Simplified, Low-Cost Method on Glucose Tolerance Testing in High-Risk Group of Diabetes, Explored by Simulation of Diagnosis

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Abstract

Objective: Explore the distribution of basic characteristics of high-risk groups of diabetes; verify the practical significance and diagnostic value of the "three-point method"; layered analysis of glycated hemoglobin and glycated serum albumin, and study its value and significance in the diagnosis of diabetes mellitus, Type II and pre-diabetes mellitus, Type II.
Methods: 1304 high-risk individuals with T2D in Shanghai, 529 males and 841 females with an average of (50.5 ± 15.2) years old, were examined by oral glucose tolerance test (OGTT), HbA1c and GA were determined. Process the data by Python and GraphPad; judge the diagnostic value of HbA1C, GA by ROC.
Results: (1) The numbers of DM, NGT, HOG, IFG, Mild–IGT and Mid–IGT in the objects were 647, 141, 70, 4, 208 and 234 respectively. In the 43-49 age group with a higher incidence, the proportion of selected high-risk groups is low. (2) The sensitivity and specificity about "three-point method" used to determine NGT is 100% and 90.11%; to determine IGR is 75.11% and 97.32%; to determine HOG is 97.14% and 100%; to determine DM is 94.67% and 100%. (3) According to ROC judgment, it is found that these 2 did not have the function of separate diagnoses, the optimal critical point of HbA1C related to DM status is 5.95%, (P<.01); HbA1C related to IGR status is 5.75% (P<.01); of GA related to DM status is 15.25% (P<.01); GA related to IGR status is 14.95% (P<.01).

Keywords

diabetes mellitus, type II, oral glucose tolerance test, fasting plasma glucose, postprandial blood glucose, big data, simulation of diagnosis

What do We Already Know About This Topic?

T2D is a heterogeneous disease, characterized by insufficient insulin secreted by pancreatic beta cells in the case of impaired insulin sensitivity, which is called insulin resistance, and OGTT has been used as the most accurate and direct experimental method for the diagnosis of diabetes.

How Does Your Research Contribute to the Field?

A simplified T2D diagnosis method–"three-point method" was proposed, which has lower cost and simpler steps compared with traditional OGTT, and may be suitable for screening diabetic patients from a large number of high-risk groups.

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What Are Your Research's Implications Towards Theory, Practice, or Policy?

Targeted screening of high-risk DM people over the age of 42 by "three-point method", based on pre-diabetes found that patients, have high clinical and economic significance.

Introduction

Since the 21st century, increasing type 2 diabetes (T2D)[1,2] has become a global public health concern. Although the mortality rate of diabetes-related complications has improved significantly, it is mainly reflected in the decline of the following events: cardiovascular disease,[3] cerebrovascular disease,[4] diabetic nephropathy,[5] diabetic lower limb amputation.[6] Despite this, the prevalence of diabetes has not been well controlled. T2D is a heterogeneous disease, characterized by insufficient insulin secreted by pancreatic beta cells in the case of impaired insulin sensitivity, which is called insulin resistance.[7] Previously, T2D was most prevalent in affluent Western countries; however, it currently exists worldwide.[8] According to the latest report from IDF Diabetes atlas,[9] an estimated 463 million adults (aged 20-79) worldwide suffer from diabetes, accounting for 9.3% of the world's total population in this age group at present, this number is expected to reach 578 million (10.2%) and 700 million (10.9%) respectively By 2030 and 2045. In terms of health expenditure, annual global health expenditure on diabetes is estimated at $ 760 billion. Expected expenditure in this area will reach $ 825 billion by 2030, and this figure will reach $ 845 billion by 2045.

The World Health Organization (WHO), International Diabetes Federation (IDF),[10-12] American Diabetes Association (ADA),[13] European Association for the Study of Diabetes (EASD),[14] and Canadian Diabetes Association (CDA)[15] continually revise the diagnosis and treatment guidelines for diabetes, especially for pre-diabetes[16] and early diabetes management,[17] and put forward new diagnostic and intervention requirements: Fasting blood glucose, 2 hours postprandial blood glucose,[18] and glycated hemoglobin,[19] glycated serum albumin[20] (some guidelines and recommendations) are used as diagnostic criteria for diabetes. OGTT has been used as the most accurate and direct experimental method for the diagnosis of diabetes. Briefly, while venous fasting blood glucose is less than 6.1 mmol/L, and the postprandial blood glucose (PBG) is less than 7.8 mmol/L, it means that the human body has a normal ability to regulate blood sugar after eating glucose, and it is a normal person (NGT); While the venous fasting blood glucose ≥ 7.0 mmol/L or the PBG ≥ 11.1 mmol/L, it indicates that the body's ability to process glucose after eating is significantly reduced, and diabetes can be diagnosed (DM); While the venous fasting blood glucose is less than 7.0 mmol/L, and the PBG is between 7.8-11.1 mmol/L, it indicates that the human body's ability to regulate glucose is slightly decreased, and impaired glucose tolerance can be diagnosed (IGT); While the venous fasting blood glucose is between 6.1-7.0 mmol/L, and the PBG is less than or equal to 7.8 mmol/L, it means that the human body has a good ability to regulate blood sugar after eating glucose, but the ability to regulate fasting blood sugar is slightly reduced, which diagnosing impaired fasting glucose (IFG), meanwhile, according to the previous study,[21] IGT can be subtyped as mild-IGT and mid-IGT; while any blood sugar level is below 3 mmol/L, the diagnosing impaired as hypoglycemia (HOG). However, the method is more tedious, it takes a long time to check, the reproducibility is poor, and the coefficient of variation is large. Therefore, the feasibility of large-scale population screening has been questioned.[22]

