The clinical value of HbA1c in combination with FPG in the early screening of the elderly with type 2 diabetes

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Abstract ***Objective:*** To investigate the FPG associated with HbA1c diagnosis of T2DM, to clear the best point of tangency HbA1c diagnosis of T2DM. ***Methods:*** Using simple random sampling method, from this group of T2DM field epidemiological investigation data in the database we randomly selected 300 cases of T2DM patients, 300 cases of healthy people. The sensitivity and specificity of FPG, HbA1c and HbA1c/FPG combination were calculated by diagnostic screening test; Using ROC curve evaluation FPG, HbA1c and HbA1c in combination with FPG diagnosis value of T2DM. ***Results:*** The cutoff point of FPG for diagnosing T2DM was 6.19 mmol/L, the sensitivity and specificity were respectively: 83.00%, 93.67%, area under the curve (AUC) was 0.928; the cutoff point of HbA1c for diagnosing T2DM was 6.40%, the sensitivity and specificity were respectively: 87.00%, 90.33%, area under the curve (AUC) is 0.935;Combined use of HbA1c and FPG in the diagnosis of T2DM, simultaneous detection of HbA1c and FPG, when HbA1c≥ 6.40% or FPG≥6.19 mmol/L diagnosed with T2DM, the sensitivity and specificity were respectively: 97.79%, 84.61%, area under the curve (AUC) is 0.960. ***Conclusions:*** The cutoff point of HbA1c for diagnosing T2DM was 6.40% , Combined HbA1c and FPG in the T2DM diagnosis, which can greatly improve the sensitivity, the combined application is more conducive to the early screening of T2DM.

1 Introduction

With the development of society by leaps and bounds, the prevalence of diabetes is in a rising trend. According to the International Diabetes Federation (IDF) latest statistics, by 2040, nearly 642 million people are expected to suffer from Diabetes, 90% to 95% of whom are in Type 2 Diabetes Mellitus(T2DM). China has now the most T2DM patients in the world [1].

Fasting Plasma Glucose (FPG) or 2 hour Postprandial Glucose(2hPG) is the most commonly used

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method in clinical diagnosis of T2DM, But it only represents the instant moment of blood Glucose levels, and chronic hyperglycemia is the main characteristic of T2DM, So only FPG or 2hPG on the diagnosis of T2DM has a certain missed diagnosis. Glycated hemoglobin A1c(HbAlc) can reflect the 2-3 months of blood Glucose levels, it can be used as indicators of T2DM patients with long-term control blood Glucose. In 2010, the American Diabetes Association(ADA) took HbA1c as a new diagnostic method for T2DM[2]. However, domestic research on HbA1c as the diagnostic standard of T2DM is still in its initial stage. Because of different sample population, people's life style and the environment are different, the value of HbA1c is different. Therefore, The elderly T2DM early screening in our region and the optimal cut-off point are studied, and results will now be reported as follows.

2 The research object and methods

2.1 The object of the research

Using simple random sampling method, From this group of T2DM field epidemiological investigation database we randomly selected 300 cases of T2DM patients, 300 cases of healthy people.

2.2 The research methods

(1) questionnaire: Main content includes gender, age, history of smoking and drinking, and other general information; (2) laboratory tests: subjects in the morning on an empty stomach phlebotomize, subjects were unified for breakfast after blood, continue to blood after 2 hours, Biochemical parameters such as FPG, 2hPG and HbA1c were determined by Hitachi 7600 automatic biochemical analyzer.

2.3 Statistical analysis

Using Stata12.0 statistical software for data analysis, The sensitivity and specificity of FPG, 2hPG and HbA1c in the diagnosis of T2DM was calculated, using ROC curve evaluation FPG, 2hPG, HbA1c diagnosis value of T2DM.

3 Results

3.1 The basic situation of the research object

From the T2DM field epidemiological survey data of this research group, 300 cases of T2DM patients were randomly selected, and 300 healthy people were studied, average age was 60.020 ± 9.684 years, The maximum is 86 years old, the minimum is 38 years old, The age distribution of the study subjects was normal distribution (Table 1); The object of study the age distribution of normally distributed (Figure 1), the distribution of FPG, 2hPG is skewed distribution (Figure 2, Figure 3), the distribution of HbA1c is basic normally distributed (Figure 4).

