

Review Article

Prediabetes and serum insulin levels

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ABSTRACT

Prediabetes remains a diagnostic dilemma. It refers to impaired glycaemic values without reaching the threshold for diagnosing diabetes mellitus. Prediabetes is an important risk factor for the development of diabetes mellitus, and it constitutes the stage during which microvascular and macrovascular complications are initiated. Early and accurate identification of this stage is the gold standard for prevention of diabetes and its consequences. Despite the multiplicity of diagnostic tests proposed for identification of this condition, a reliable test remains elusive. This article aims at reviewing the different available tests for diagnosis of prediabetes states with a focus on serum insulin levels. Insulin plays a major role in the pathophysiology and development of prediabetes. Different mechanisms of insulin resistance and insulin secretion are established in different subtypes of prediabetes. Therefore, fasting insulin level seems to be a reliable and promising tool for diagnosis and management of prediabetes.

Keywords: Prediabetes, Insulin level

INTRODUCTION

Prediabetes is a state of hyperglycaemia characterized by elevation of blood glucose levels higher than normal but lower than the values of frank diabetes.¹⁻³ To date, prediabetes remains a topic of concern for many researchers because of its deleterious complications on health. Prediabetes does not only put the patient at higher risk for developing diabetes mellitus, but is also associated with negative consequences on renal, retinal, and peripheral nervous tissues.^{4,5} The benefit of identification of this state is that multiple prospective studies confirmed that early lifestyle modifications and dietary intervention at this prediabetic state had

significantly improved the outcome and prevented long-term complications.⁶

Despite the well-established risk and consequences of prediabetes, conflicts remain about the definition, diagnostic criteria, and diagnostic tests of this state. Fasting plasma glucose level, oral glucose tolerance test, and haemoglobin A1c tests are used for the diagnosis of prediabetes, and recent studies suggest insulin level can also be useful for diagnosis.^{6,7}

This article will discuss the definition, epidemiology, diagnosis, and pathophysiology, and it will focus on insulin levels in this state.

PREDIABETES DEFINITION

Prediabetes is an intermediate state of hyperglycaemia in which glycaemic measures (such as glucose level and HbA1c) are elevated at levels higher than normal but lower than the diagnostic thresholds for diabetes mellitus.² It has longer been accepted that prediabetes is a risk factor for developing diabetes mellitus in the future. However, recent researchers argued the importance of not defining prediabetes on a glucocentric basis because it is well-established that this state of hyperglycaemia is associated with microvascular dysfunction, macrovascular consequences and early end-organ damage same as diabetes. Retinopathy, neuropathy, and nephropathy were found in up to 10% of prediabetic patients. Similarly, prediabetes was also associated with metabolic syndrome, cognitive disturbances, neoplasms, hormonal changes, fatty liver disease, and obstructive sleep apnoea.⁴

Currently, there are many definitions for prediabetes that are mainly based on biochemical measures. Each organization propose a different definition for prediabetes depending on its sensitivity and specificity to identify the individuals at risk for developing microvascular and macrovascular complications of the poor glycaemic control, and the morbidity and mortality associated.² The American Diabetes Association (ADA), the World Health Organization (WHO), and the International Expert Committee define prediabetes depending on four main markers namely fasting blood glucose, oral glucose tolerance test, combined fasting blood glucose and glucose tolerance test, and haemoglobin A1c levels.³

Because none of the aforementioned glycaemic measures were accurate and reliable for diagnosing and predicting the outcome of prediabetes, new multidimensional approaches are suggested for defining prediabetes. These approaches propose adding other factors (e.g. the existence of microvascular or macrovascular complications of diabetes) to the cut-off thresholds for glycaemic variables.² Such definition would better identify individuals at risk at earlier stages of the disease. However, this idea is still under research and need extensive discussion and studying of cost-effectiveness. Developing a standardized reliable definition for prediabetes is essential not only to prevent the progression of the state to frank diabetes, but also to delay the development of microvascular or macrovascular complications of impaired glycaemic states.