To explore a low-cost way to screen large numbers of high-risk individuals for diabetes, this study used a retrospective study and was selected for the basic information and blood glucose-related indicators of 1304 patients at high risk for diabetes in recent years. Statistically analysis the distribution of age, gender, and other characteristics of the high-risk groups of diabetes participating in the test, and find out the basic rules of them; analyze the value of various time points in OGTT for assessing the stage of diabetes and try to propose more clinically meaningful detection methods; stratified analysis by glycated hemoglobin, glycated serum albumin, research its value and significance in the diagnosis of diabetes and pre-diabetes. Through sample analysis, simulation diagnosis, and other methods, a simplified T2D diagnosis method was proposed, which has lower cost and simpler steps compared with traditional OGTT, and may be suitable for screening diabetic patients from a large number of high-risk groups.

Methods

Research Objects

A total number of 1304 patients were screened for the high-risk DM group by the Department of Endocrinology, Tongren Hospital affiliated to Shanghai Jiaotong University From January 2011 to October 2018. The study population met at least one of the following criteria: (1) Family history of diabetes; (2) Body Mass Index (BMI) ≥ 24 kg/m2; (3) Women with a large child delivery history (neonatal weight ≥ 4 kg); (4) FPG (fasting plasma glucose)≥ 6.1 mmol/L; (5) High blood pressure, or are taking antihypertensive drugs; (6) Lipid metabolism disorders, or taking lipid-lowering drugs. All subjects underwent OGTT, and the subjects excluded liver, kidney, and other endocrine and metabolic diseases, and no acute infection. All subjects were divided into normal glucose tolerance (NGT) group, hypoglycemia (HOG) group, impaired glucose regulation (IGR) group, and diabetic Mellitus (DM) group according to the 1999 DM diagnostic criteria of the World Health Organization (WHO) and the department. IGR group can be subdivided into impaired fasting glucose

(IFG) group, mildly impaired glucose tolerance (Mild-IGT) group, and middle impaired glucose tolerance (Mid-IGT) group.

Oral Glucose Tolerance Tests

The test refers to the National Clinical Laboratory Practice (4th edition),[23] briefly, the tester took venous blood on an empty stomach in the morning, and the FPG test was performed by the hexose kinase method, which was detected by Roche P800 automatic biochemical analyzer (2011-2017.11) and Siemens ADVIA2400 automatic biochemical analyzer (2017.11-2018.10). Then, 75 g of anhydrous glucose was orally administered, and blood glucose was measured by taking venous blood at 0.5h (.5-hour postprandial blood glucose, 0.5h PG), 1h (1-hour postprandial blood glucose, 1h PG), 2h (2-hour postprandial blood glucose, 2h PG) and 3h (3-hour postprandial blood glucose, 3h PG) after the sugar load. Serum separator tubes (SST) were used for blood collection and measurement of glucose at each time point without delay. Glycosylated Hemoglobin (HbAlc) was analyzed by high-pressure liquid phase method using TOSOH *syemex* G8 detector; glycated serum albumin (GA) was detected and analyzed by Asahi Kasei Manufacturing Co., Ltd reagent and analyzer. Tests were performed in the center by specialist nurses and technicians.

Statistical Processing

The original data were processed and filtered by Python 3.6, statistics were performed by SPSS 13.0 and GraphPad Prism 7.0. The measurement data were expressed in terms of the amount ± s. Simple correlation used Pearson correlation analysis. The subject characteristic working curve (ROC curve) was used to analyze the HbAlC, GA value and determine the sensitivity and specificity of DM.

