Dysglycemia: A New Concept

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ABSTRACT

Type 2 diabetes is a strong risk factor for CHD in both men and women. The risk of CHD is high even at the time of diagnosis of type 2 diabetes. Since the prediabetic states are also associated with this increased risk there seems to be a continuous relation between the blood glucose levels and the risk of CHD, starting from the postprandial glucose levels just above the normal to the diabetic range. Dysglycemia is a term used to describe blood glucose levels which are higher than normal but do not qualify for the diagnosis of diabetes. In addition to the prediabetic states namely IFG and IGT, it also includes blood glucose levels just above the normal levels.

Dysglcemia is commonly associated with the metabolic syndrome, characterized by the clustering of CHD risk factors like obesity, hypertension and dyslipidemia in a single individual. These risk factors increase the risk of development of type 2 diabetes and also have a multiplicative effect on the risk for development of CHD. Recognition and treatment of the metabolic syndrome would help in prevention of type 2 diabetes and CHD.

Lifestyle modification plays a very important role in preventing the development of type 2 diabetes and CHD. Drugs such as metformin, glitazones and acarbose also have a role to play in correcting the insulin resistance. Judicious use of drugs to treat hypertension and dyslipidemia also produces significant benefits.

The estimates of WHO indicate that the prevalence of diabetes is increasing at a rapid pace. In 2000 an estimated 171 million people had diabetes and it is projected that by 2030, the number of people with diabetes will be 366 million.[1] India had 32 million diabetics in 2000 and this is expected to increase to 80 million by 2030. In addition, there is a large pool of subjects with impaired glucose tolerance with a high risk of conversion to diabetes. The National Urban Diabetes Survey in India has shown age standardized prevalence of diabetes and IGT to be 12.4% and 14% respectively with no gender difference. Subjects under 40 years of age had a higher prevalence of IGT than diabetes (12.8 vs. 4.6%; $p<0.001$).[2] Diabetes contributes to considerable morbidity and mortality in the form of metabolic complications, vision disorders, neuropathy, renal failure, peripheral vascular disease, ulceration and heart disease, stroke, infections and amputations.

In 1980 the WHO proposed a classification of diabetes mellitus based on the recommendations of the US National Diabetes Data Group (NDDG). This classification was revised in 1985 based on the advances in the knowledge of the etiology and pathogenesis of diabetes. The earlier descriptive terms of juvenile onset diabetes and maturity-onset diabetes were replaced with the terms IDDM and NIDDM respectively based on the therapy required.[3]

In this classification a new category of impaired glucose tolerance (IGT) was introduced in recognition of an area of diagnostic uncertainty between normal and diabetes. The diagnosis of IGT is made on an OGTT with 2hr values between 140-200mg/dl. This group of patients had an increased risk of developing type 2 diabetes and its macrovascular complications. They are generally asymptomatic and a portion of them will revert to normal.

In 1997 an expert committee of the ADA was constituted with representation from different countries to review the classification and diagnostic criteria in the light of newer developments and data based on the cut-off values (indicating risk of microvascular complications). This committee revised the diagnostic criteria and changed the nomenclature based on the etiology as Type 1 DM and Type 2 DM instead of IDDM & NIDDM. The diagnostic criteria for fasting blood glucose were lowered from 140 to 126 mg/dl while retaining the two hour value at 200 mg/dl. The expert committee introduced a new class of impaired fasting glucose (IFG). The IFG denotes an abnormally high fasting glucose concentration which falls short of diagnosis of diabetes (plasma glucose 110-125 mg/dl)[4] (Table 1). In a recent review the ADA has proposed further lowering of the cut-off value for the diagnosis of IFG as 100mg/dl.[5]

The ADA proposed the measurement of fasting glucose as the principal means of diagnosis of diabetes. The WHO

Table 1 : Categories of Glucose Tolerance

Category	Fasting Plasma Glucose (mg/dl)	2hr Post Glucose Plasma Glucose (mg/dl)
Normal	<100	<140
IFG	100 - 125	<140
IGT	<100	140-199
Diabetes	≥126	≥200

expert committee endorsed the recommendations of the new classification and diagnostic criteria but placed emphasis on OGTT as a gold standard with both fasting and 2 hr post glucose values being taken into consideration.

