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Article

Performance of diabetes screening tests: an evaluation study of Iranian diabetes screening program

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Abstract: Background: Diabetes is a common non-communicable disease that is responsible for about 9% of all deaths and 25% reduction in life expectancy and nearly half of the diabetic patients are not aware of their disease. In this regard; diabetes screening to identify un-known diabetic patients is of great importance. **Aims:** The aims of this study were first to evaluate the performance of two commonly used diabetes screening tests that are currently recommended by the Iranian national screening program for diabetes (NSPD). **Methods:** The validities of the two diabetes screening tests were measured among 1057 participants older than 30 years. The studied screening tests included Capillary fasting blood glucose (CBG) and glycated hemoglobin (HbA1c). The golden standard for measuring the validity of the tests was venous fasting plasma glucose (VPG). **Results:** According to the results; the sensitivity of CBG and HbA1c tests were 69.01% and 84.5% and the specificity of the tests were 95.7% and 79.3% respectively. Positive and negative predictive values were 53.84% and 97.72% for CBG and 22.72% and 98.61% for HbA1c respectively. The recommended cut-points for CBG and HbA1c were 116.5 mg/dl and 7.15% respectively. Using these values as the new cut-points; sensitivity and specificity of CBG and HbA1c changed to 80.30% and 89.10%, and 77.50% and 94.20% respectively. **Conclusions:** Compared to several other countries; the performance of NSPD is relatively higher in Iran. ROC analysis suggested new cut-points for significantly better performance of NSPD.

Keywords: Diabetes mellitus; screening; HbA1c; fasting plasma glucose

Background:

Several factors including socio-economic development and significant progress in health and medical cares reduced mortality at a younger age and raised life expectancy. On the other hand, these changes along with the new sedentary lifestyles caused sharp rises in several chronic diseases. (1) Diabetes mellitus (DM) is a common metabolic disease (2) that about one-half of the patients are unaware of their condition (3). In addition, about 9% of total deaths and 25% reduction in life expectancy are directly or indirectly associated with diabetes (4, 5). For example, cardiovascular diseases are among the most common diabetes-related causes of deaths and about 43% of deaths due to diabetes occur among individuals under 70 years of age (6). This means that DM kills patients when they are still socio-economically active. (1). It is also estimated that about 12% of the global health budget is being spent on diabetes and its related conditions (7). Apart from the above facts,

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figures suggest that DM is alarmingly on rising and it is becoming a serious problem threatening global health and economy (8). Reports suggested that the global prevalence of DM among individuals over 18 years of age was about 9% in 2014. (9) However, the international diabetes federation (IDF) has estimated that the prevalence of diabetes is yet to be raised to 9.9% in 2030. (10) With regard to the geographical distribution of diabetes, it is estimated that 20% of the world's diabetic patients are living in South East Asia and it is predicted that in the near future, the Asian population is more seriously affected by DM compared to the population of the other parts of the world (11, 12).

As the epidemic of DM is expanding, the costs of the disease, including the cost of diagnosis and treatment of its complications are also rising sharply. It is because, on average, the cost of medical complications among DM patients is about 3.2 times higher than the costs of treating non-diabetics patients for the corresponding conditions (13). As a result, in addition to the severity and a wide range of health conditions, the economic damages caused by DM in various countries are remarkable. This is why the socio-economic burden of DM in low or middle-income countries affects their development (14). Similar to the rest of the world including the Middle East, in Iran over the past three decades the prevalence of diabetes has become doubled. Based on an estimate in 2013, the prevalence of DM in Iran was 13.8% (12) and the incidence was about 1.6 per 100 person-year among individuals older than 20 years of age (15). It is also estimated that in 2014, 38079 deaths occurred among the Iranian population due to cardiovascular complications caused by DM (16). Reports suggested that in Iran a huge amount of money is being spent on the treatment of diabetes and its related health problems. In this regard, early DM detection is essential in the prevention and management of the severe and irreversible complications (17).