Table 1. The basic data of subjects.

variable	n	$(\bar{x} \pm s)$	minimum	maximum
age	600	60.020±9.684	38	86
FPG	600	6.813±2.359	4.280	20.130
2hPG	600	11.310±5.428	2.700	32.120
HbA_1c	600	6.723±1.496	3.400	15.100

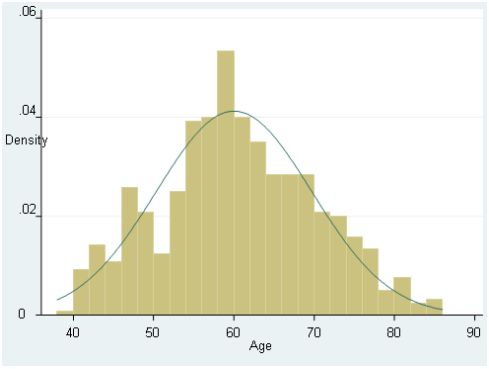

Figure 1. The age distribution of subjects.

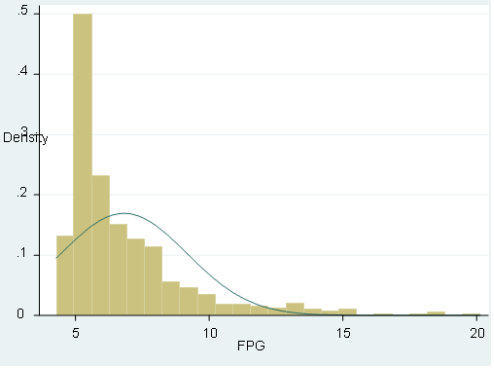

Figure 2. Fasting plasma glucose distribution of subjects.

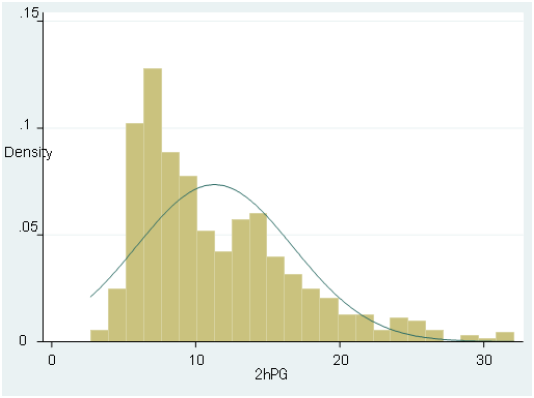

Figure 3. 2h Postprandial glucose distribution of subjects.

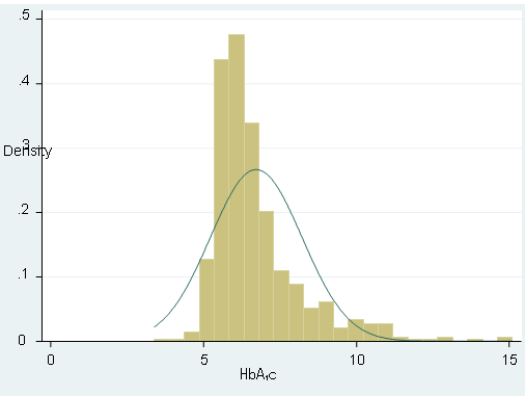

Figure 4. HbA1c distribution of subjects.

3.2 To evaluate the diagnostic value of FPG, 2hPG, HbA1c, HbA1c and combined with FPG in T2DM

3.2.1 The sensitivity and specificity of FPG in the diagnosis of T2DM

Application of FPG alone in the diagnosis of T2DM, when FPG≥6.19mmol/L, the sensitivity and specificity were respectively: 83%, 93.67% (Table 2).

Table 2. Sensitivity and specificity of diagnosis for T2DM using FPG

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 4.28)	100.000%	0.000%	50.000%	1.000	
(>= 4.39)	100.000%	0.330%	50.170%	1.003	0.000
…					
(>= 6.17)	83.000%	92.670%	87.830%	11.318	0.184
(>= 6.18)	83.000%	93.000%	88.000%	11.857	0.183
(>= 6.19)	83.000%	93.670%	88.330%	13.105	0.182
(>= 6.20)	82.670%	93.670%	88.170%	13.053	0.185
(>= 6.22)	82.330%	93.670%	88.000%	13.000	0.187
…					
(>= 20.13)	0.330%	100.000%	50.170%	0.997	
(> 20.13)	0.000%	100.000%	50.000%	1.000	

3.2.2 The sensitivity and specificity of 2hPG in the diagnosis of T2DM

Application of 2hPG alone in the diagnosis of T2DM, when 2hPG≥11.18mmol/L, the sensitivity and specificity were respectively: 84.33%, 100.00% (Table 3).