The two conditions IGT and IFG have lower values of blood glucose than those diagnostic of diabetes. These two together constitute the prediabetes state.

Type 2 diabetes is a strong risk factor for CHD in both men and women. The data from several studies suggests that the risk of cardiovascular disease is 2-4 times higher in type 2 diabetes than in people without diabetes. The risk for CHD is high even at the time of diagnosis of type 2 diabetes since the prediabetic states are also associated with an increased risk of CHD. Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes and the risk of myocardial infarction in diabetic individuals who did not have previous myocardial infarction can be as high as in non-diabetic individuals with a history of myocardial infarction. This has led to the NCEP ATP III panel to consider diabetes as a CAD equivalent.[6] What is now being recognized is that raised blood glucose level even below the threshold necessary to diagnose diabetes or even impaired glucose tolerance is also associated with an increased risk of CHD. Thus there seems to be a continuous relation between the risk of CHD and raised postprandial glucose concentrations that extends from barely elevated levels right into the diabetic range.

That the glucose concentrations associated with an increased risk for CHD are lower than those required for diagnosis of diabetes, should not be surprising, since these criteria are based on specific glucose concentrations above which the individuals are at a risk for development of nephropathy and retinopathy and not cardiovascular disease.

The postprandial glucose levels above which the patients are at an increased risk of cardiovascular disease is not yet defined but it may be as low as 98 mg/dl. Since this value is lower than that which would qualify for a diagnosis of IGT - the term dysglycemia is suggested to define the range of glucose concentrations associated with increased risk of CHD.[7] Dysglycemia therefore includes, in addition to the prediabetic states (IFG and IGT), blood glucose values above this threshold.

IMPAIRED FASTING GLUCOSE AND IMPAIRED GLUCOSE TOLERANCE

IGT and IFG are not synonymous in terms of pathophysiology and in the development of the long term complications. The term prediabetes is a practical and convenient term for impaired fasting glucose and impaired glucose tolerance, which places individuals at risk of developing diabetes and its complications. Both IGT and IFG appear well before type 2 diabetes is diagnosed thereby presenting an opportunity for intervention to reduce the future burden of diabetes. Not all individuals with prediabetes will necessarily progress to diabetes. A significant proportion of people who are diagnosed with IGT will revert to normoglycemia.

IFG and IGT are associated with the metabolic syndrome which includes obesity, dyslipidemia of the high triglyceride and /or low HDL type and hypertension. Identifying people with prediabetes particularly in the context of the metabolic syndrome indicates those who would benefit from cardiovascular risk modification.

While people with isolated IFG/IGT do not have risk for microvascular disease, they have a higher risk for the development of diabetes and cardiovascular disease. IGT is more strongly associated with CHD outcomes. However, individuals identified as having both IFG and IGT are at higher risk for diabetes as well as CHD. Lifestyle interventions have been shown to be highly effective in delaying or preventing the onset of diabetes in people with IGT. Evidence has not yet accumulated for reduction in total or CHD mortality.

Dysglycemia is therefore a qualitative term used to describe blood glucose that is abnormal, without defining a threshold. The adoption of this term reflects uncertainty about optimal blood glucose ranges and the current understanding that the cardiovascular risk and mortality risk exist in people with even slightly elevated blood glucose levels.[8] In the NHANES III data, it was found that impaired fasting glucose had twice the prevalence of CHD compared with normal glucose levels and diabetes had three times the prevalence.[9] Not surprising therefore it has been suggested that as many as 50% of newly diagnosed patients with type 2 diabetes may already have evidence of CHD.

