The Importance of Testing for Pre-diabetes—Using the Right Tool

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Abstract

Diabetes is one of the most prevalent chronic diseases affecting the US healthcare system today, and increasing emphasis is being placed on disease prevention and screening. Early detection of pre-diabetes can be of great benefit to patients as studies have shown that signs of early diabetic complications often exist at the time of diagnosis. Early intervention has been shown to delay, and in some cases prevent, the progression from pre-diabetes to diabetes. Venous blood sampling and core laboratory analysis remain the gold standard for diagnosis. While point-of-care testing (POCT) devices are convenient and readily available, many variables affect the technical performance of POCT devices to allow their use as a reliable diagnostic method. Future diagnostic techniques may include glycated hemoglobin (HbA_{1c}) testing or genotyping and antibody screening. Currently, the HbA_{1c} assay is used in the monitoring of diabetes, but its potential for diagnosis of diabetes is currently being examined. Genotyping and antibody screening for type 1 diabetes are showing promise as they add to the understanding of type 2 diabetes. However, this research is still in the early stages and is not yet available for clinical use.

Keywords

Pre-diabetes, fasting plasma glucose (FPG), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), oral glucose tolerance test (OGTT), point-of-care testing (POCT)

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Type 2 diabetes, formerly referred to as non-insulin-dependent or adult-onset diabetes, is a chronic medical condition caused by insulin resistance, inadequate insulin secretion, or a combination of both.[1] It differs from type 1 diabetes in that it can be acquired due to a multitude of lifestyle and medical factors rather than being caused by the autoimmune destruction of insulin-secreting beta cells in the pancreas. The influence of lifestyle on the development of type 2 diabetes makes it the most common form of diabetes in developed countries.[1] The annual cost of diabetes care in the US approaches $100 billion, including both acute conditions and long-term complications of diabetes.

As healthcare costs rise, there has been an increased emphasis on disease prevention. Prevention strategies have led to screening recommendations for various conditions, including colon and breast cancer, with minimally invasive techniques such as occult blood testing and breast exams, respectively. Diabetes, which is currently one of the foremost chronic diseases worldwide, should be approached no differently. The American Diabetes Association (ADA), the World Health Organization (WHO), and various international organizations have made efforts to increase screening for type 2 diabetes with corresponding lifestyle, dietary, and drug interventions.

Pre-diabetes can be thought of as an intermediate stage along a spectrum between normal glucose and frank hyperglycemic plasma levels.[2] It represents a subset of patients who are found to have impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. The progression from pre-diabetes to type 2 diabetes occurs over many years, but the pre-diabetic state is not without risk. Pre-diabetes itself presents increased risk for development of microvascular and macrovascular diseases and their complications,[2] and is also a risk factor for future development of type 2 diabetes. By identifying patients with pre-diabetes and initiating early interventions—lifestyle and/or pharmacological—the progression to type 2 diabetes can be delayed, or in some cases even prevented.

Type 2 diabetes is diagnosed by either random fasting plasma glucose (FPG) levels or oral glucose tolerance testing (OGTT) in the physician's office. As it is not feasible to test the entire population, currently only individuals at high risk for developing type 2 diabetes are screened with blood tests. These include patients with a family history of diabetes or a personal history of hypertension, dyslipidemia, or cardiovascular disease, or those belonging to certain ethnic groups known to have a higher risk, such as African-Americans.[3] Of the two blood tests, studies have shown that the OGTT detects pre-diabetes more reliably than FPG levels.[3–5]