Table 3. Sensitivity and specificity of diagnosis for T2DM using 2hPG.

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 2.70)	100.000%	0.000%	50.000%	1.000	
(>= 2.92)	100.000%	0.330%	50.170%	1.003	0.000
…					
(>= 10.96)	84.330%	99.330%	91.830%	126.500	0.158
(>= 11.00)	84.330%	99.670%	92.000%	252.998	0.157
(>= 11.18)	84.330%	100.000%	92.170%	0.157	
(>= 11.22)	84.000%	100.000%	92.000%	0.160	
(>= 11.25)	83.670%	100.000%	91.830%	0.163	
…					
(>= 32.12)	0.330%	100.000%	50.170%	0.997	
(> 32.12)	0.000%	100.000%	50.000%	1.000	

3.2.3 The sensitivity and specificity of HbA1c in the diagnosis of T2DM

Application of HbA1c alone in the diagnosis of T2DM, when HbA1c≥6.40%, the sensitivity and specificity were respectively: 87.00%, 90.33% (Table 4).

Table 4. Sensitivity and specificity of diagnosis for T2DM using HbA1c.

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 3.40)	100.000%	0.000%	50.000%	1.000	
(>= 4.10)	100.000%	0.330%	50.170%	1.003	0.000
...					
(>= 6.20)	90.330%	78.670%	84.500%	4.234	0.123
(>= 6.30)	88.330%	85.670%	87.000%	6.163	0.136
(>= 6.40)	87.000%	90.330%	88.670%	9.000	0.144
(>= 6.50)	83.000%	93.000%	88.000%	11.857	0.183
(>= 6.60)	76.330%	94.670%	85.500%	14.313	0.250
...					
(>= 15.1)	0.33%	100.00%	50.17%	0.9967	
(> 15.1)	0.00%	100.00%	50.00%	1.0000	

3.2.4 The sensitivity and specificity of HbA1c combined with FPG in the diagnosis of T2DM

When HbA1c≥ 6.40% , HbA1c screening test is positive, or FPG ≥ 6.19 mmol/L for screening test is positive, combined use of HbA1c and FPG, namely HbA1c≥ 6.40% or FPG≥6.19 mmol/L in the two indicators as long as there is a positive, and then combined screening test is positive. from the table(2-4), combined use of HbA1c and FPG diagnosis of T2DM, when HbA1c≥6.40% or FPG≥6.19 mmol/L, which can calculate the sensitivity and specificity were respectively: 97.79%, 84.61%.

3.3 FPG, 2hPG, HbA1c, combination HbA1c and FPG ROC curve

From application of FPG, 2hPG, HbA1c diagnostic screening test, you can see that separate

application of FPG, 2hPG, HbA1c, the area under the curve AUC were respectively : 0.928, 0.959, 0.935, 95% ci respectively: (0.905, 0.950), (0.943, 0.975), (0.915, 0.955); HbA1c combined with FPG area under the curve AUC was 0.960, 95% CI (0.944, 0.976); Single application of FPG, 2hPG, HbA1c, and HbA1c combined with FPG diagnostic screening test area under the curve orderly was HbA1c+FPG > 2hPG > HbA1c > FPG (0.960 > 0.959 > 0.935 > 0.928), They have statistical significance (Table 5, Figure 5).

Table 5. ROC area in FPG, 2hPG, HbA1c and combination HbA1c and FPG in diagnosis of T2DM.

		ROC	-Asymptotic Normal—	
variable name	Obs	Area($\bar{x} \pm s$)	[95% Conf. Interval]	
FPG	600	0.928±0.012	0.905	0.950
2hPG	600	0.959±0.008	0.943	0.975
HbA1c	600	0.935±0.010	0.915	0.955
HbA1c+FPG	600	0.960±0.008	0.944	0.976