The Iranian National Screening Program for Diabetes (NSPD):

Due to the high cost of treatment, life-threatening complications, and relatively high prevalence, applying effective screening programs to identify people with undiagnosed DM is of utmost importance to the Iranian ministry of health. As a result, the Iranian ministry of health has recently implemented a routine diabetes screening program (DSP) into primary health care services. The program is to detect undiagnosed diabetes cases among the rural population who are older than 30 years of age. From 2016, DPS is being conducted by health centers and health houses to diagnose diabetes among the target population with at least one of the following risk factors: BMI ≥30, whist circumference ≥100 for men (or ≥86 cm for women), family history of DM and history of gestational diabetes (among women). In that regard, all rural residences over 30 years of age are to be annually screened by the public health service providers (Figure1). Accordingly, the individuals are invited to the health houses to be visited by rural health nurses and voluntary health workers. The eligible individuals are asked to fast for at least 8 hours prior to the morning that they have an appointment to visit the health house that they are registered with. In the health house, the person's capillary fasting blood glucose (CBG) is measured with a glucometer. If the result of the CBG test was positive (FBS≥126mg/dl), the individuals are referred to a health center to take a Venus plasma glucose (VPG) test (as a diagnostic test). A VPG test result equal to or bigger than 126mg/dl is considered positive for DM.

Aims:

This study is conducted to evaluate the performance of Iranian DSP and its recommended cut points for the selected screening tests. In particular, this study aimed to evaluate sensitivity, specificity, and predictive values of CBG and HbA1c test, using fasting plasma glucose (VPG) as the gold standard (18).

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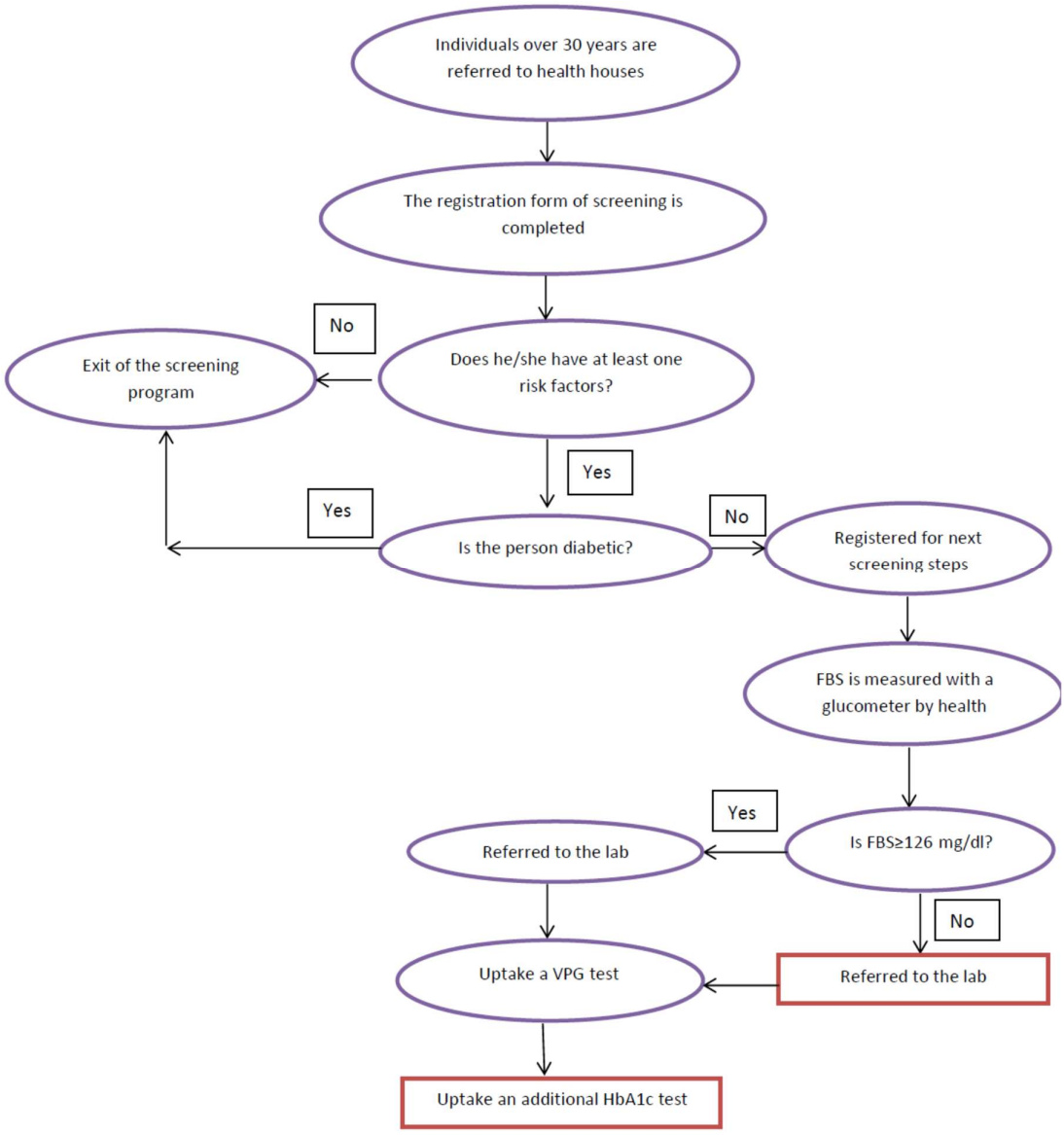
Material and methods:

The settings:

This study was conducted among rural residences of Gerash county, which is located in the southern part of Fars province, Iran. The county consists of 25 villages with about 14456 rural residents. In the study area, 7 health houses and 2 rural health centers deliver primary health services to the defined population.

Figure 1. presents the flowchart of the procedures of the Iranian DSP and the additional steps taken by the current study (rectangles).

Figure 1. Flowchart of the Iranian diabetes screening program and the current study (rectangles represent additional steps taken by currents.



Data collection:

The present study recruited 1057 participants living in rural areas of the County. All participants were over 30 years of age and had at least one of the screening criteria defined by DSP (mentioned

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before). The participants were invited to the health houses and were interviewed by 7 experienced and trained health nurses. The required data was collected via an interview-administered questionnaire, which was specially designed and evaluated for DSP by the ministry of health. The questionnaire includes demographic data and a history of DM in the participants or their relatives. In addition, CBG was measured with a glucometer (Easy Gloco). The blood sample was taken from the toe of the middle finger of the left hand. After CBG test was conducted, irrespective of the result, the participants were referred to a public laboratory based in the nearby health center for conducting VPG test. The test was performed by a classic Alpha auto analyzer. In addition, at the same time, all participants gave a HbA1C test which was conducted by nicocard reader device using the glucose oxidase method. Like many other studies, which measured sensitivity and specificity of diabetes screening tests, this study followed WHO's recommendations suggesting VPG as the gold standard for evaluation capillary blood glucose and HbA1C tests (18).

Inclusion criteria: All participants were included providing they were over 30 years of age, had either of the above-mentioned risk factors defined by DSP, and reported no history of DM. Women were also to be not pregnant or breastfeeding. As many of the participants were illiterate, verbal informed consent was obtained from each participant before the interview. The study protocol is approved by Shiraz University of Medical Sciences research committee (approval number=94-01-04-10908).

Sampling and statistical methods:

Sample size (n=1010) was calculated based on the global prevalence of diabetes and using the formula provided by Karim Allah Hajian (19). In practice, however, all individuals over 30 years of age with one or more of the previously mentioned risk factors were recruited (n=1057).

The collected data was analyzed in SPSS 19 using frequency, cross-tabs and chi-square test. In addition, R4.0 was used to conduct ROC analysis to define the best cut points for CBS and HbA1c in screening DM among the study population.