For practical reasons, FPG alone is often used for diabetes screening. This method is relatively convenient and less expensive than OGTT.[4] For an FPG test, a venous blood sample is drawn in the physician's office following a 12-hour overnight fast. This specimen is analyzed in a core laboratory. According to the 2003 ADA consensus guidelines, an FPG level between 100mg/dl (5.5mmol/l) and 125mg/dl (6.9mmol/l)is defined as IFG, or pre-diabetes. For an OGTT, a venous blood sample is also drawn in the physician's office after a 12-hour overnight fast. The patient is administered a 75g oral dose of glucose. The patient must remain in the physician's office until a second venous blood sample is collected two hours after the glucose dose. Both fasting and two-hour samples are analyzed in a core laboratory. If the first result falls in the impaired fasting glucose range, or the two-hour post-dose result lies between 140mg/dl (7.8mmol/l) and 199mg/dl (11.1mmol/l), these results are indicative of IGT, or pre-diabetes. As mentioned, FPG alone is commonly used to screen for diabetes, but an OGTT more reliably detects diabetes. The same can be said for the detection of pre-diabetes. Studies have demonstrated that FPG alone detects only 30–65% of patients with diabetes, while OGTT detects around 90%.[3,5] For this reason, OGTT is still considered a standard method for diagnosis of diabetes.

Pre-diabetes and the Benefits of Intervention

The importance of identifying diabetes and pre-diabetes is related to the risk of developing complications from elevated blood glucose levels.[2] Studies[6–11] have shown that early signs of diabetic complications such as retinopathy and cardiovascular disease were found relatively early in the diagnosis of diabetes, suggesting that these disease states were already present or developing well before an official diagnosis of diabetes was made.[2] Since patients can develop complications of diabetes before diagnosis, early detection and intervention can be of great benefit. The risk of progression from pre-diabetes to type 2 diabetes is quite high, especially if left untreated. When detected early, the patient may not only delay but even prevent progression to diabetes. Disease prevention is significantly less expensive than the treatment of frank hyperglycemia and diabetic complications.

The primary intervention for pre-diabetes, as with type 2 diabetes, is lifestyle modification. Weight loss, reduced fat intake, increased fiber intake, and increased physical activity[2] have consistently demonstrated benefits in preventing or delaying the progression from pre-diabetes to diabetes.[2] The difficulty of maintaining even modest lifestyle changes makes compliance with this treatment option challenging and maintenance of new habits difficult.[12] A considerable amount of effort and motivation from fitness trainers and nutritionists is needed to implement and foster these lifestyle modifications.[12] However, even modest changes in weight or exercise can lead to a reduction in the incidence of diabetes.[12] While lifestyle modifications provide improved outcomes, better strategies are still needed to aid patients in compliance. Currently, there are no provisions in the US healthcare system to aid or reimburse patients for periodic lifestyle counseling.[12] Other treatment options for pre-diabetes are pharmacological. Three diabetes prevention trials have tested the use of different medications to delay progression of pre-diabetes. The Diabetes Prevention Program (DPP) administered metformin and saw a 31% risk reduction for diabetes.[9–11] The use of acarbose, an α-glucosidase inhibitor, in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial saw a similar reduction in pre-diabetes progression (32%).[13] The third study used troglitazone and saw the most dramatic risk reduction (56%).[14] Data from this trial suggest true prevention, rather than simply a delay of progression.[14] Of note, the use of metformin was most successful in a small subset of patients with pre-diabetes, namely those who were younger (24–44 years of age) and more overweight (body mass index [BMI] $\geq$35kg/m^2).[12]

While lifestyle modification is relatively free of side effects, pharmacological intervention is not. Even though medications such as acarbose, metformin, or troglitazone may have benefits, the benefits should outweigh the risks for any individual patient. Drug therapy of any kind is generally associated with side effects, some of which may be severe; for this reason, pharmacological intervention should be considered a second choice after lifestyle changes.[12]