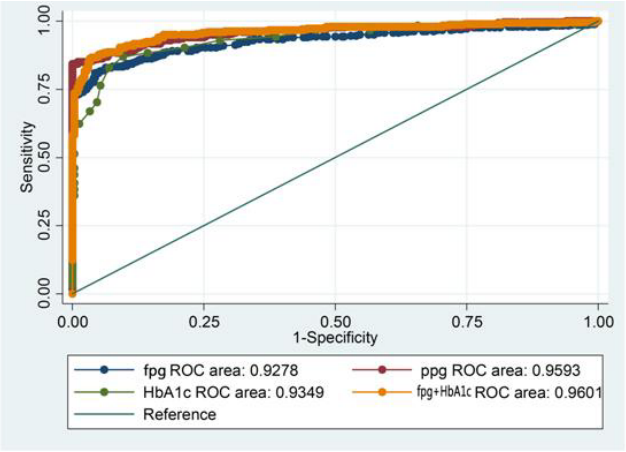

Figure 5. ROC curve of FPG, 2hPG, HbA1c and combination HbA1c and FPG in diagnosis of T2DM.

4 Discussion

4.1 HbA1c the clinical diagnostic value and the best point of contact

Though T2DM in China has increased dramatically in recent years, yet a lot of T2DM patients were not diagnosed early. HbA1c as T2DM in Europe and the United States has been one of the standards of diagnosis. Selvin [3] research shows that the coefficient of variation of 2hPG, FPG and HbA1C shows a decreasing trend (16.7% > 5.7% > 1.7%), The advantages of HbA1c coefficient of variation are small, so HbA1c is more reproducible than FPG as a tool for the diagnosis of T2DM. HbA1c can be done at any time, and do not require patients to fast or do any preparation. Furthermore FPG, 2hPG lifestyle changes would be a short time, and HbA1c status is not affected by diet, movement and whether the effects of taking certain medications, so it can be a reliable basis for monitoring of blood glucose control is good or not. So ADA in 2010 and in diabetes guidelines issued the HbA1c≥6.5% as one of the diagnostic criteria for T2DM.

Although HbA1c in the diagnosis of T2DM has more advantages than the FPG, 2hPG, there are ethnic and regional differences, which followed by a lot of T2DM researchers according to different ethnic regions, HbA1c application study on a large number of experiments in early diagnosis of T2DM, HbA1c and ADA in the diagnosis of the T2DM patients the best cut-off points were compared.

In the multi-ethnic population of Canada, the best cut-off value of HbA1c was 5.9%, the sensitivity and specificity were 75% and 79.1%[4]. In South Korea in 2012 a study also showed that people in the area of diagnosed T2DM HbA1c and the best cut-off value was 5.95%. The sensitivity of 77.0% and a specificity of 89.4% [5]. In some areas of our country, HbA1c has been used in the early diagnosis of T2DM in community population. BaoY et al[6] Study on the community population in Shanghai showed that when the HbA1c was 6.3%, the sensitivity and specificity were 62.8% and 96.1% respectively. Zhou XH[7] on the Qingdao community population study found that when HbA1c was 6%, the sensitivity and specificity of screening T2DM reached the best balance point. Ye Xiangjun et al [8] research shows that using HbAlc in patients with T2DM diagnosed the best cut-off value was 6.35%. The sensitivity and specificity were 80% and 89%.

In this study, 300 male and female subjects were studied , the number of subjects who are 40 to 64 years accounted for 68.45%, the number of subjects who are 65 years old and above accounted for 31.55%. the cutoff point of FPG for diagnosing T2DM was 6.19 mmol/L, with sensitivity and specific degrees respectively: 83.00% and 93.67%; the cutoff point of 2hPG for diagnosing T2DM was 11.18 mmol/L, with sensitivity and specific degrees respectively: 84.33% and 100.00%; the cutoff point of HbA1c for diagnosing T2DM was 6.40%, with sensitivity and specific degrees respectively: 87.00% and 90.33%; The corresponding rate of missed diagnosis was 17%, 15.67% and 13%, which further showed that the rate of missed diagnosis of HbA1c was lower than that of FPG and 2hPG in the diagnosis of T2DM. The Relationship of ROC area for $AUC_{2hPG} > AUC_{HbA1c} > AUC_{FPG}$ (0.935> 0.959> 0.959), Tips for early diagnosis of T2DM, HbA1c than application FPG has higher diagnosis rate, Although application 2hPG to diagnosis sensitivity and specificity of T2DM more high, 2hPG has operation problem, poor repeatability and long time, detection result is easy to change, considering application HbA1c as T2DM index of early diagnosis is more effective.