Results

Basic Clinical Data of the Research Objects

There were 529 males and 841 females (including 66 pregnant women), with an average of (50.5 ± 15.2) years old. Since the execution of pregnant women in the clinical diagnostic criteria independent of blood sugar, and taking into account not statistically significant in number, so choose in the process of screening DM excluded 66 cases of pregnant women. On this basis, FPG is (5.89 ± 1.81) mmol/L; 0.5h PG is (10.10 ± 2.73) mmol/L; 1h PG is (11.26 ± 4.12) mmol/L; 2h PG is (9.63 ± 4.65) mmol/L; 3h PG is (6.7 ± 3.88) mmol/L. According to OGTT, 647 cases were diagnosed as DM, 298 males, and 349 females; 141 cases were diagnosed as NGT, 33 males, and 108 females; 70 cases were diagnosed as HOG, 38 males, and 32 females; 4 cases were diagnosed as IFG, 2 males, and 2 females; 208 cases were diagnosed as Mild–IGT,

72 males, and 136 females; 234 cases were diagnosed as Mid–IGT, 86 males, and 148 females.

Age and Gender Distribution Characteristics of the Study Population

As is shown in Figure 1(A), the high-risk population of diabetes is mainly concentrated in the 30-70 age group, and the proportion of women in the 20-40 age group is greater than that of men. The main reason may be that some women in this age group need to undergo pre-pregnancy examination, pre-production inspection, and post-production examination. Among people over 70 years of age, the number of high-risk groups participating in the test decreased as the number of confirmed diabetes and mortality increased. It is interesting to note that, according to our statistics, there is a trough in the 40-49 age group. The main reason is that in China, most young people will face a pre-employment medical examination at the age of 24 to 30, and people around 55 will undergo a comprehensive medical examination before retirement.

Given this, we conducted further statistics and analysis of the diagnosis of the 40-59 age group. In Figure 1(B), for the proportion of people diagnosed with diabetes and pre-diabetes (DM + IGR), 41-42 age groups were below the average of the entire objects; for the 43-49 age groups, the proportion of people diagnosed with diabetes and pre-diabetes were above the average of the entire objects as a whole.

The Chinese Medical Association Endocrinology Branch (CSE) in the CSE Consensus[24] lieutenant divided the high-risk population of diabetes into 2 parts—the high-risk group with normal blood sugar and the pre-diabetes group. In this case, the high-risk group of blood glucose is defined as one of the criteria for age ≥ 40 years old, and as is shown, with increasing age, the progression of diabetes was on the rise. The overall trend is consistent with our previous experience and speculation is consistent.

Therefore, it is important to strengthen the management of blood glucose testing in the high-risk population of 40-59 years old. At the same time, over 43 years of age is a significant node in the increased rate of diabetes and pre-diabetes, and through data feedback in many places around the world, the incidence of diabetes in men is higher than that of women. Based on the above, compared with 40-59 years old, strengthening the management of blood glucose testing in high-risk populations aged 43-49, especially for the men, maybe more clinically and economically significant.

Evaluation Value of Each Blood Glucose Period in OGTT

Diagnostic Value with FPG, 1h PG, and 3hPG. FPG is the most intuitive and simple method for blood glucose measurement, and its diagnostic significance is unquestionable. During
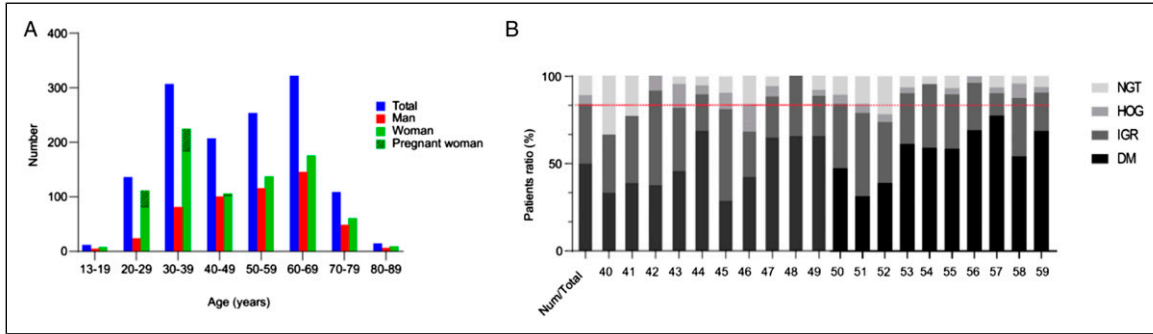
Figure 1. Basic characteristics of research objects (A) and prevalence of objects between 40-49 (B).

fasting, to maintain normal blood sugar levels, the body will secrete hormones to promote blood sugar rise, and also affected by physiological factors, blood sugar will be maintained at a certain level. Because of this mechanism of the body, FPG is more accurate in diagnosing diabetes.