EPIDEMIOLOGY AND RISK FACTORS FOR PREDIABETES

Prediabetes is more prevalent than diabetes worldwide⁴, and the figure is expected to increase over the next decades.⁸ The prevalence is variable according to the definition of prediabetic state as well as the ethnic group. For instance, a review study about the prevalence of prediabetes among ethnicities reported that prediabetes

was more common among Caucasian. The prevalence of impaired fasting plasma glucose was 58.0% among Caucasian and 48.1% among Asian. Impaired glucose tolerance, however, was prevalent among 20.3% of Caucasian and 27.7% of Asian.⁹ According to the National Diabetes Statistics reports (2017)¹⁰, it is estimated that about 44% of the United States adults and 43% of elderly above 65 years have prediabetes. Only 11.6% of them were not educated by their healthcare professionals about their condition. Prediabetes was stated in this report to be more prevalent among men (36.6%) than women (29.3%).¹⁰

Risk factors for prediabetes have been studied by many researchers. Abdominal obesity, hypertension, and low HDL-cholesterol levels were the most significant modifiable risk factors for prediabetes.¹¹ Abdominal obesity was the strongest factor associated with prediabetes in both genders suggesting that it is an independent risk factor for this hyperglycaemic state. Male gender was the most established non-modifiable factor associated with high risk for development of prediabetes.¹² Sex, body mass index (BMI) and family history of diabetes were predictors for progression to type two diabetes mellitus among prediabetic patients.^{7,12} Thus, screening for prediabetes is recommended by the American Diabetes Association (ADA) 2016 to be performed for all overweight or obese individuals (BMI>85th percentile for age and sex, weight>120% of ideal weight, or weight for height >85th percentile) with two or more risk factors including: first or second-degree relative with type 2 diabetes, maternal history of gestational diabetes during the child's pregnancy type diabetes, signs of insulin resistance (e.g. acanthosis nigricans, dyslipidemia, hypertension, polycystic ovarian syndrome), or certain ethnic group such as African American, Native American, Pacific Islander, Latino, or Asian American descent.¹³

Management of prediabetes is primarily non-pharmacological. Lifestyle modifications are the mainstay treatment for individuals with impaired glycaemic measures. Weight loss, regular exercise, health low-fat and high fibre-diet, active non-sedentary life, and smoking cessation are effective measures for lowering blood glucose levels to normal values. Some alternative therapies such as banaba, fenugreek, magnesium, ginseng, white mulberry, gymnema, and cassia cinnamon are proposed, but not yet established as effective measures for treating prediabetes.

DIAGNOSIS OF PREDIABETES

According to the American diabetic Association (ADA) 2016 clinical practice recommendations, prediabetes can be diagnosed on basis of three tests: fasting blood glucose, oral glucose tolerance test, and HbA1c levels.¹³ Prediabetes is defined as fasting blood glucose between 100-125 mg/dl (5.6-6.9 mmol/l), Two-hour postprandial glucose level between 140-199 mg/dl (7.8-11.0 mmol/l),

or haemoglobin A1C level between 5.7-6.4% (39-46 mmol/mol).

The first consensus-based criteria for definition of prediabetes were proposed by the American National Diabetes Data Group (NDDG) association in 1979 and were changed several times. Basically, prediabetes (or non-diabetic hyperglycaemia) diagnostic criteria included: a fasting plasma glucose concentration less than that defined for the diagnosis of diabetes (<140 mg/dl), 2-hour oral glucose post plasma level between 140-199 mg/dl, and a midtest plasma glucose value of ≥ 200 mg/dl. Clinical manifestations are not included in the diagnostic criteria of prediabetes. Therefore, many terms were proposed for defining this non-diabetic hyperglycaemic state e.g. "chemical diabetes", "borderline diabetes", "impaired glucose tolerance", and recently "prediabetes".¹⁴ The World Health Organisation (WHO) is different from the American National Diabetes Data Group (NDDG) in defining prediabetes as regards some points. For instance, the WHO consider a person prediabetic when his fasting plasma glucose and 2-hour post prandial glucose values are elevated without requiring an additional midtest value of ≥ 200 mg/dl.¹⁵ This definition is more inclusive than the NDDG group definition because it includes patients with impaired fasting glucose and impaired 2-hour glucose tolerance with midtest glucose levels <200 mg/dl.¹⁵

Fasting plasma glucose

Fasting plasma glucose (FPG) level is measured after 6-8 hours of fasting. It is considered normal if the level was below 100 mg/dl (5.6 mmol/l). Prediabetes is considered when FPG level lies between 100 and 125 mg/dl (5.6-6.9 mmol/l), and diabetes is diagnosed when the level is ≥ 126 mg/dl (7.0 mmol/l) or more.¹³ Cut-off values for impaired fasting plasma glucose (prediabetes) were a subject for discussion. For example, the ADA in 2003 recommended lowering the cut-off value of impaired fasting glucose to 100 mg/dl (5.6 mmol/l) based on the results of review studies to maximize the sensitivity of detecting early prediabetes and consequently preventing diabetes. This lowering was associated with lower cardiovascular complications and lower risk for developing diabetes.¹⁶ However, the WHO refused lowering this cut-off value and maintained the defining value for impaired fasting glucose at 110 mg/dl to avoid the major increase in prevalence of prediabetes with its social, economic, and personal negative consequences. In fact, an exact value for defining a cut-off level for prediabetes remain a matter of challenge because one of the studies indicated that the mild increase of fasting plasma glucose from 81 mg/dl (4.5 mmol/l) to 86 mg/dl (4.8 mmol/l) was significantly associated with increased risk for developing type 2 diabetes mellitus.¹⁶ Similarly, 50% of patients with fasting plasma glucose ≥ 106 mg/dl (5.9 mmol/l) developed diabetes in another study.¹⁷ This indicates that the reliability of using fasting plasma glucose as an indicator for prediabetes diagnosis remains