Data from the DECODE study emphasizes the importance of prediabetic dysglycemia in determining subsequent prognosis. Baseline fasting glucose levels and glucose levels 2hr after a 75 gm OGTT were analyzed from 10 prospective European cohort studies involving a total of 22,514 individuals who were then followed up for an average period of 8.8 years. Subjects who were found to have IFG and IGT were at greater risk of mortality than those with normal glucose tolerance, while subjects with established diabetes whether diagnosed using fasting or postload values were at the highest risk.[10] A further observational cohort study subjected 2710 individuals to an OGTT in 1987 and followed them for 10 years.[11] Subjects who had elevated post-load glucose were at increased risk of developing CAD and at a higher risk of death from cardiovascular disease or from any cause. Interestingly, these associations were equally strong in subjects who did not go on to develop diabetes as those who did, confirming the prognostic importance of prediabetic dysglycemia.

Glycosylated hemoglobin and Dysglycemia

Glycosylated hemoglobin level has also found to be an independent progressive risk factor for the development of incident cardiovascular disease even in non-diabetic individuals, who would therefore be dysglycemic.[12] Every 1% absolute increase above a normoglycemic level predicts a 20% increase in the incidence of cardiovascular events.[13] In another study, the level of glycosylated hemoglobin has been found to be related to the degree of atherosclerosis (as measured by the carotid intima

Table 2 : Clinical Identification of the Metabolic Syndrome (NCEP ATP III)

Risk Factor	Defining Level
Abdominal Obesity (waist circumference)	>102 cm (40 inch)
Men	> 88 cm (32 inch)
Women	
Triglycerides	≥ 150 mg/dl (1.7mmol/L)
HDL cholesterol	
Men	< 40 mg/dl (1.0 mmol/L)
Women	< 50 mg/dl (1.1 mmol/L
Blood Pressure	≥ 130 / 85 mmHg
Fasting Plasma glucose	≥ 110 mg/dl

Diagnosis is established when ≥ 3 of these risk factors are present

media thickness), irrespective of the diabetes.[14,15] Hence, the presence or absence of diabetes is likely to become less important than the level of glycosylated hemoglobin in the assessment of cardiovascular risk (similar to the fact that a diagnosis of hyperlipidemia has become less important than the level of LDL cholesterol).[12] The increasing prevalence of diabetes and IGT probably indicate that the glycosylated hemoglobin levels of the larger non-diabetic population are also gradually rising. This dysglycemic epidemic may be a harbinger of a future epidemic of cardiovascular disease.

METABOLIC SYNDROME

The metabolic syndrome which often precedes the development of type 2 diabetes refers to a clustering of CHD risk factors - hypertension, dyslipidemia, central obesity in a single individual. The syndrome is characterized by insulin resistance and is also known as the Insulin Resistance Syndrome. The pathogenesis of this syndrome has multiple origins, but obesity and sedentary lifestyle coupled with diet and still largely unknown genetic factors clearly interact to produce the syndrome.[16] Clustering together of these risk factors increases the risk of developing diabetes and has a multiplicative effect on the development of cardiovascular disease.

For the purpose of identification and treatment several organizations have attempted to define the metabolic syndrome – originally described by Reaven, Kaplan and others.

The recent US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommended that at least three of the following components are require to confirm the diagnosis of metabolic syndrome - upper body obesity, increased triglycerides, decreased HDL cholesterol, HTN and impaired fasting glucose[6] (Table 2).

The definition proposed by WHO also includes fasting insulin, microalbuminuria and glucose tolerance although some of these measurements may not be possible in routine clinical practice.[17] The risk factors that comprise the metabolic syndrome worsen continuously across the spectrum of glucose tolerance categories. Using the criteria for diagnosis proposed by WHO a study of 4483 subjects (35-70 yrs) participating in a large family study of type 2 diabetes in Finland and Sweden showed that metabolic syndrome was present in 10% of subjects with normal glucose tolerance, in 50% of subjects with IGT and 80% of subjects with

Table 3 : WHO Definition of the Metabolic Syndrome

A working definition is glucose intolerance, IFG/ IGT or diabetes mellitus and/or insulin resistance together with two or more of the following:

- Impaired glucose regulation or diabetes
- Insulin resistance
- Raised arterial pressure ≥160/90 mmHg
- Raised plasma triglycerides (≥1.7 mmol/L, 150 mg/dL) and/or low HDL-C (men <0.9 mmol/L, 35 mg/dl; women <1.0 mmol/L, 39 mg/dL)
- Central obesity
- Microalbuminuria (UAER ≤20 μg/min or albumin: creatinine ratio ≥20 mg/g)

type 2 diabetes.[18] The high prevalence of the metabolic syndrome observed in this study population has also been observed using the NCEP ATP III definition.