From the OGTT curve analysis and point distribution (Figure 2), a large part of the peak blood glucose will fall within 1h PG (A-B), and this phenomenon becomes more pronounced as diabetes progresses (C-F). In theory, the state of reflecting diabetes and impaired glucose tolerance in 1h PG should be more sensitive than 0.5h PG and 2h PG, which may be more accurate for screening of patients with diabetes and impaired intermediate glucose tolerances, it is consistent with previous research theories.[25]

Through statistics and calculations, for the time point that blood glucose level less than 3.0 mmol/L (G), the occurrence of 3h PG accounts for 90.1%, and most of them appeared in the HOG group. It can be judged that 3h PG is an important indicator for identifying HOG from the research objects.

Correlation of FPG-1h PG and FPG-3h PG. To verify the correlation between the 3 points, Person correlation linear analysis was performed on FPG-1h PG and FPG-3h PG respectively. In Figure 3, Pearson correlation analysis showed that 1h PG significantly positively correlated with FPG (R^2=.6226, P<.01), correlation linear equation: Y=1.779*X + .8102; 3h PG were significantly positively correlated with FPG (R^2=.5837, P<.01), correlation linear equation: Y=1.612*X −2.669.

The Evaluation Value of the "Three-Point Method" in OGTT. Based on the above results, the objects were evaluated by the "Three-Point Method" (FPG, 1h PG, 3h PG), and the traditional OGTT diagnosis results are used as the "gold standard" to verify it.

The TP (True-Positive), FP (False-Positive), TN (True-Negative) and FN (False-Negative) for each groups's diagnosis has shown in Figure 4, for NGT diagnoses, TP = 141, FP = 115, TN = 1048, FN = 0; for IGR diagnoses, TP = 335, FP = 23, TN = 835, FN = 111; for HOG diagnoses, TP = 68,

FP = 0, TN = 1234, FN = 2; for DM diagnoses, TP = 622, FP = 0, TN = 657, FN = 25.

The above data could be used to calculate the SENS (Sensitivity), SPEC (Specificity), PPV (Positive Predictive Value), NPV (Negative Predictive Value) and ACC (Accuracy), detailed calculation quations:

$$SENS = \frac{TP}{TP + FN} \times 100\% \qquad (1)$$

$$SPEC = \frac{TN}{TN + FP} \times 100\% \qquad (2)$$

$$PPV = \frac{TP}{TP + FP} \times 100\% \qquad (3)$$

$$NPV = \frac{TN}{TP + FP} \times 100\% \qquad (4)$$

$$ACC = \frac{TP + TN}{TP + TN + FP + TN} \times 100\% \qquad (5)$$

The calculated results were reflected in Table 1, and we can be obtained from the table that for HOG and DM, the three-point method showed excellent diagnostic values (SENS = 97.14%, 94.67%; SPEC = 100%, 100%; PPV = 100%, 100%; NPV = 99.84%, 96.33%; AAC = 99.85%, 98.08%). For NGT and IGR, the three-point method showed good diagnostic values (SENS = 100%,75.11%; SPEC = 90.11%, 97.32%; PPV = 55.08%, 93.58%; NPV = 100%, 88.27%; AAC = 91.18%, 89.72%). PPV(NGT) = 55.08% attributed to individual differences, briefly the blood sugar of some patients can't reach the peak value of 1h PG, which leads to some DMs being identified as NGT in the process of simulation diagnosis. Besides, in Mild – IGT group, the peak of OGTT to some objects had fallen at the node of 0.5h PG. Nevertheless, the "three-point method" that proposed in this article still has a high potential diagnostic value in clinical.