Results:

In total, 1057 individuals, who were over 30 and were living in rural areas of Gerash county participated in this study. The sex ratio (female/male) of the sample was 2 ($P<0.05$) and almost similar age distributions in the two genders were observed ($P>0.05$). The frequency distribution of the participants based on their test results is presented in Table1. Accordingly, the rate of positive results of FBS test (setting ≥126mg/dl as a cut point) based on CBG and VPG (8.60% and 6.70% respectively) were significantly different ($P<0.001$). However, according to the results of HbA1c, the prevalence of DM was 25% when the cut point was set at 6.50% (as recommended by DSP) (20).

Table 1. Prevalence of DM based on the results of three diagnosis testes (CBG, VBG and HbA1c).

variable	N	N†	%*
	Total	Suspected DM	
CBG	1057	91	8.60
VBG	1057	71	6.70
HbA1c	1057	264	25

†Based on WHO recommended cut points (≥126 mg/dl for CBG and VPG and 6.50% for HbA1c)

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The validity of CBG and HbA1c tests:

Using VPG (≥126mg/dl) as the gold standard for diagnosis of DM, sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for CBG and HbA1c are calculated and presented in table 2. As presented in Figure 2, receiver operating characteristic analysis provided new cut-points for the screening of diabetes based on CBG and HbA1c. Accordingly, at the DSP recommended cut-points, the areas under the curve (AUC) were 88.6% and 92.8% for CBG and HbA1c respectively. However, the suggested new cut points obtained by ROC analysis for the screening tests seem to provide better performance among the study population (Table 3). Accordingly, the optimum cut points for CBG (116.50 mg/dl) and HbA1c (7.15%) are considerably lower than those that were recommended by NSPD. Using these values as new cut points, sensitivity and specificity of CBG raised from 69.01% to 80.30% and decreased from 95.74% to 89.10% respectively. Similarly, using 7.15% as a cut point for HbA1c test, sensitivity and specificity changed from 84.50% to 77.50% and from 79.31% to 94.20% respectively (Table 4).

Table 2. Sensitivity, specificity, PPV and NPV of CBG and HbA1c based on WHO's recommended cut points.

Screening Variable	Clinical reference†	N Total	Sensitivity	Specificity	PPV††	NPV†††
CBG*	VBG†	1057	49/71 (69.01%)	944/986 (95.74%)	49/91 (53.84%)	944/966 (97.72%)
HbA1c^	VBG†	1057	60/71 (84.50%)	782/986 (79.31%)	60/264 (22.72%)	782/793 (98.61%)

†CBG ≥126 mg/dl

†VPG ≥126 mg/dl and clinical diagnosis

††PPV=Positive predictive value

†††NPV=Negative predictive value

^HbA1c≥6.5%

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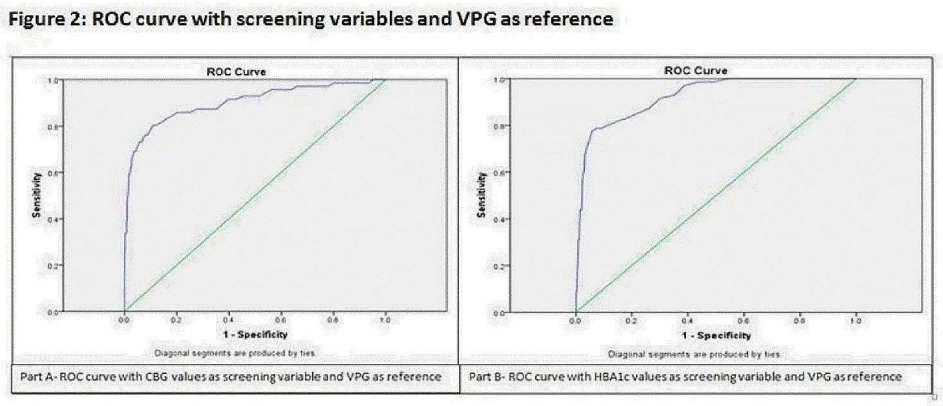

Figure 2. ROC curve with screening variables and VPG as reference.

Table 3. ROC curve indexes for CBG and HbA1c vs. VPG tests.