In a recent study from North India the prevalence of IFG was found to be 11.7% in the population. Individuals with IFG had a clustering of cardiovascular risk factors and the prevalence of the Metabolic Syndrome as per NCEP ATP III criteria was 61% in this group with IFG compared with 16% in those with normoglycemia ($p<0.001$).[19]

The major risk factors (cigarette smoking, hypertension and dyslipidemia) contribute to the cardiovascular risk in diabetic populations. For each CHD risk factor analyzed in the MRFIT trial the risk of CHD was approximately three-fold greater in the diabetic than in the non-diabetic population.[20]

Dyslipidemia is present in over 50% of the diabetic population and constitutes a major risk factor for CHD, particularly as it persists despite the treatment of hyperglycemia. Diabetic dyslipidemia is characterised by moderate hypertriglyceridemia and low levels of HDL cholesterol. The levels of total cholesterol and LDL cholesterol are similar to that in the non-diabetic population. However, the distribution of LDL particles in diabetic subjects is shifted towards smaller denser particles that are thought to be particularly atherogenic. Hypertriglyceridemia is a major determinant of the distribution of LDL particles - the higher the fasting triglyceride level, the greater the preponderance of the small dense LDL in the total LDL concentration.[21] Triglycerides are also associated with increased concentration of important procoagulant factors such as plasminogen activator inhibitor-1 (PAI-1). Thus elevated triglyceride levels directly influence thrombus formation.

MANAGEMENT ISSUES

The metabolic syndrome is a powerful determinant of diabetes and cardiovascular disease. Non-diabetic dysglycemic persons with metabolic syndrome have an increased mortality from all causes including cardiovascular disease. Given the high prevalence of the metabolic syndrome it may have a substantial impact on healthcare and an attempt should be made to diagnose and treat metabolic syndrome even in non-diabetic subjects. The markedly increased risk of progression from IGT to type 2 diabetes and the strong association of both prediabetic dysglycemia and type 2 diabetes with increased cardiovascular risk emphasize the need for diabetes prevention. There is increasing evidence that intensive lifestyle changes or pharmacological interventions can reduce progression from IGT to type 2 diabetes. Preliminary

evidence suggests that such interventions also reduce the burden of cardiovascular disease.

The management of metabolic syndrome therefore has a two-fold objective of preventing type 2 diabetes and also preventing cardiovascular disease. The management would be based on the following principles i) to reduce contributory factors (by improved diet, and increased physical activity) ii) to aggressively treat modifiable risk factors like HTN and dyslipidemia.

Weight loss and increased physical activity may decrease insulin resistance and related metabolic disorders. The evidence for this has been brought out by four well controlled clinical trials, which evaluated the effect of lifestyle changes and/or pharmacological agents on the development of type 2 diabetes in individuals with IGT, have clearly shown the important role of life style changes. In addition, the role of drugs like acarbose, metformin and the glitazones has also been brought out by trials.

The Da Quin IGT and diabetes study

A multicentre randomized study assessed the effect of intervention of diet, diet + exercise relative to control in 530 Chinese subjects with IGT. Over a period of 6 years there was significant risk reduction in the cumulative incidence of diabetes of 31% (43.8% vs. 67.7% p=0.03) with diet alone, 46% (41.1% vs. 67.7% p<0.005) for exercise and 42% (46% vs. 67.7% p=0.005) with diet + exercise.[22]

