells (Incretin enhancers; incretin mimetics) as possible modalities of long-term intervention in IFG and IGT.

What is of utmost concern is that having incorporated the term prediabetes for categories of glucose intolerance i.e. IFG and IGT, there is an intrinsic motivation to initiate drug treatment because of inherent connotation of diabetes in such diagnostic labeling. International Conferences are now being held regularly on Prediabetes and Metabolic Syndrome. It is not difficult to imagine as to who would ultimately gain from this thought propagation amongst the professionals. Irrespective of the possible incentives to the stakeholders, and it is not difficult to imagine as to who they are, it would be wise to remember the first commandant of clinical ethics: primum non nocere i.e. do no harm. This concept of non-maleficence, coupled with the tenet of beneficence (serve best the interest and welfare of patient) must determine all our actions which ultimately must be evidence-based.

In conclusion, what can be recommended without any risk of contradiction, are life-style interventions aimed at weight reduction with the goal of normalization of weight. Smoking must be stopped, sound principles of medical nutrition therapy must be adopted, and a daily physical exercise regime must be initiated. Finally, at the time of first detection of some degree of glycemia, screening and appropriate management of other risk factors such as hypertension and dyslipidemia would be mandatory. Screening for macro- and microvascular complications must be undertaken. Annual follow-up with 75g OGTT need to be continued along with physical examination and clinical assessment. This will ensure beneficence and non-maleficence!

As Albert Camus stated: Do not wait for the last judgement: it takes place everyday.

REFERENCES

8. Bajaj JS. Diagnosis of prediabetic state. MD Thesis submitted to the All India Institute of Medical Sciences, February, 1962.


