Effect of HbA1C detection on the diagnostic screening for glucose metabolic disorders in polycystic ovary syndrome

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Summary

Purpose: This study aimed to assess the effect of hemoglobin A1C (HbA1C) detection on the diagnostic screening for glucose metabolic disorders in women with polycystic ovary syndrome (PCOS). *Materials and Methods:* A total of 161 patients with PCOS (mean age = 23.68 ± 4.23 years) were subjected to an oral glucose tolerance test (OGTT). The receiver operating characteristic (ROC) curve was plotted to evaluate the fasting plasma glucose (FPG), and HbA1C was used to probe the sensitivity and specificity of abnormal glucose tolerance. *Results:* Based on the traditional standards of blood sugar, the prevalence of type 2 diabetes was 5.6%, and the pre-diabetes prevalence was 7.5%. Based on the HbA1C standards, 4.3% of patients were diagnosed with type 2 diabetes, and 10.6% of the diabetic patients can be considered as high-risk populations. Based on the combined standards of OGTT and HbA1C, the prevalence of type 2 diabetes was 6.2%, and the pre-diabetes prevalence was 12.4%. OGTT is considered the gold standard for identifying abnormal glucose tolerance, and HbA1C detection is considered to be stronger than FPG. The areas under the ROC curves of HbA1C and FPG were 0.968 and 0.672, respectively ($p < 0.01$). The American Diabetes Association (ADA) recommends the cut-off value of HbAlc ≥ 5.7% and FPG ≥ 5.6 mmol/l for identifying abnormal glucose tolerance. The sensitivity and specificity were 76.7% and 89.5% for HBA1C, as well as 40.5% and 94.3% for FPG, respectively. The positive and negative likelihood ratios were 7.3 and 0.26 for HbA1C, as well as 7.1 and 0.63 for FPG, respectively. *Conclusion:* HbA1C detection can be used as a method for diagnosis and screening.

Key words: Polycystic ovary syndrome; Oral glucose tolerance test; Receiver operating characteristic curve.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of childbearing age. It causes amenorrhea, infertility, hirsutism, and acanthosis nigricans. It also increases the risks of metabolic and cardiovascular disorders. The authors previously found that patients with PCOS have abnormal glucose and lipid metabolism. Thus, a simple screening method for abnormal glucose metabolism is needed. In early 2010, the American Diabetes Association (ADA) formally considered hemoglobin A1C (HbA1C) as one of the criteria for diagnosing diabetes and identifying high-risk populations [1]. Many researchers believe that HbA1C detection is a simple and reliable method of diabetes diagnosis [2, 3]. Indeed, HbA1C detection has been extensively applied in diagnosing and screening diabetes [4]. However, pertinent studies on patients with PCOS are rare. In the present study, the oral glucose tolerance test (OGTT) was regarded as the gold standard for diagnosing and screening of diabetes. Moreover, the effects of HbA1C and fasting plasma glucose (FPG) on the screening of glucose metabolic disorders in patients with PCOS were analyzed and compared.

Materials and Methods

Subjects

A total of 161 patients with PCOS in the Fifth Affiliated Hospital of Zhengzhou University were selected from June 2009 to October 2012. PCOS diagnosis was based on the Rotterdam standards. Patients with thyroid, adrenal, ovarian, and sex-hormone disorders were excluded. All patients without essential hypertension, diabetes, and history of hormone application for three months were included. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Zhengzhou University. Written informed consent was alsoobtained from all participants.

Research methods

All enrolled patients fasted overnight (10 hours) and received 75 g of oral glucose for OGTT. Their height, weight, and body mass index (BMI) were measured. Then, blood tests for FPG, two-hour plasma glucose (2hPG), fasting insulin, two-hour insulin, and blood lipids were performed. The measurements were made by a specially assigned person. Intravenous plasma glucose was detected by the glucose oxidase method and insulin and lipids were measured by chemiluminescence. HbA1C was measured by high-pressure liquid ion-exchange chromatography and insulin resistance was assessed by a homeostasis model assessment for insulin resistance.

Diagnostic criteria of the glucose metabolic state

The classification of the glucose metabolic state was based on the 2010 ADA diagnostic criteria [1]. The OGTT criteria were as follows: for normal glucose tolerance (NGT), FPG < 5.6 mmol/l and 2hPG < 7.8 mmol/l; for pre-diabetes and impaired fasting glucose (IFG), FPG = 5.6-6.9 mmol/l and 2hPG < 7.8 mmol/l; for impaired glucose tolerance (IGT), FPG < 5.6 mmol/l and 2hPG = 7.8-11.0 mmol/l; for impaired glucose regulation (IGR), FPG = 5.6-6.9 mmol/l and 2 h PG = 7.8-11.0 mmol/l; and for diabetes, FPG ≥ 7.0 mmol/l or 2hPG ≥ 11.1 mmol/l. The HbA1C detection criteria were as follows: normal, < 5.7%; pre-diabetes mellitus (PreDM), 5.7% - 6.4%; diabetes, ≥ 6.5%.