In this study, when HbA1c is 6.4%, its sensitivity and specificity were the best, which was close to the research results of BaoY[6] and so on, which may be due to we are in the old revolutionary base areas, compared to other developed cities, economic development is relatively backward here, the majority of samples are older workers and farmers, and they like salty, spicy as well as pickled products and their health consciousness is not strong. Some may early suffer from T2DM, because they lack regular physical examination, they did not find T2DM in time to prevent intervention as soon as possible.

4.2 Value of combined application of HbA1c and FPG in the diagnosis of T2DM

2hPG is currently the "gold" standard in the diagnosis of T2DM, but it consumes long time and more energy, and it is tedious in operation and poor in repeatability, so it does not apply to large-scale epidemiological survey. Separately using HbA1c to early diagnosis of T2DM may also cause misdiagnosis, but if combine HbA1C with FPG for early diagnosis of T2DM will greatly improve the sensitivity of diagnosis and reduce the rate of misdiagnosis. At present, many abroad studies Has also suggested that a combination of HbA1c and FPG for early diagnosis of T2DM. Such as Yoshihik [9] according to a study in the samples of 109 patients diagnosed with T2DM combined HbA1c and FPG test, finding that 18 patients with T2DM FPG is normal, and HbA1c is higher than normal, so a separate use FPG misdiagnosis in early diagnosis of T2DM has certain, Combination use of HbA1c and FPG in early diagnosis of T2DM, which can reduce the rate of missed diagnosis of T2DM. besides, the results of Kim KS et al[10] show that the sensitivity can reach 95.5% when combine HbA1c ≥6.1% and FPG≥6.1mmol/L for early diagnosis of T2DM, which is much higher than any single application of HbA1c ≥6.1%or separate application of FPG≥6.1mmol/L, thus the rate of misdiagnosis will be reduced misdiagnosis. China survey found that heart disease of coronary heart disease an important with disease or diabetes, mostly T2DM, but for many patients with coronary heart disease FPG is normal or near normal, but the rise in blood glucose after load, that is to say after the OGTT experiment 2hPG blood glucose is very high, and the patients with coronary heart disease only by FPG to diagnose T2DM or pre diabetes would result 75 percent of the rate of missed diagnosis, for the people of the disease have to be tested by combination with HbA1c and FPG [11].

Hu Y [12] to high-risk groups such as screening for T2DM research shows that 2298 from ruijin hospital check-up crowd as the research object, when the HbA1c was 6.1% and a separate FPG was 6.1 mmol/L, the sensitivity and speciality was also 81%; But if HbA1c and FPG combined application in the early diagnosis of T2DM, which greatly improved the sensitivity and specificity. When HbA1c was 6.1% and FPG is 6.1 mmol/L, the sensitivity and specificity of early diagnosis of T2DM were increased to 96.5%, 96.3% respectively, Their combination can also be used to screen for impaired glucose, with a sensitivity of 82.4%. There are a lot of research is also supported by the combination of HbA1c and FPG to diagnose T2DM [13, 14].

Our study separately analyzes the sensitivity of FPG and HbA1c when diagnosing T2DM , respectively83.00%, 87.00%, It is suggested that both FPG and HbA1c may cause missed diagnosis and the missed diagnosis rate is 17% and 13% respectively; Combined use of HbA1c and FPG diagnosis of T2DM, simultaneous detection of HbA1c and FPG, when HbA1c ≥6.40% or FPG≥6.19 mmol/L diagnosed with T2DM, the sensitivity was 97.79%, the missed diagnosis of just 2.21%. So united HbA1c and FPG can improve the sensitivity of T2DM in early diagnosis, reduce missed diagnosis. In this study area under the ROC curve is greater than 0.9, and the area of the largest is the combined use of HbA1c and FPG, so the combined use of HbA1c and FPG diagnosed T2DM diagnosis rate is highest.

The combined application of HbA1c and FPG has better sensitivity and specificity in the diagnosis of T2DM, On early detection, early diagnosis and early treatment of T2DM combined use of HbA1c and FPG has good effect, and can once pump blood and get two a different of results, in other words, it can early diagnosis whether with T2DM, which reduces patients' and medical personnels' trouble of two times pumping blood, which also avoids separately application FPG in the diagnosis of T2DM which needed more trouble of repeatly pumping blood. Combined application can reflect the situation of glucose metabolism from two different levels of the instant instant blood glucose level and the relative long-term blood glucose level, and it is a convenient and effective method for early diagnosis of T2DM in the elder.

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