Finnish Diabetes Prevention Study

Five hundred twenty two middle aged overweight subjects (172 men and 350 women) with a mean age of 55years and mean BMI of 31kg/m^2 with impaired glucose tolerance (IGT) were randomly assigned to receive either brief diet and exercise counseling (control group n=257) or intensive individualized instructions on weight reduction, food intake and guidance on increasing physical activity (intervention group n=265). The goals set for the intervention group were i) reduction in weight by 5% or more; ii) reduction in fat intake to less than 30% total energy intake; iii) reduction in saturated fat intake to <10% of total energy intake; iv) increase in fiber intake to at least>15 gm/day/1000 Kcal diet and v) increase in exercise to at least 30min/day (>150 min/week).[23]

After an average follow up of 3.2 years, 11% in the intervention group compare to 23% in the control group developed diabetes. There was a 58% reduction in the incidence of diabetes in the intervention group compared with the control group.[23]

Ranking of the subjects in both groups on the basis of success of achieving the goals showed a strong inverse correlation between the success score and the incidence of diabetes. None of the subjects who achieved four of the five goals (49 subjects in the intervention group and 15 in the control group) developed diabetes.

Diabetes Prevention Program

Three thousand two hundred thirty four non-diabetic persons with elevated fasting (95-125mg/dl) and post-load glucose (140-199mg/dl) to either intensive lifestyle modification program (1079) with an objective to achieve 7% weight loss and150 min of physical activity per week; or to placebo (1082) or metformin 850 mg twice daily (1073). The latter two interventions were combined with standard diet and exercise recommendations. The mean age of the subjects was 51 years and mean BMI was 34.0 kg/m^2.

After an average follow up of 2.8 years (range 1.8 - 4.6 years), a 58% relative reduction in the progression to diabetes was observed in the lifestyle group, a 31% relative risk reduction in the progression to diabetes in the metformin group (absolute incidence 4.8% in intensive lifestyle group, 7.8% in metformin group compared with 11% in control subjects). On an average 50% of the lifestyle group achieved the goal of ≥ 7% weight reduction and 74% maintained at least 150 min /week of modestly intense activity. No serious side effects were noted in any of the groups.[24]

Oral antidiabetic agents

Use of oral antidiabetic agents either before or after development of diabetes is one of the options.

The STOP NIDDM trial used 100mg of acarboes thrice daily as compared to placebo in 1429 subjects with IGT. Follow up for 3.3 years showed that the incidence of diabetes was 42% in placebo group vs. 32% in acarbose group, indicating a significant 25% reduction in risk of progression to type 2 diabetes with acarbose (p=0.0016). The beneficial effect of acarbose was independent of age, sex and BMI.[25]

Acarbose treatment was associated with a significant reduction in risk of combined cardiovascular endpoints and of myocardial infarction in the small number of cardiovascular events noted in the STOP NIDDM trial. A meta-analysis of seven randomized placebo controlled trials involving a total 2180 patients revealed a significant reduction in the incidence of a combined cardiovascular endpoint and of myocardial infarction with acarbose.[26]

The UKPDS showed that metformin reduced the cardiovascular morbidity and mortality in obese patients with type 2 diabetes.[27] The role of metformin was also brought out in the DPP study, although not as good as that of lifestyle medications.

PPAR agonists

The peroxisome proliferator-activated receptors (PPARs) form a subfamily in the nuclear receptor superfamily with three isoforms: PPARγ, PPARα, and PPARδ. The thiazolidinediones (TZD's) are a class of oral antidiabetic agents which improve insulin sensitivity by stimulating the PPARγ receptors. PPARγ is expressed mainly in the adipose tissue where it promotes adipogenesis, lipogenesis and glucose uptake. Stimulation of PPARγ alters transcription of several genes that regulate glucose and fat metabolism such as the lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl CoA synthase, glucokinase, phosphoenolpyruvate carboxykinase and the GLUT4. This results in increased adipocyte lipogenesis, decreasing circulating free fatty acids and lipid levels in liver and muscle. This alters the glucose-fatty acid cycle (Randle's cycle) so as to favor glucose utilization by muscle.[28,29] Stimulation of PPARγ also reduces the production by the adipocyte of several mediators that cause insulin resistance such as the cytokine TNFα and the hormone resistin. It also mediates the increased production of the hormone adiponectin and the insulin signalling intermediate PI3K - both

improving the insulin sensitivity.[28,29] Stimulation of PPARγ receptors present in the liver and muscle also contributes to the antihyperglycemic effects of the TZDs.[29]

Several other tissues express the PPARγ receptors including the pancreatic β-cells. Preliminary evidence from animal studies has shown that chronic treatment with PPARγ agonists can improve β-cell morphology and insulin content.[30]

Several new drugs that have PPARγ agonistic activity are being developed (non-TZD) as potential new antidiabetic drugs. Some PPARγ agonists also have antiatherogenic and antithrombotic properties.