Laboratory Testing

To date, the measurement of fasting plasma glucose levels on venous blood samples has been the standard means of diagnosing diabetes. An abnormal fasting plasma glucose test that is followed by an OGTT aids in the discrimination of IFG, IGT, or overt diabetes. In recent years, great advances have been made in the field of point-of-care testing (POCT). The ability to perform tests and obtain results faster at the point of care (POC) has been especially significant in the monitoring and management of diabetes. Patients and practitioners are able to check a patient's blood glucose rapidly at the bedside, at home, or in the doctor's office. However, POC blood glucose monitoring is especially susceptible to errors due to pre-analytical, analytical, and post-analytical effects,[15] given that a range of clinical staff and patients without laboratory experience are performing the test. It is this rise in the use of POCT that has led to the question of whether POCT can be used in the diagnosis of diabetes. Before POC glucose meters can be used in the diagnosis of diabetes, the device results should match the technical performance of any currently accepted diagnostic tool. One of the most important technical criteria is the accuracy or agreement between glucose meter results and the laboratory glucose levels analyzed in a centralized laboratory. The ADA recommends that glucose meter results agree with a central laboratory within ±5%, 100% of the time. This goal has been difficult to achieve because of the many factors that influence POCT.[15]

Operator effects are the most important influences on glucose meter results and include level of training, motivation, device portability, and ease of use. Clinical staff such as nurses do not have the level of laboratory experience or training compared with medical technologists and are generally motivated more by patient care than by laboratory concerns.[15] Device maintenance can become a secondary issue despite its importance in the accuracy of test results. Precision, which is the measure of reproducibility of results, can also be affected. As the number of operators with varying degrees of motivation and experience perform the same test, result variability can increase. Patients, in turn, may neglect device maintenance, most likely due to a lack of understanding of the importance of device calibration and quality control. Glucose meter performance and subsequent results greatly depend on technique. This includes device ease of use, simplicity of strip insertion, and blood application.[15]

Other factors influencing accuracy and the comparability between glucose meter and central laboratory results include external factors such as environmental effects, the patient's general health status, and interference from other substances. Environmental effects refer to factors that influence the glucometer and/or test strips prior to or during use. Light, temperature, humidity, and air exposure can all affect the test strips and alter the stability of the delicate enzymes and reagents contained within the test strips.[15] Exposure of test strips and meters to environmental extremes in cars, at the gym, or during transport can compromise results. The patient's general health status also plays an important role. Circulatory problems can lead to capillary specimens that do not reflect central venous levels. Alterations in fasting status, oxygen therapy, pH, or hematocrit can all interfere with analysis.[15] Chemical interferences can occur from the presence of maltose, ascorbic acid, salicylate, and other drugs. Maltose is a common problem in the inpatient setting as it is frequently used in various parenteral substances. Maltose can cross-react with some POC glucose meters, leading to falsely elevated results and the potential to overdose required insulin. Ascorbic acid and salicylates can act as alternate electron carriers[15] and also affect the enzymatic processes within the strip.

Another major factor causing differences between glucose meter and core laboratory results is the type of specimen used for analysis. Most laboratory methods analyze plasma, while POC devices analyze whole blood.[15] Core laboratories receive whole-blood specimens from which they separate the cells and utilize the plasma portion for analysis. When using a glucose meter, a drop of the patient's (whole) blood is applied to the glucose test strip. The blood diffuses through multiple layers of absorbent materials that filter out erythrocytes allowing the plasma to diffuse though to the enzyme reagents in the strip.[15] There is commonly an 11% difference between whole-blood glucose and results from plasma methods that is largely attributed to the relationship of glucose to water. Glucose diffuses freely in the water space of whole blood. However, erythrocytes contain less water (per unit volume) than plasma and therefore whole-blood results are lower than plasma results at any glucose concentration.[15] This relationship makes glucose meter results dependent on hematocrit levels, since a higher erythrocyte mass will lead to greater differences. Most manufacturers attempt to normalize the whole blood to plasma differences through calibration, using normal volunteers to establish calibration settings. However, calibration volunteers with normal hematocrits add additional biases when the glucose meters are utilized on hospitalized patients with abnormal hematocrits. One POC glucose analyzer system currently on the market aims to address this issue. The HemoCue Glucose 201 Analyzer uses saponin in its proprietary cuvette technology to lyse red cells prior to analysis. Using this technology enables the device to perform blood glucose analysis on whole blood rather than plasma.[15] However, this is one of the few devices that still analyze whole blood. The majority of glucose meters utilize methodologies that are heavily hematocrit-dependent. It is because of the increased variability of POCT results that the ADA continues to recommend the use of plasma glucose for the diagnosis of diabetes.