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Table 1. — *The general characteristics of study subjects (± s).*

Group	Case	Age	BMI (kg/ m²)	FPG (mmol/l)	2hPG (mmol/l)	HbA1C (%)	INS (mU/l)	2hINS (mU/l)	TG (mmol/l)	TC (mmol/l)	HDL (mmol/l)	LDL (mmol/l)	HOMA-IR
NGT	119	22.46 ± 5.80	25.63 ± 5.72	4.55 ± 0.49	5.95 ± 1.12	5.1 ± 0.6	16.42 ± 15.42	79.3 ± 20.1	1.62 ± 0.62	1.33 ± 0.83	1.98 ± 0.35	2.42 ± 0.84	3.52 ± 3.15
IGT	36	24.43 ± 7.88	29.63 ± 6.451	5.23 ± 0.32	9.27 ± 0.34	5.9 ± 0.4	21.75 ± 13.62	124 ± 70.2	3.32 ± 0.87	4.52 ± 0.45	1.12 ± 0.25	2.69 ± 0.76	4.98 ± 3.34
DM	6	27.80 ± 1.30	33.85 ± 7.01	6.72 ± 1.82	13.8 ± 2.57	6.7 ± 0.5	24.83 ± 10.58	198 ± 72.0	5.74 ± 0.91	5.18 ± 0.91	0.94 ± 0.33	2.74 ± 1.10	5.70 ± 2.45
Total	161	23.68 ± 4.23	27.4 ± 2.20	4.9 ± 0.41	7.04 ± 1.02	5.6 ± 0.6	19.22 ± 8.04	142.8 ± 0.6	1.95 ± 1.02	4.42 ± 0.81	1.32 ± 0.25	2.58 ± 0.62	4.15 ± 0.15

Note: INS: ? ; 2hINS: ? ; TG: triglyceride; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA-IR: homeostasis model assessment - insulin resistance.

Table 2. — *The population distribution based on glucose metabolic state.*

OGTT	HbA1c			Total
	< 5.7% (NGT)	5.7 – 6.4% (PreDM)	≥ 6.5% (DM)	
NGT	131	8	1	140
PreDM				
IFG	0	0	0	0
IGT	6	6	0	12
IGR	0	0	0	0
DM				
Single FPG ≥ 7.0 mmol/l	0	1	2	3
Single 2hPG ≥ 11.1 mmol/l	0	2	1	3
FPG ≥ 7.0 mmol/l and 2hPG ≥ 11.1 mmol/l	0	0	3	3
Total	137	17	7	161

Statistical analysis

All data were statistically analyzed by SPSS 18.0 software. Measurement data were represented by $\bar{x} \pm s$. FPG and HbA1C were obtained from ROC curves, which represented the sensitivity and specificity related to the OGTT diagnosis of metabolic disorders. The ROC curves formula was as follows: positive likelihood ratio (LR+) = sensitivity / (1 – specificity); negative likelihood ratio (LR-) = (1 – sensitivity) / specificity. A $p < 0.05$ was considered statistically significant.

Results

General characteristics of subjects

The data of 161 patients with PCOS (average age = 23.68 years) were analyzed. The grouping depended on OGTT results. Table 1 lists the body measurement indicators and laboratory data of each group.

Diagnosis of glucose metabolic disorders

Table 2 lists the glucose metabolic states of all subjects. The diagnosis depended on OGTT results and HbA1C standards. Based on the OGTT standard, nine (5.6%) out of the 161 cases with PCOS were diagnosed with diabetes. Among them, three cases with only TPG or 2hPG met the diagnostic criteria, and six cases with both criteria met the standards; 12 patients (7.5%) met the diagnostic criteria for pre-diabetes, and all were IGT. Based on the HbA1C level, seven cases (4.3%) were diagnosed as diabetes, and 17 cases (10.6%) met the diagnostic criteria for pre-diabetes. Based on the combined standards of OGTT and HbA1C, ten cases (6.2%) were diagnosed as diabetes, and 20 cases (12.4%) were diagnosed as pre-diabetes.