debatable. Therefore, the diagnostic criteria for prediabetes were subjected to major changes over time.

Oral glucose tolerance test

Oral glucose tolerance test is performed through giving the patient 75 g of glucose after an eight-hour period of fasting, then measuring the post prandial plasma glucose level after 2 hours. A 2-hour postprandial plasma level less than 140 mg/dl (7.8 mmol/l) is normal. Levels between 140 and 199 mg/dl (7.8-11.0 mmol/l) are definitive for prediabetes, and levels ≥ 200 mg/dl (11.1 mmol/l) are diagnostic for diabetes mellitus.¹³ The reason behind inclusion of impaired glucose tolerance (IGT) as a criterion for diagnosis of prediabetes is that it carries a considerably higher risk for developing type 2 diabetes mellitus in comparison to individuals with normal glucose tolerance. About 1-5% of patients with IGT develop diabetes yearly, whilst less than 1% of individuals with normal glucose tolerance do. On the other hand, up to 10% of patients with IGT remains in the IGT state for 10 years without developing diabetes. IGT is also not essentially an independent risk factor for the development of nephropathy, neuropathy, or retinopathy. However, it was found to be associated with higher mortality rates due to cardiovascular diseases.¹

Glycated haemoglobin HbA1c levels

Haemoglobin A1C (HbA1C) use was introduced later on and was established as an important criterion for defining prediabetes. HbA1C indicated the average plasma glucose level for the past 2-3 months. It measures the percentage of glycated-haemoglobin that reflects the hyperglycaemic state during the half-life of the red blood cells tested. In general, HbA1C level below 5.7% is considered normal, prediabetes is defined with HbA1C level between 5.7 and 6.4%, and diabetes is diagnosed when HbA1C is $\geq 6.5\%$ on two separate tests.¹⁸ Haemoglobin A1C reflects long-term glucose concentration rather than a point measure that can be affected by food intake. It is also a better representative indicator for chronic complications of impaired glycaemic control. In spite of its higher cost, its use is a rationale approach for diagnosis for diagnosis of prediabetes. Whereas a value of 6.5% is the cut-off value for diabetes, a level of 6% was initially proposed for diagnosing prediabetes. Individuals with HbA1c levels between 6 and 6.5% were 10 times riskier for developing diabetes than those with HbA1C levels $\leq 6\%$. However, debates also exists about this cut-off value for defining prediabetes because many studies had reported high risk of diabetes among individuals with lower HbA1C levels (5.5% and 5.7%).¹⁹ Therefore, the latest ADA diagnostic criteria adopted the value of 5.7% as a cut-off level for diagnosing prediabetes.¹³ However, further studies are recommended for identifying a reliable level for predicting the actual risk for developing diabetes mellitus.

INSULIN AND PREDIABETES

As aforementioned, many diagnostic tests have been proposed and established for diagnosis of prediabetes. And despite their multiplicity, a reliable test remains elusive. Serum insulin level is a promising test for diagnosing prediabetes and predicting the risk of developing diabetes mellitus. Various epidemiological studies reported that the pathophysiological characters of impaired fasting plasma and impaired glucose tolerance were significantly different from the actual pathophysiology of diabetes.²⁰ Low insulin level and insulin resistances are the main pathophysiological mechanisms in type 2 diabetes mellitus. Therefore, recent researches are concerned with studying the role of measuring insulin levels as well as insulin resistance as predictive indicators for diabetes in prediabetic hyperglycemic states. In type 2 diabetes, there is either low insulin level or considerable insulin resistance in spite of high insulin level in the blood.¹⁶ Insulin resistance refer to the low response of different tissues and organs to respond to endogenous or exogenous insulin leading to increased plasma glucose levels.²¹

