Prediabetes: A pragmatic triage for preventive pharmacotherapy

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Abstract

Prediabetes is a commonly encountered condition that bears a significant risk of progression to diabetes. While lifestyle modification remains the treatment of choice, drug therapy is emerging as a therapeutic option to prevent its progression to diabetes and associated complications. This paper proposes a comprehensive triage system to identify persons with prediabetes who may benefit from preventive pharmacotherapy.

Keywords: Acarbose, Diabetes, GLP1RA, Metformin, Obesity, Pioglitazone, Prevention, SGLT2 inhibitors.

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Introduction

Prediabetes refers to a condition of borderline glycaemic derangement where plasma glucose levels are greater than normal but not high enough to be categorized as diabetes. The diagnostic criteria for prediabetes are based on levels of fasting plasma glucose (FPG), 2-hour plasma glucose following oral glucose tolerance test (OGTT), and glycated haemoglobin (HbA1c). Though there are subtle differences in the cut-offs proposed by the American Diabetes Association (ADA) and World Health Organization (WHO) (Table-1), there is consensus regarding the existence and relevance of this condition.[1,2]

Table-1: Diagnosis of prediabetes.

Criterion	ADA	WHO	Metonym
Fasting plasma glucose (FPG)	100 to 125 mg/dl	110 to 125 mg/dl	Impaired fasting glucose
2-hr plasma glucose during 75 gm OGTT	140 - 199 mg/dl	140 - 199 mg/dl	Impaired glucose tolerance
Glycosylated haemoglobin (HbA1c)	5.7-6.4%	6.0-6.4%	

ADA= American Diabetes Association; WHO=World Health Organization.

Significance

Diagnosis of prediabetes has strong clinical significance. It not only predicts the risk of progression to diabetes, but also is associated with an increased risk of cardiovascular and some of the microvascular complications of diabetes.[3,4] At the same time, it represents a window of opportunity as intervention during this pre-disease state can prevent progression to overt diabetes, thereby avoiding diabetic complications. Therefore, early diagnosis and management of prediabetes can be termed as primordial prevention of diabetes complications, primary prevention of diabetes, and secondary prevention of prediabetes per se.

A Word of Caution

One must remember, however, that unwarranted intervention may be as dangerous as non-intervention or delayed intervention. This is the crux of the philosophy of quaternary prevention in diabetes.[5] Our approach to the management of prediabetes is characterized in the Latin phrase 'Auxiliendo, primum non nocere', which means 'Hasten to help, without doing harm".[6]

Diagnosis

The diagnosis of prediabetes is biochemical rather than clinical. The correct method must be followed to estimate plasma glucose and HbA1c before labelling a person as having prediabetes. At least two abnormal values must be documented before the diagnosis.[1,2] The frequency of screening for prediabetes is a matter of debate. South Asians belong to a high-risk ethnic group who rapidly progress from prediabetes to diabetes, and develop diabetes-related complications at a relatively early age. Hence, more frequent screening (perhaps annually) may be indicated from a younger age (possibly from 30 years) in South Asian countries. Opportunistic screening in persons at high risk of diabetes may be more pragmatic than universal screening, provided that high-risk persons are counselled and followed up appropriately.[7]

Differential Diagnosis

Prediabetes is usually asymptomatic and other etiologies should be searched to explain the presence of any symptom. If an individual with prediabetes complains of

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any symptom, detailed history taking, and physical examination should be undertaken along with the rational application of investigations to rule out possible causes. Commonly encountered conditions that may contribute to ill-health in prediabetes include anaemia, hypovitaminosis D, hypothyroidism and obstructive sleep apnoea. Relevant comorbid metabolic, medical and endocrine conditions must be ruled out.

Aims of Management

The aim of managing prediabetes is to prevent progression to frank diabetes with its associated complications, and if possible, to promote reversion to euglycaemia. This is facilitated by achieving excess weight loss, ensuring control of associated metabolic and vascular abnormalities, and instituting preventive measures for cardiovascular health whenever required. Maintenance of well-being, both physical and psychosocial, is an integral part of comprehensive prediabetes care.

Non-Pharmacological Management

Lifestyle modification is the cornerstone of the management strategy for prediabetes and includes dietary modification, regular physical activity or exercise, and stress management.[8,9] Alternatives such as yoga and nutraceuticals may be tried. Successful institution and maintenance of lifestyle modification need commitment and support from all stakeholders. These include the person with diabetes, the family and community, the physician, and paramedical diabetes professionals. It is the physician's responsibility to advocate for a diabetes-friendly health care system and society.[10] Structured programmes with expert multidisciplinary guidance can help in achieving desired results. Such programmes are now available through e-portals.

Preventive Pharmacological Therapy

Preventive pharmacological therapy may be indicated in selected individuals with prediabetes. The American Association of Clinical Endocrinologists/American College of Endocrinologists suggests stratification of individuals with prediabetes criteria. Drug therapy is to be considered if two or more of the criteria for diagnosis of prediabetes are present along with obesity.[9] The ADA encourages drug therapy in persons who are at high risk of progression to diabetes. Examples include persons undergoing treatment for schizophrenia and those with a history of gestational diabetes mellitus.

Triage for Intervention in Prediabetes

We propose a pragmatic and inclusive method of triage or stratification. This stratification strategy is based on factors both global in relevance, and unique to South Asia.