Table 3. — *The effect of HbA1C and FPG on identification of IGT.*

Method	Susceptibility (%)	Specificity (%)	Positive ratio	Negative ratio
HbA1C ≥ 5.7%	76.7	89.5	7.3	0.26
FPG ≥ 5.6 mmol/l	40.5	94.3	7.1	0.63

HbA1C screening of abnormal glucose metabolism

OGTT was considered as the gold standard for diabetes screening and diagnosis. HbA1C ≥ 5.7% and FPG ≥ 5.6 mmol/l were also regarded as the screening standards. The glucose metabolic disorders, sensitivity, specificity, positive likelihood, and negative LRs are shown in Table 3. The sensitivity of HbA1C ≥ 5.7% was 76.7%, whereas that of FPG ≥ 5.6 mmol/l was 40.5%; the specificity of the latter was stronger than that of the former. In the ROC curves, the diagnostic capacity of HbA1C for IGT was superior to that of FPG. The areas under the curve were 0.968 (95% CI = 0.927 –0.989) for HbA1C and 0.672 (95% CI = 0.593 – 0.744) for FPG ($p < 0.01$).

Discussion

Although FPG detection is considered as the primary method for screening glucose metabolic disorders, this approach has some limitations. First, it requires fasting for at least eight hours. Second, the diet, exercise, and storage time of subjects in the first few days before detection can affect the test results. Thus, a single FPG detection can result in a misdiagnosis in people with normal FPG and abnormal glucose tolerance, which delays timely interventions [3].

HbA1C reflects the average plasma glucose levels for the past eight to 12 weeks prior to testing [5], and has long been considered as an important indicator of blood glucose control. HbA1C is also regarded as an important clinical basis for determining whether treatment programs need to be adjusted [6]. Recent studies have used the HbA1C test as a diagnostic criterion for screening diabetes and high-diabetes-risk populations [7]. Compared with FPG, HbA1C detection does not require fasting. Its results are also not influenced by recent diet, exercise, and specimen storage methods, such as delayed detection or refrigeration. Moreover, HbA1C detection is more objective, accurately reflects long-term blood sugar changes, and is more closely correlated with chronic complications [8–13]. With the international standardization of HbA1C detection, several studies have shown that HbA1C detection can be used as an effective indicator for diabetes diagnosis and screening [14–20]. Recently, the International Diabetes Expert Group has systematically reviewed and discussed these pieces of evidence, and finally recommended HbA1C detection as one of the methods for diabetes diagnosis and screening [7]. In 2009, the ADA recommended two detection results for diagnosing diabetes, and HbA1C $\geq$ 6.5% was selected. In 2011, the WHO suggested that it become the diagnostic cut-off point of diabetes [21, 22].

In the current study, the new ADA standard was applied. Among the 161 cases with PCOS, seven cases had HbA1C $\geq$ 6.5%, among which three reached the 2hPG and FPG levels of diabetes, one showed elevated 2hPG and normal FPG, two reached the FPG diabetes standards and had normal 2hPG, and one showed increased HbA1C. These results suggested that HbA1C and FPG equally affected diabetes diagnosis.

Furthermore, the sensitivities of HbA1C $\geq$ 5.7% and FPG $\geq$ 5.6 mmol/l were compared by ROC analysis to analyze their effects. The result showed that HbA1C was better than FPG; the areas under the curve were 0.968 and 0.672, and the sensitivities were 76.7% and 40.5% for HbA1C and FPG, respectively. Therefore, about 60% of patients with abnormal glucose tolerance had missed diagnosis by FPG screening alone, and this rate of misdiagnosis can be reduced to about 23% by HbA1C screening. The combined application can reduce the rate of misdiagnosis of glucose metabolic disorders to a certain extent.

However, considering the long half-life of red blood cells in the blood, HbA1C cannot promptly reflect the short-term blood glucose levels and changes. A single HbA1C detection may miss patients with short-term abnormal glucose metabolism, and the update rate of hemoglobin can affect the HbA1C levels. Moreover, HbA1C measurements may be affected by various genetic, hematologic, and disease-related factors [23]. Therefore, these factors should be considered in the application of HbA1C screening or diagnosis of abnormal glucose metabolism. Overall, FPG or HbA1C was not the perfect indicator for screening abnormal glucose metabolism. However, their combination may reduce the misdiagnosis rate of glucose metabolic disorders to some extent. High-risk groups may still need to be subjected to OGTT to confirm the diagnosis.

References

[1] American Diabetes Association: "Standards of medical care in diabetes — 2010". *Diabetes Care,* 2010, *33,* S11.

[2] Bennett C.M., Guo M., Dharmage S.C.: "HbA (1c) as a screening tool for detection of type 2 diabetes :a systematic review". *Diabet. Med.,* 2007, *24,* 333.

[3] Saudek C.D., Herman W.H., Sacks D.B., Bergenstal R.M., Edelman D., Davidson M.B.: "A new look at screening and diagnosing diabetes mellitus". *J. Clin. Endocrinol. Metab.,* 2008, *93,* 2447.