Diagnostic Values of HbA1c on DM and IGR

HbA1c is a product of the combination of hemoglobin in red blood cells and sugars in serum, which is formed through a
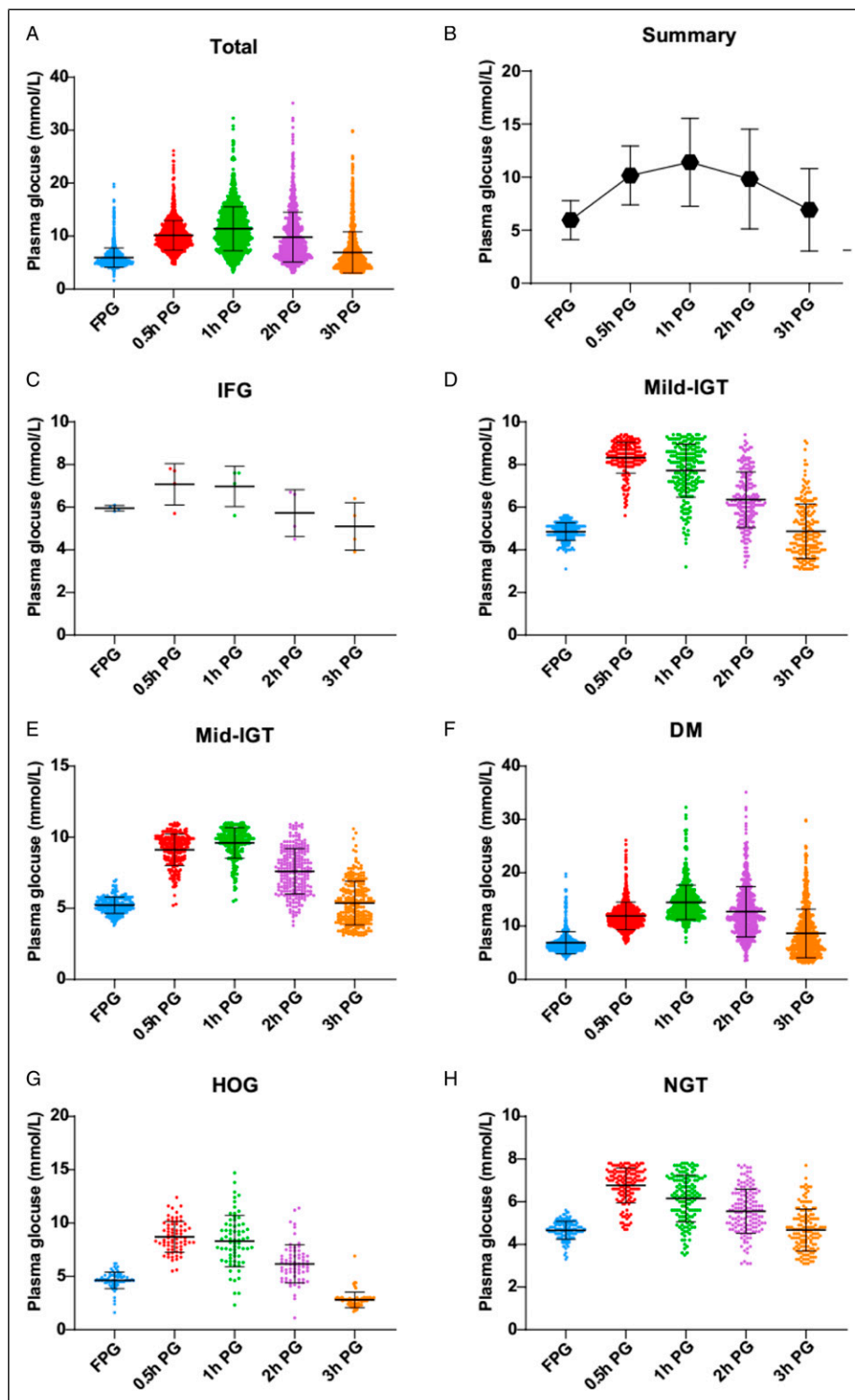
Figure 2. Point distribution and trend of High-risk population (A-B) and different grouped samples (C-H).

slow, continuous, and irreversible glycation reaction. The content of HbA1c depends on the blood glucose concentration and the contact time between blood glucose and hemoglobin. Therefore, HbA1c can effectively reflect the macroscopic situation of blood glucose in patients with diabetes in the past 1-2 months (Figure 5).

A total number of 522 objects with HbA1c measurements taken within 2 months after the OGTT examination, OGTT as

the gold standard for diagnosing DM and IGR, draw ROC curves of HbA1c diagnostic DM and IGR.

By analyzing the ROC curves of HbA1c diagnostic DM, HbA1c have high diagnostic value: Area under the curve (AUC) = .882; P<.01; Asymptotic 95% confidence interval (95%CI) = .860~.904. The best cut-off point for HbA1c diagnosis of MD is HbA1c≥ 5.95%: SENS = 79.1%, SPEC= 83%, Youden's index (YI) = .621.

By analyzing the ROC curves of HbA1c diagnostic IGR, HbA1c have high diagnostic value: AUC = .828; P<.01; 95% CI = .792 ~ .865. The best cut-off point for HbA1c diagnosis of IGR is HbA1c≥ 5.75%, while SENS = 69.4%, SPEC= 84.6%, YI=.54.