Glycated Hemoglobin

Another test that has recently been suggested for the diagnosis of diabetes is the glycated hemoglobin (HbA_{1c}) assay. Currently, HbA_{1c} is used by physicians in the office setting to monitor the long-term glycemic status of patients. HbA_{1c} is expressed as the percentage of hemoglobin that is glycosylated. It is formed non-enzymatically by the exposure of hemoglobin to glucose. Once a hemoglobin molecule is glycosylated, it remains glycosylated until the red blood cell is destroyed and hemoglobin is metabolized. HbA_{1c} therefore reflects the average level of glucose to which the cell was exposed during its life-cycle (approximately 120 days or four months).[16,17]

In 2008, a new study relating HbA_{1c} to blood glucose levels was published. The A1c-Derived Average Glucose (ADAG) study analyzed data from 507 patients with type 1 and type 2 diabetes as well as patients without diabetes from 10 centers in the US, Europe, and Africa. For three months, each participant performed three types of multipoint self-monitoring measurement, which resulted in 2,700 blood glucose tests per participating subject. The patients also had HbA_{1c} levels drawn at baseline and monthly for three months. The authors extrapolated a simple formula to calculate an estimated average glucose (eAG) level from measured HbA_{1c} percentages[16] based on the study data. This equation enables physicians to explain long-term glycemic status to patients in the familiar terms of glucose levels in mg/dl or mmol/l rather than HbA_{1c} in units of percent total hemoglobin.

While this relationship and calculation can greatly enhance physician–patient communication, its value in the setting of diagnosis is not yet established. The study itself has a number of limitations pertaining both to the HbA_{1c} assay itself and to study parameters. HbA_{1c} can be artificially lowered if a patient is in a chronic hemolytic state and therefore has shortened red cell survival. The HbA_{1c} can also be falsely elevated if the patient has prolonged red cell survival, such as after splenectomy. Additionally, HbA_{1c} can be formed only if a patient has normal hemoglobin, excluding patients with sickle cell disease or various forms of thalassemia.[17] The study only included six centers in the US, three in Europe, and one in Cameroon. Another center in Asia was eliminated from the data due to improper specimen storage. Participants were between 18 and 70 years of age, but did not include children or pregnant women.[16,17] The study was also limited in terms of the number of ethnic groups with a high prevalence of diabetes, such as African-Americans, American-Indians and Eskimos. An argument could be made as to whether these factors are relevant to the hemoglobin/average glucose relationship, since glucose–hemoglobin binding is non-enzymatic. However, very little research has been undertaken on the utility of HbA_{1c} outside its traditional use in monitoring dietary and lifestyle compliance and insulin management. All current treatment and diagnostic recommendations are based on the Diabetes Control and Complications Trial (DCCT), which examined direct blood glucose levels, not HbA_{1c}.[6,7,17]

Just this year, the ADA commissioned an International Expert Committee on diabetes to re-examine the concept of HbA_{1c} for the diagnosis of diabetes. Taking into consideration long-term glycemic levels and the timing of onset of diabetic complications, the committee was able to set the diagnostic threshold for diabetes at an HbA_{1c} percentage of ≥6.5% and a range of 6.0 to <6.5% for pre-diabetes. These numbers, while not being absolute dividing lines, are sufficiently sensitive and specific to identify individuals at risk for developing diabetic complications and could

therefore be used to diagnose patients as having diabetes or pre-diabetes.[18] Along with setting these thresholds, the authors identified a number of advantages for the use of HbA_{1c} in diagnosing diabetes, including the fact that laboratory measures that express long-term glycemic exposure should provide a better marker for presence and severity of disease than single measures of glucose concentration.[18] Other advantages of HbA_{1c} focused on the convenience and ease of sample collection for the patient, as no fasting or other preparation is necessary.[18]