South Asians show a relatively rapid progression from prediabetes to diabetes. The CURES study from Chennai, India reported conversion of 58.9% of persons with prediabetes over 1000-person-years.[11] Predictors of progression were advancing age, family history of diabetes, 2-h plasma glucose during OGTT, HbA1c, low HDL cholesterol, and physical inactivity. A work score developed by Yokota et al. lists the following significant, independent predictors for conversion to diabetes; positive family history, male sex, higher systolic blood pressure, plasma glucose values (fasting, 1-hr and 2-hr during 75 gm OGTT), HbA1c and alanine aminotransferase.[12] Thus objective determinants of risk of progression to diabetes are now available.

South Asians living with prediabetes (and their physicians) also face a high burden of acute morbidity, usually infectious in nature, e.g., tuberculosis, respiratory virus infection, dental and oral infections, etc. Western guidelines do not give such morbidity due importance.

Table-2: Factors for triage.

Health Status	Factors Favouring Use Of Drug Therapy
History	- Male Gender - Increasing Age - Family history - History of GDM
Metabolic status	- Obesity - Central obesity - Acanthosis nigricans - High risk ethnic group - Elevated plasma glucose (Fasting + 2-hour post-OGTT) - Elevated HbA1c - Elevated systolic blood pressure - Elevated liver enzymes
Acute comorbidity	- Acute medical illness which may resolve faster if euglycaemia is maintained e.g., infectious illness, ulcer/wound - Acute surgical illness, i.e., postoperative period - Acute traumatic illness, e.g., fracture - Obstetric condition, e.g., pregnancy
Chronic vascular comorbidity	- Increased risk of/concurrent macrovascular complications e.g., coronary artery disease, heart failure - Increased risk of/concurrent microvascular complications e.g., neuropathic symptoms, chronic kidney disease
Concomitant illness	- e.g., psoriasis, schizophrenia, hepatitis B, HIV
Concomitant medication	- e.g., corticosteroids, immunosuppressants, HAART, atypical antipsychotics
Lifestyle triage	- Unwillingness/inability to modify lifestyle e.g., shift workers, arthritis - Physical Inactivity

Other comorbid illnesses and concomitant medication that may predispose to hyperglycaemia may also be encountered in prediabetic conditions (Table-2).

Psychosocial factors such as unwillingness or inability to follow lifestyle modification or lack of resources to prescribe/support a healthy lifestyle may complicate the issue (Table-2).

We therefore propose a comprehensive triage strategy for persons with diabetes. The factors listed in this triage (Table-2) may favour the use of drugs in prediabetes. We support a rational approach to this triage, using the biopsychosocial model of health. It reiterates the responsibility of the physician to practice resource husbandry, and encourage adherence to lifestyle modification measures. The help of trained paramedical staff (multipurpose diabetes workers, physiotherapists) can be taken if diabetes and exercise physiologists are not available.[13] The physician should also shoulder the responsibility of ensuring provision of quality services and involving the community in tackling diabetes. Technology can be harnessed to enhance awareness about the prevention of diabetes.[14,15]

The triage system does not suggest an absolute glycaemic cut off for the institution of pharmacotherapy. Rather it encourages risk assessment according to factors such metabolic, acute and chronic comorbidity, and concomitant drug therapy, combined with psychological and social factors.

Choice of Pharamacotherapy

Various drugs can be used safely in prediabetes.[9] Metformin is suggested as a first-line pharmacotherapy for prediabetes if lifestyle modification proves ineffective or impractical; if the physician judges the patient to be at high risk of progression to diabetes; or if the patient has an acute medical, surgical or traumatic condition which may resolve faster if euglycaemia is achieved.

In situations where metformin is contraindicated, not tolerated, or ineffective, one may consider glucagon-like peptide 1 receptor agonists (GLP1RA), sodium glucose cotransporter-2 inhibitors (SGLT2i), alpha glucosidase inhibitors, or pioglitazone. The pleiotropic and cardiovascular risk-reducing effects of these molecules must be taken into consideration while choosing the drug. Liraglutide, for example, will help in weight reduction. Both liraglutide and acarbose are proven to have cardiovascular benefit.[16,17] Alpha glucosidase inhibitors are indicated in post-prandial hyperglycaemia, while pioglitazone can reduce the risk of stroke.[18] SGLT2i are being used in an expanding array of indications, and are preferred in persons with prediabetes and chronic kidney disease, or prediabetes and heart failure.[19,20]

Drug therapy, however is not a substitute for lifestyle modification and must be promoted to all individuals with prediabetes.

Follow Up

Persons identified to have prediabetes must be followed up regularly. Glucose-monitoring at monthly intervals, and HbA1c every six months, usually suffice. However, more frequent glucose monitoring may be indicated if there are changes in health status or medication, which may impact glycaemic levels.

Summary

Metabolic medicine is an ever-evolving field. Newer glucose-lowering drugs, with established efficacy and safety have been developed, and are increasingly being used in non-diabetic indications. We suggest a pragmatic triage system for persons with prediabetes, to help identify those who may benefit from preventive pharmacotherapy. This triage is based upon a comprehensive assessment of personal, metabolic medical and vascular health. Such an approach can help optimize long term outcomes in an effective manner.

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