In studies in different regions of China, the best cut-off point for HbAlc diagnosis of DM is mainly between 5.7% - 6.5%.[26] For this study, the best cut-off point for HbA1c to diagnose DM is 5.95%; the best cut-off point for HbA1c to diagnose IGR is 5.75%. On the other hand, due to the long half-life of hemoglobin in the blood, which have a certain influence on the update rate HbA1c, and therefore in the

diagnosis, some patients with acute onset of T2D, such as fulminant type or duration shorter than 3 months, HbA1c may not accurately reflect the occurrence and severity of the disease. Maybe, for this reason, DM diagnosed in this study, 20% of patients with HbA1c <5.95%.

Diagnostic Values of GA on DM and IGR

Non-enzymatic glycosylation occurs between the glucose in the human body and the N-terminus of serum proteins. Most of them combine with lysine at position 189 in the serum protein chain to form a high-molecular ketamine structure, which is collectively called glycated serum protein of these, more than 90% were GA. Therefore, GA can reflect the overall level of glycated serum albumin. GA is an indicator that reflects average blood glucose levels over the past 2-3 weeks.

A total number of 535 objects with GA measurements taken within 2-3 weeks after the OGTT examination, OGTT as the gold standard for diagnosing DM and IGR, draw ROC curves of GA diagnostic DM and IGR.
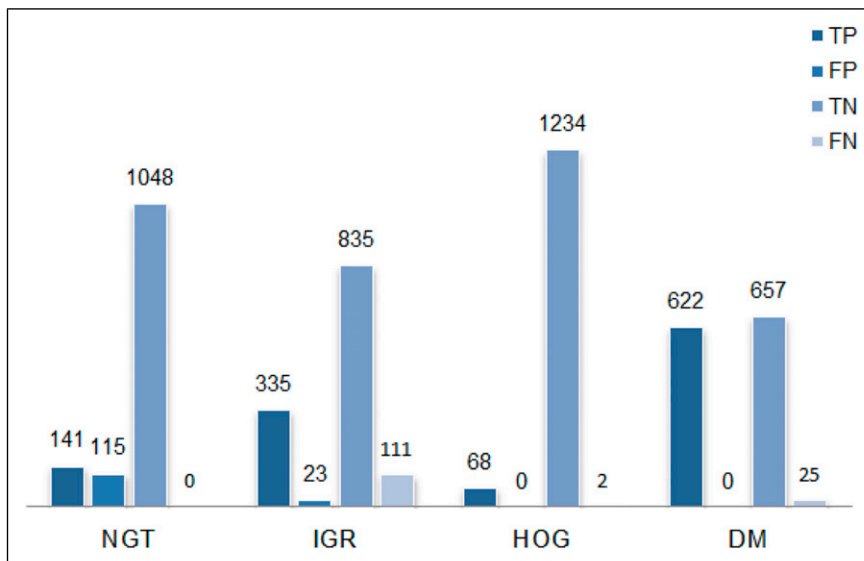
By analyzing the ROC curves of GA diagnostic DM, GA has medium diagnostic value: AUC = .772; P<.01; 95%CI = .733 ~ .811. The best cut-off point for GA diagnosis of MD is GA≥ 15.25%, while SENS = 59.5%, SPEC= 83.3%YI=.428.
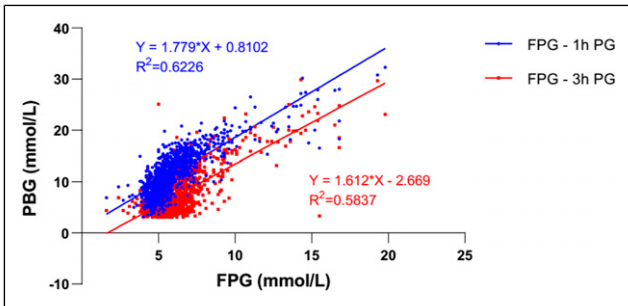

Figure 3. Pearson linear regression fitting line and regression equation of FPG − 1h PG and FPG − 3h PG.

Table 1. Diagnostic indicators for each group.

Groups	SENS, %	SPEC, %	PPV, %	NPV, %	ACC, %
NGT	100	90.11	55.08	100	91.18
IGR	75.11	97.32	93.58	88.27	89.72
HOG	97.14	100	100	99.84	99.85
DM	94.67	100	100	96.33	98.08