	CBG	HbA1c
Cut point (as recommended)	126 (mg/dl)	6.5 (%)
No. positive	91	264
No. negative	966	793
AUC	.0902	0.925
SE	0.023	0.015
p-value	<0.001	<0.001
95%CI:	0.856 - 0.948	.0896 - 0.954
Sensitivity	80.30	77.50
Specificity	89.10	.9420
Optimal cut point	116.50	7.15

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Table 4. Sensitivity, specificity, PPV and NPV for CBG and HbA1c vs. VPG based on cut points defined by ROC curve analysis.

Screening test	reference	N	Sensitivity	Specificity	PPV	NPV
CBG	VPG	1057	57/71 (80.28%)	879/986 (89.14%)	57/164 (34.75%)	879/893 (98.43%)
HbA1c	VPG	1057	55/71 (77.46%)	929/986 (94.21%)	55/112 (49.10%)	929/945 (98.30%)
P^			0.001	0.001		

CBG ≥ 116.5 0(mg/dl); VPG ≥ 126 (mg/dl) and clinical diagnosis; PPV= Positive predictive value; NPV= Negative predictive value; HbA1c≥7.15; ^compared with indexes based on WHO's recommendation cut points (CBG ≥126 mg/dl & HbA1c ≥6.5%).

Discussion:

Early detection of DM is essential in the prevention and management of the related life-threatening complications. An efficient screening program for early diagnosis of DM is essential to prevent the DM complications. Although several tests are introduced to identify diabetic patients, serious debates are still going over the validity and reliability of the results (21-23). The inconsistency in the validity of test results is due to several reasons. For example, in a study conducted in India, a bimodal distribution of fasting blood glucose was observed. Obviously, this phenomenon could not be detected by FBS with a cut-point between 140-120 mg/dl. (24) In addition, the American Diabetes Association (ADA) has suggested that glucose level of blood changes over time depending on several factors including the disease progress (22). In fact, despite the presence of DM, the metabolic changes maybe not big enough to detectably raise blood sugar (25). CBG is a test that is more frequently used due to its low cost and ease of use in DM screening programs. However, in several studies, the validity of the results of CBG test has been questioned (23, 26). Technical issues as well as environmental, psychological and medical conditions are listed as factors that affect the validity of the results of a test run by a glucometer (23).

In this study, sensitivity, specificity and positive and negative predictive values of the two DM diagnostic (selecting VBG as a gold standard test) were almost similar for CBG (69.01%, 95.74%, 53.84% and 97.72% reported by the current study respectively) but significantly lower for HbA1c (84.50%, 79.31%, 22.72% and 98.61% reported by the current study respectively) when compared to what reported by Benja Muktabhant et al, (27). According to the report, the sensitivity, specificity, and positive and negative predictive values for CBG and HbA1c were 81.4%, 97.8%, 71.4% and 98.7%, and 39.70%, 96.70%, 56.80% and 93.70% respectively. However, another study on pregnant women by Balaji Bhavadharini et al. provided different results (28). Accordingly, the sensitivity, specificity, positive and negative predictive values for CBG test were 70.80%, 63.00%, 18.00% and 95.00% respectively that are in accordance with sensitivity and negative predictive value of the current study. It is to be noted that sensitivity and specificity are independent of the prevalence of the disease in a community, but the positive predictive value increases when prevalence increases and negative

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predictive value increases when the prevalence of the disease decreases. As a result, the predictive values of a test in a community are not comparable to those communities with different prevalence rates (29).