Dual PPARγ PPARα agonists

PPARα receptors are expressed in muscle and liver and mediate increased oxidation of fatty acids through increased transcription of acyl-CoA oxidase and thiolase. Fibrates produce their effects of triglyceride lowering by stimulation of PPARα receptors. Drugs which have an agonistic effect on both the PPARγ and PPARα will lower both glucose and lipids. Several TZD and non-TZD having dual agonistic properties are being investigated. Muraglitazaar and Naveglitazone are two such compounds. Muraglitazaar is an oxybenzylglycine analog (a non-TZD) which has a great potential for both glucose lowering and lipid lowering,[31] but data from larger trials are needed to confirm its safety and efficacy. Laveglitazone is another non TZD PPARα /γ dual agonist which has been found to have positive effects on glucose and lipid metabolism.[32]

Role of Antihypertensives and Lipid Lowering

Although relatively few studies have examined the effectiveness of hyperlipidaemia and HTN therapy specially in subjects with the metabolic syndrome there is ample evidence that antihypertensive and lipid lowering interventions in diabetic subjects are at least as effective as in non-diabetic subjects.

Different classes of anti-HTN drugs do however vary in regard to their effects on insulin sensitivity. In populations at high risk for diabetes there is need to select an anti-hypertensive agent that can effectively control blood pressure without producing adverse metabolic effects. Most studies indicate that treatment with an ACE inhibitor or ARB is superior to more conventional treatment in patients with the metabolic syndrome. In many individuals monotherapy is not sufficient to meet the targets of blood pressure control and in such situations combination of antihypertensives is required. Addition of a calcium antagonist to any of these two classes of these drugs is beneficial. A combination of the ACEI with ARB provides a complete blockade of the RAAS and thereby produces significant benefit. In the HOPE study ramipril has also been shown to reduce the development of type 2 diabetes compared to controls.[33]

LDL cholesterol is the principal atherogenic lipoprotein and thus the primary target for lipid management. The NCEP ATP III advocates that diabetes should be regarded as a CAD risk equivalent and the guideline recommended a LDL cholesterol goal of <70 mg/dl similar to the recommendation of the ADA. Statins are considered to be the drugs of first choice to reduce the LDL cholesterol levels. Once the levels of LDL are reduced, the aim of lipid management will be to increase the HDL levels to greater than 45 mg/dl in men and > 55mg/dl in women. Statins have now been found to have several additional benefits such as anti-inflammatory effect, plaque stabilizing and membrane stabilizing effects. In the WOSCOPS study, statins have also been shown to prevent the development of type 2 diabetes.[34]

These studies suggest that intensive lifestyle changes or medical interventions are likely to decrease the risk of progression from IGT to type 2 diabetes in high-risk individuals from different regions and cultures. Lifestyle interventions and weight loss are important components of strategies for preventing or delaying the progression to type 2 diabetes in prediabetic individuals. However, they are not effective in all subjects. Co-morbid conditions like arthritis and other cultural issues may present barriers to successful intervention. On the other hand pharmacological interventions may be implemented more easily in such individuals.

CONCLUSION

Thus prediabetic dysglycemia is an important entity associated with the metabolic syndrome, carrying a significant risk of type 2 diabetes as well as an unacceptable burden of cardiovascular disease. Recognition of individuals with the metabolic syndrome based on the suggested clinical criteria is important in identifying individuals at high risk of type 2 diabetes and cardiovascular disease. Introduction of lifestyle changes and appropriate medication in these individuals will help in reducing the epidemic of type 2 diabetes and cardiovascular disease.

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