Despite this correlation of HbA_{1c} percentages to risk of developing diabetic complications, significant limiting factors for the use of this assay remain. Some include hemoglobinopathies and conditions of altered red cell turnover, as previously described. Others include the observations that HbA_{1c} levels tend to rise with age, or differ among ethnic groups.[18] The lack of standardization of the HbA_{1c} assay worldwide also continues to be a limiting factor. While the current recommended method for diagnosing diabetes remains the OGTT, HbA_{1c} may become a useful diagnostic test in years to come.

Genotyping and Antibody Screening

The future of diabetes screening is promising and may involve genotyping and antibody screening. Multiple clinical trials are currently under way using type 1 diabetes as the template for autoimmune-mediated causes of diabetes. These trials suggest that the risk for developing type 1 diabetes is a combination of the presence of high-risk human leukocyte antigen (HLA) genes and autoantibodies.[19] Early observations include the idea that patients who are genetically at risk but do not have autoantibodies have a lower risk of developing type 1 diabetes unless there is a triggering event.[19] The nature of the necessary triggering event is not yet known. Antibody screening, in turn, could be used as an indicator of whether an immune response against pancreatic islets has been activated.

Currently, four major antibodies have been identified: insulin antibodies (IAA), glutamic acid decarboxylase (GAD65), a tyrosine-kinase-like molecule (IA-2), and the zinc transporter ZnT8. Having any two of the four is considered positive for an activated immune response.[19] As more discoveries are made with regard to type 1 diabetes, researchers are finding that the diagnostic divide between type 1 and type 2 diabetes is getting smaller, suggesting the possible utility of these new developments in the future diagnosis of type 2 diabetes and pre-diabetes. Type 2 diabetes is defined by the combination of insulin resistance and inadequate insulin secretion. Based on type 1 diabetes research, it has been observed that insulin resistance can accelerate the effect of the autoimmune attack on islets, thus showing an overlap between type 1 and type 2 diabetes.[19] Similarly, inflammation has been examined in type 1 diabetes and, recently, in type 2 diabetes. A new study from 2007 showed some benefit in patients with type 2 diabetes after they received the anti-inflammatory drug anakinra.[19,20] Promising as some of these developments may be, they are still a long way from routine clinical use.[19]

Conclusion

Diabetes is one of the most prevalent chronic diseases affecting the US healthcare system today. While it is important to address the acute and chronic treatment needs of those already diagnosed, an increasing emphasis is being placed on disease prevention and screening. Pre-diabetes is an important stage on the spectrum between normal blood sugar and frank hyperglycemia. Patients can benefit greatly from the early detection of this state. Studies have shown that patients with diabetes often show signs of early diabetic complications at the time of diagnosis. Early intervention with lifestyle modifications and/or pharmacological therapy can often delay, and in some cases prevent, the progression from pre-diabetes to diabetes. Despite the availability of various testing methods, venous blood sampling and core laboratory analysis remain the standard. Fasting plasma glucose levels, and specifically OGTTs, detect pre-diabetes most reliably. While POCT devices are convenient and readily available, variables such as operator effects continue to plague the reliability of POCT devices as diagnostic tools. Future diagnostic tests may include HbA_{1c} testing or genotyping and antibody screening. The HbA_{1c} assay, while familiar to both clinicians and patients, has not been evaluated for diagnosis of diabetes or pre-diabetes. Genotyping and antibody screening are showing promise as these tests are furthering the understanding of type 2 diabetes through research in the realm of type 1 diabetes. It seems that causes of type 2 diabetes may be similar to those of type 1, especially in the setting of the body's autoimmune response to pancreatic islet cells. To date, however, this research is in its early stages and is not yet ready for routine clinical use. ■

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