As recommended by American and European Diabetes Associations, HbA1c is commonly used as a test for screening or clinical diagnosis of diabetes (8, 30). Recently, the International Diabetes Federation and the World Health Organization also recommended HbA1c test as the diagnostic test for diabetes (8, 30). In Iran, following WHO, HbA1c test is used for the diagnosis of diabetes with a cut-point at 6.50% (20). However, some studies indicated significant contradictions in the results of the test. For example, according to a report from the International Expert Committee for Diagnosis and Classification of Diabetes, HbA1c test results may be affected by conditions such as hemoglobinopathies, pregnancy, uremia, blood transfusion, and hemolytic anemia and also by the applied laboratory methods. However, based on the results of a study by D. M. Nathan et al., due to the strong correlation between HbA1c test result and diabetic complications, the test is highly recommended as a DM care assessment measure (31). However, the use of HbA1c is more costly and requires sophisticated laboratory facilities which are hardly affordable by many developing countries. In addition, in a study, results of HbA1c compared to two-hour blood glucose levels and fasting blood glucose was less accurate in identifying people who were at risk of diabetes (32). The researchers used HbA1c as a screening test and they announced sensitivity, specificity, and positive and negative predictive values for HbA1c as 84.50%, 79.31%, 22.72% and 98.61% respectively. However, Farahani et al compared HbA1c results with VPG as the gold standard test (with a cut-point at 110 dl/ mg) and obtained 100% sensitivity, 12.50% specificity, 82.10% positive and 66.70% negative predictive values (33), figures fundamentally different from what observed by the current study.

The current evaluation study on 1057 participants, who had no history of diabetes, measured the validity indexes of DSP in the Iranian population. Based on the results, when CBG (with a cut point at 126 mg/dl) as a screening test and VPG (with a cut point at 126 mg/dl) as a gold standard test were applied, sensitivity, specificity and positive predictive value of the tests appeared to be convincingly high when compared to the results from other countries. In addition, based on the results from ROC curve analysis, the recommended cut-point for CBG was calculated at 116.50 mg/dl with optimal sensitivity and specificity. When the performance of the NSPD is compared with the results of studies from European (AUC=0.844) and Arab (AUC=0.847) countries, the performance of HbA1c and CBG for the Iranian DSP is significantly better (AUC=0.925 for HbA1c and AUC=0.902 for CBG)(18). However, using CBG test, 30.99% of people with DM were not detected while 4.26% of the healthy subjects undergone unnecessary clinical and laboratory procedures (false positive). When HbA1c was used as a screening test, 15.50% of diabetes patients were not detected while 20.69% of the healthy subjects undergone unnecessary clinical and laboratory procedures (false positive). In that regard, the best cut point for HbA1c was at 7.15%, with sensitivity and specificity of 77.50% and 94.20% respectively.

Compared to several other countries, the performance of the Iranian SDP is reasonably better. This may be due to the differences in the defined criteria for selecting populations for screening (high-risk groups) in different countries. In this study, ROC analysis suggested new cut-points for even better performance of DSP in Iran. Further studies are needed to understand different aspects of the suggested cut points and the risk factors selected by DSP to define the high-risk population to achieve a better performance of the program.

Implications for Policy & Practice

This study evaluated the performance of diabetes screening of Iran using a population-based sampling method

All procedures, instruments, and personnel used in this study were similar to what is used by the national screening program making the results more representative and applicable

New cut points are provided to increase the performance of the screening tests

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Limitations:

The participants in this study were all rural residences with different lifestyles of the urban population. As a result, our findings should be validated in urban populations.

Acknowledgment:

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Decelerations:

Ethics approval and consent to participate:

The participants were assured that their information is used for research proposes only. Because of the illiteracy of a significant number of parents, verbal consents were obtained from the parents. The study protocol was reviewed and approved by the ethical committee of Shiraz University of Medical Sciences.

Consent for Publication:

Not Applicable

Availability of data and material:

The datasets generated and/or analyzed during the current study are not publicly available due to its being the intellectual property of Shiraz University of Medical Sciences but are available from the corresponding author on reasonable request.

Competing interests:

The authors declare no conflict of interest.

Funding:

This study was conducted as a thesis for MSc degree in epidemiology and was financially supported by Shiraz University of Medical Sciences, Shiraz, Iran. (Grant number:1634).

Authors' contributions:

F.K and M.D were responsible for data collection and data analysis; M.M was responsible for coordination and management and manuscripts preparation; J.H was responsible for measurement methods and interpretation of results. M.F was responsible for coordination and management of the project and data analysis and preparation of the manuscript. All authors have read and approved the manuscript.

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