Figure 4. Quantity distribution of True - Positive, False - Positive, True - Negative, and False − Negative for each groups' diagnosis.
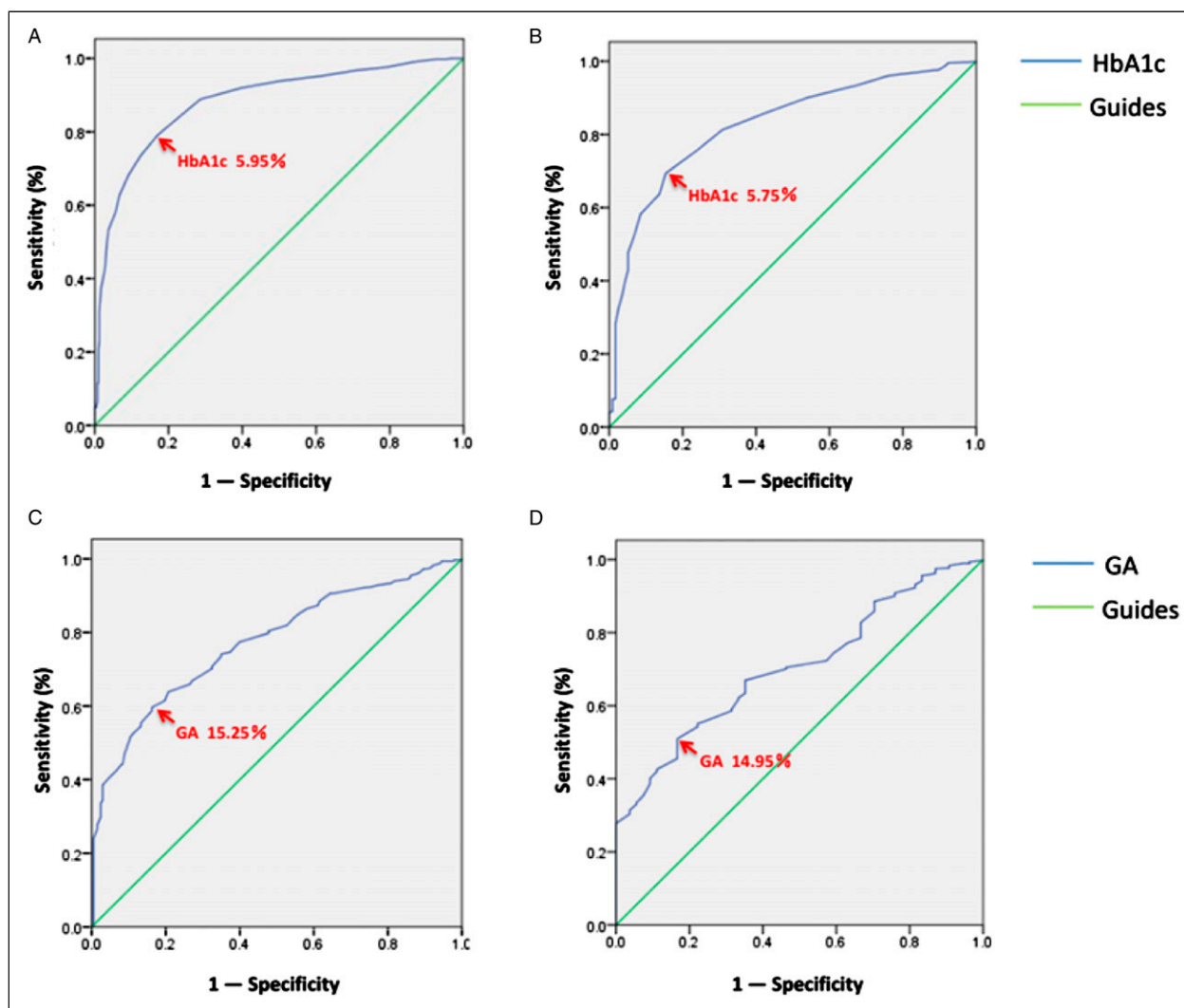
Figure 5. ROC curve of HbA1c diagnosis DM (A) and IGR (B); GA diagnosis DM (C) and IGR (D).

By analyzing the ROC curves of GA diagnostic IGR, GA have low diagnostic value: AUC = .705; P<.01; 95%CI = .644 ∼ .766. The best cut-off point for HbA1c diagnosis of IGR is GA≥ 14.95%: SENS = 50.9%, SPEC= 83.3%, YI=.342.

GA is the product of non-enzymatic reaction between serum protein (mainly albumin) and glucose,[27] because the half-life of albumin is 17-20 days, GA reflects the average level of blood glucose in the 2-3 weeks before the measurement. GA is measured quantitatively on the basis of GSP (glycated serum protein), using the percentage of serum GA and serum albumin to express the level of GA, removing the influence of serum albumin level on the test results.[28] This removes the influence of serum albumin levels on the test results and is therefore more accurate than GSP.[29] However, GA results are usually affected by a number of factors such as the rate of albumin renewal, BMI,[30] and thyroid hormones[31]: for example, thyroid hormones promote albumin catabolism, which can affect serum GA levels, and hyperthyroidism can decrease the results and hypothyroidism can increase them.