[4] Cohen R.M., Haggerty S., Herman W.H.: "HbAlc for the diagnosis of diabetes and prediabetes: is it time for a mid-course correction?" *J. Clin. Endocrinol. Metab.,* 2010, *95,* 5203.

[5] Nathan D.M., Turgeon H., Regan S.: "Relationship between glycated haemoglobin levels and mean glucose levels over time". *Diabetologia,* 2007, *50,* 2239.

[6] Weykamp C., John W.G., Mosca A.: "A review of the challenge in measuring hemoglobin A1c". *J. Diabetes Sci. Technol.,* 2009, *3,* 439.

[7] International Expert Committee: "International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes". *Diabetes Care,* 2009, *32,* 1327.

[8] Manley S.: "Haemoglobin A1c—a marker for complications of type 2 daibetes: the experience from the UK Prospective Diabetes Study (UKPDS)". *Clin. Chem. Lab. Med.,* 2003, *41,* 1182.

[9] Perry R.C., Shankar R.R., Fineberg N., McGill J., Early Diabetes Interverntion Program (EDIP): "HbAlc measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP)". Diabetes Care, 2001, 24, 465.

[10] Dilley J., Ganesan A., Deepa R., Deepa M., Sharada G., Williams O.D., *et al.*: "Association of A1C with cardiovascular disease and metabolic syndrome in Asian indians with normal gulcose tolerance". *Diabetes Care,* 2007, *30,* 1527.

[11] Velling Magnussen L., Mumm H., Andersen M., Glintborg D.: "Hemoglobin A1c as a tool for the diagnosis of type 2 diabetes in 208 premenopausal women with polycystic ovary syndrome". *Fertil. Steril.,* 2011, *96,* 1275.

[12] Sved I.A., Khan W.A.: "Glycated haemoglobin—a marker and predictor of cardiovascular disease". *J. Pak. Med. Assoc.,* 2011, *61,* 690.

[13] Cheng Y.J., Gregg E.W., Geiss L.S., Imperatore G., Williams D.E., Zhang X., *et al.*: "Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population: Implications for diabetes diagnostic thresholds". *Diabetes Care,* 2009, *32,* 2027.

[14] Rohlfing C.L., Little R.R., Wiedmeyer H.M., England J.D., Madsen R., Harris M.I., *et al.*: "Use of GHb (HbAlc) in screening for undiagnosed diabetes in the U.S. population". *Diabetes Care,* 2000, *23,* 187.

[15] Buell C., Kermah D., Davidson M.B.: "Utility of A1C for diabetes screening in the 1999-2004 NHANES population". *Diabetes Care,* 2007, *30,* 2233.

[16] Kim J.J., Choi Y.M., Cho Y.M., Jung H.S., Chase S.J., Hwang K.R., *et al.*: "Prevalence of elevated glycated hemoglobin in women with polycystic ovary syndrome". *Hum. Reprod.,* 2012, *27,* 1439.

[17] Shabir S., Jham S., Harper L., Ball S., Borrows R., Sharif A.: "Validity of glycated haemoglobin to diagnose new onset diabetes after transplantation". *Transpl. Int.,* 2013 [Epub ahead of print].

[18] Dye B.A., Genco R.J.: "Tooth loss, pocket depth, and HbAlc information colltcted in a dental care setting may improve the identification of undiagnosed diabetes". *J. Evid. Based Dent. Pract.,* 2012, *12,* 99.
[19] Braatvedt G.D., Cundy T., Crooke M., Florkowski C., Mann J.I., Lunt H., *et al.*: "Understanding the new HbAlc units for the diagnosis of Type 2 diabetes". *N. Z. Med. J,.* 2012, *125,* 70.
[20] Dankner R., Bergman M., Danoff A., Qureshi S., Whitford I., Kaviani N., *et al.*: "The metabolic deterioration that antedates diabetes: personal trajectories of HbA(lc) and fasting glucose as early indicators and possible triggers for intervention". *Diabetes Metab. Res. Rev.,* 2013, *29,* 1.
[21] Herman W.H., Fajans S.S.: "Hemoglobin A1c for the diagnosis of diabetes: practical considerations". *Pol. Arch. Med .Wewn.,* 2010, *120,* 37.
[22] World Health Organization: "Use of glycated hemoglobin (HbAlc) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation". *Geneva W.H.O.,* 2011, 11.
[23] Gallagher E.J., Roith D.L., Bloomgarden Z.: "Review of hemoglobin A1c in the management of diabetes". *J. Diabetes,* 2009, *1,* 9.

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