Insulin resistance as a pathophysiology of prediabetes

In prediabetes, it has been found that insulin resistance is significantly higher than individuals with normal glucose levels.¹⁶ Of interest, there are different mechanisms for insulin resistance among prediabetic patients in relation to the glycaemia-measuring tools used. For instance, patients with isolated impaired fasting plasma glucose display a considerable hepatic insulin resistance, whilst patients with isolated impaired glucose tolerance exhibit significant peripheral insulin resistance.^{22,23} It is stated that the main pathophysiologic mechanism in prediabetic patients with impaired fasting plasma glucose is impaired suppression of hepatic production of glucose in spite of hyperinsulinemia. Hepatocytes continue to synthesize excessive amount of glucose and seem to be non-responsive to elevated blood insulin levels. In contrast, peripheral insulin resistance remains intact with values closely similar to the normal euglycemic individuals. Thus, hepatic insulin resistance is proposed to be the main pathophysiological mechanism in impaired fasting glucose state.²² Conversely, prediabetics with impaired glucose tolerance have significantly higher peripheral insulin resistance, when measured with the euglycemic hyperinsulinemic clamp, when compared to normal individuals.²⁴ Prediabetics who have both impaired glucose tolerance and impaired fasting glucose exhibit both peripheral and hepatic resistance.²²

Insulin secretion in prediabetes

In its essence, diabetes develops due to the progressive failure of the pancreatic beta cells to produce insulin. Insulin secretion is stimulated by glucose administration either orally or parenterally. Oral administration promotes insulin secretion not only via direct stimulation

of the pancreas but also through the additional effect of incretin, a metabolic hormone that is secreted after eating. After glucose administration, insulin is secreted from the pancreas in two phases: an early phase characterized by a sharp increase in insulin level and a late slower phase of secretion.²⁵

In prediabetes, failure of pancreatic beta cells to secrete adequate amounts of insulin is the earliest pathophysiological mechanism of hyperglycemia. Pancreatic beta cell failure mechanisms are different according to the subtype of prediabetes. In isolated impaired glucose tolerance subtype, early phase insulin secretion is significantly lower than normal individuals, whilst late stage phase secretion is closely similar to healthy population. Other studies reported reduction of both early and late phase insulin levels among those patients.²³ In contrast, prediabetics with isolated impaired fasting glucose have significantly lower late-phase insulin secretion and relatively intact early-phase insulin levels in comparison with normoglycemic controls.^{26,27} Furthermore, the two subtypes of prediabetes are different as regards the stimulatory mechanisms for insulin secretion. In prediabetics with isolated fasting glucose impairment, disorder of insulin secretion results from direct pancreatic beta cell dysfunction after oral and intravenous glucose administration, whereas incretin dysfunction plays a role when impaired glucose tolerance is encountered.^{24,27}

Hence, there seems to be a considerable difference in the pathophysiological mechanisms of the two subtypes of prediabetes. Considering these different mechanisms can be of a clinical significance when thinking about the management of prediabetes. Basically, the mainstay management of prediabetes was non-pharmacological. It focused on lifestyle changes, and dietary modifications, and weight loss. These simple non-pharmacological measures were proved to improve the glycemic control, prevent the development of frank diabetes, and delay the development of microvascular complications.²⁸ However, when pharmacological interventions are to be studied according to the proposed insulin resistance and insulin secretion mechanisms, more positive outcomes may be encountered. Incretin-based therapies and GLP-1 antagonists are currently studied in prediabetes with promising results. However, the safety of these agents remains a topic of debate.^{29,30}

Insulin level for diagnosis of prediabetes

Given the important pathophysiologic role of insulin in prediabetes, many researchers argue the importance of measuring insulin level as reliable criterion for diagnosis of prediabetes. Johnson et al, in their retrospective study on 965 diabetic patients, reported that fasting insulin level of 9.0 micro IU/ml could be found in 80% of patients during the prediabetes states, indicating that it may be considered the most reliable clinical tool for identifying prediabetes.³¹ Similarly, a more recent study reported that

using insulin metabolites to measure insulin resistance was another reliable test for diagnosis of prediabetes.³² Despite the few reported literature study about insulin level measurement in prediabetes, it seems to be a promising reliable tool for accurate diagnosis of this state.

CONCLUSION

Prediabetes is an important risk factor for the development of diabetes mellitus, and it constitutes the stage during which microvascular and macrovascular complications are initiated. Early and accurate identification of this stage is the gold standard for prevention of diabetes and its consequences. Despite the multiplicity of diagnostic tests proposed for identification of this condition, a reliable test remains elusive. Insulin plays a major role in the pathophysiology and development of prediabetes. Different mechanisms of insulin resistance and insulin secretion are established in different subtypes of prediabetes. Therefore, fasting insulin level seems to be a reliable and promising tool for diagnosis and management of prediabetes.

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