On the other hand, for the same blood glucose level, GA levels are lower in individuals with an accelerated rate of blood albumin renewal.[32]

GA is related to a large number of glycation sites and the reactive lysine residues. Because the glycation reaction itself is fast, it can sensitively detect the temporary blood glucose rise. In fact, in diabetes with large blood glucose fluctuations, the increase of GA value is faster than that of HbA1c; in addition, after using drugs that reduce postprandial hyperglycemia, the decrease of GA value is faster than that of HbA1. Therefore, the diagnostic value of GA as a separate indicator is worth exploring. For this study, when GA diagnoses DM and IGR, YI max=.428, .342, thence there is little diagnostic value.

Discussion

(1) Type 2 DM is caused by the combined effect of insulin resistance and insulin secretion deficiency. Due to its hidden onset, many patients have

developed chronic complications of DM when the typical clinical manifestations of DM appear.[33] Through stratified age management, high-risk groups can be identified at an early stage. Regular glucose metabolism indicators of high-risk groups can not only detect DM and pre-DM early, but may also help to find DM retinopathy, microalbuminuria, and peripherals as early as possible Neuropathy and significantly increased risk of macrovascular disease. For this study, the management of blood glucose testing in the high-risk group of the 40-49 age group is inadequate; by analyzing the proportion of diabetes and early diabetes in the selected sample in each age group, focus on strengthening the high-risk group of the 43-49 age group Management of blood glucose testing may have more clinical and economic value;

(2) Though OGTT is a gold standard for diabetes testing, it is limited by a series of realistic factors in clinical application, by simplifying glucose tolerance tests finds powerful clinical findings in early and pre-diabetic patients.

FPG has a high weight in the diagnosis, but it is very easy to miss the diagnosis of patients with early diabetes; 1h PG is more valuable for evaluating DM and IGR than 0.5h PG and 2h PG; 3 h PG is frequently to find HOG. The three-point method (FPG, 1h PG, 3h PG) proposed in this article is used to simplify OGTT and has certain diagnostic advantages. On the other hand, a complete OGTT costs about $ 10, in contrast to this, the three-point method can save 40% of the cost, which can significantly reduce social medical costs

(3) In 2009, an expert committee jointly organized by ADA, EASD, and IDF recommended HbAlc ≥6.5% as the diagnostic standard for DM,[34] but whether it applies to the Chinese population still needs more evidence. At present, some domestic clinical studies on HbAlc for diagnosing DM have been carried out to find the cut-off point for HbAlc to diagnose DM. HbAlc has the advantages of good repeatability and stability as a gold index for blood glucose control in patients with DM. However, when it is used in the diagnosis of DM, the measurement method has not been standardized and the biological variability is large, so it is controversial. For this study, the best cut-off point for HbA1c to diagnose DM is 5.95%; the best cut-off point for HbA1c to diagnose IGR is 5.75%.

GA is closely related to insulin secretion, especially early insulin secretion. Compared with HbA1C, GA may better reflect postprandial blood glucose levels and blood glucose fluctuations. Patients with islet B cell secretion defects caused a significant increase in blood glucose after meals and increased blood glucose fluctuations may be one of the

important mechanisms leading to elevated GA levels. Therefore, as a separate indicator, GA may not have clinical significance either, for the diagnosis of DM, nor the diagnosis of IGR. Through our research, it is found that these 2 do not have the function of separate diagnoses. As an important reference, simplifying based on OGTT may be one of the directions of our future research.

Conclusions

Pre-diabetes can be considered as a sign or watershed. If it appears, it indicates that the risk of diabetes, cardiovascular and cerebrovascular diseases, microangiopathy, tumors, and dementia will increase in the future.[35] For China, a critical period in the economic development of countries with large populations, without intervention, Among China's 120 million pre-diabetics, 93% will develop diabetes within 20 years. Obviously, no intervention in this high-risk group of diabetes and death is unacceptable. Moreover, the benefits of China's economic development will be greatly reduced by raging diabetes. There is sufficient evidence that effective intervention in the pre-diabetes phase can significantly reduce the likelihood of its conversion to diabetes.[36-38] Therefore, timely detection and effective management of pre-diabetes population is the key to preventing diabetes.

Based on the research in this article, we found, targeted screening of high-risk DM people over the age of 42 by "three-point method", based on pre-diabetes found that patients can save a lot of medical expenses; Timely lifestyle interventions for people with pre-diabetes can greatly reduce the incidence of type 2 diabetes and a series of serious complications, and further reduce social medical expenses in terms of diabetes and its complications, it can help to curb the global diabetes epidemic and its consequences if widely used. This approach has important implications, both in terms of disease control and economics.

Author Contributions

Kan Shao and Gong Chen contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Compliance with Ethical Standards

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