Screening for Diabetes: Sensitivity and Positive Predictive Value of Risk Factor Total

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OBJECTIVE: Screening for diabetes is recommended for individuals ≥45 years of age, or earlier if they manifest ≥ one specific risk factors. This study examined the sensitivity and positive predictive value (PPV) of risk factor total for identifying individuals with diabetes and prediabetes.

DESIGN: Subjects were interviewed to assess the presence of risk factors. Fasting plasma glucose levels were obtained.

SETTING: The study occurred at a health fair in Greensburg, PA.

PATIENTS: Six hundred sixty-one Caucasians between the ages of 19 and 100.

RESULTS: Using the criterion of screening individuals with ≥ one risk factors detected 100% of both diabetics and prediabetics. This dropped to 91.2% when screening individuals with ≥ two factors. The PPV of the risk factor total was poor (80% of individuals with a total of four factors were not diabetic). The ability of the risk factor total to predict individuals with impaired glucose metabolism (prediabetics + diabetics) was considerably better, and increased almost linearly with the risk factor total. Of the subjects with normal glucose values, the mean glucose increased as the risk factor total increased.

CONCLUSION: While the sensitivity of using ≥ one risk factor as an algorithm to screen is 100% for identifying diabetics, the PPV of risk factor analysis for identifying diabetics is poor. The same algorithm works well to identify at-risk individuals, presumably allowing early intervention and education.

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ABBREVIATIONS: FPG = fasting plasma glucose; PPV = positive predictive value.

INDEX TERMS: diabetes mellitus; euglycemia.

Clin Lab Sci 18(4):221

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Hyperglycemia is a risky business. Elevated glucose levels in diabetes mellitus are associated with the risk of retinopathy, kidney failure, and neurologic damage.[1] Coronary vascular disease is strongly associated with diabetes; in fact, it is the leading cause of diabetes related deaths.[2] An individual with diabetes has the equivalent risk of suffering a major coronary event as a person who already has coronary heart disease.[3] An increasing number of Americans are exposed to this risk: 6.3% of the U.S. population can be classified as diabetics.[4] A diagnosis of diabetes can be made three ways. The first is by an individual having the classic symptoms of diabetes, e.g., polydipsia, polyuria, and unexplained weight loss, and a casual glucose value ≥11.1 mmol/L (200 mg/dL). The second is by an individual having a fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL), confirmed by repeat testing on a different day. The third method is a two-hour post glucose load value ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test, repeated on a different day.[5] The cutoff values are based on the increased incidence of retinopathy that is associated with glucose values at or above these levels. There is no threshold glycemic value that predicts macrovascular risk.

Individuals who have type 2 diabetes may already bear some of its 'scars' at the time of diagnosis. Newly detected type 2 diabetics have a higher degree of early atherosclerosis than non-diabetics.[6] Nephropathy may be found at this time as

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well; therefore, newly diagnosed diabetics should be screened for microalbumin.[1] Frank diabetes follows a 'prediabetic' period. Recently, the FPG range that defines this stage has been lowered to include 5.6 mmol/L to 6.9 mmol/L (100 mg/dL to 125 mg/dL); 21.1% of Americans age 40 to 74 fall into this new range.[4,7] Individuals with prediabetes have a relative risk of heart disease of 1.19 to 1.33 compared to euglycemic individuals.[8,9] The benefit of classifying an individual as prediabetic is to intervene and attempt to prevent subsequent diabetes. Several studies have shown that life style changes and/or pharmacologic therapy targeted at prediabetics can substantially reduce the incidence of progression to diabetes.[10]

The American Diabetes Association does not recommend screening the general population for diabetes, but instead uses a risk-based approach. Since age is a risk factor in becoming diabetic, screening should begin at age 45, and be performed every three years thereafter.[11] Other factors that are associated with increased risk of developing diabetes are being overweight (body mass index ≥25 kg/m^2), family history of diabetes, race other than Caucasian, hypertension (even if treated), dyslipidemia, history of gestational diabetes or delivering a baby > nine pounds, and habitual physical inactivity. Individuals that have one or more of these risks should be screened for diabetes at a younger age.[11] The correlation between risk factors and diabetes is not expected to be 100%, but the greater the number of risk factors, the greater the chance is that an individual has or will develop diabetes.[11] Risk factor assessment is a simple method for prediction, does not weight any factor higher than another, and does not take into account possible interactions between the factors. Its advantage is that it is easy to perform, all factors have an equivalent risk, and they are summed. If an individual has one or more risk factors, the physician may decide to screen the individual for diabetes before their 45th birthday.

This study enrolled a large group of Caucasian men and women who attended a community health screen, and correlated the risk factor total to the prevalence of diabetes and prediabetes in that population to determine the sensitivity and PPV of risk factor total as a screening tool for diabetes. This study also examined the level of FPG in euglycemic individuals with respect to risk factor total.

MATERIALS AND METHODS

Subjects were solicited at a health fair in Greensburg, Pennsylvania in April 2003. Six hundred sixty-two people (264 males and 398 females) enrolled in the study. Each completed a health survey and provided informed consent. Subjects ranged in age from 19 years to 100 years, with a mean of 60.6 (SD 14.0) and a median of 61. All of the subjects were non-Hispanic Caucasians except for one African-American man. Because race other than Caucasian is a known risk factor for diabetes, and only one participant was not Caucasian, he was excluded from this study. Survey materials were approved by the Institutional Review Board at the University of West Florida. There was no financial incentive for participation. Participants were fasting 10 to 12 hours prior to phlebotomy.

Samples were collected in lithium heparin tubes with separator gels and centrifuged within one hour of collection. Testing was performed on a Roche Hitachi Modular® Analytics Instrument (Roche Diagnostics Corporation) at Westmoreland Regional Hospital in Greensburg PA by a qualified technical staff. The population was sorted into three groups using FPG value and history of diabetes: nondiabetics with FPG <5.6 mmol/L (99 mg/dL) were classified as euglycemics, nondiabetics with FPG between 5.6mmol/L and 6.9 mmol/L (100 to 125 mg/dL) were classified as prediabetics, and individuals with a history of diabetes were classified as diabetics regardless of their FPG. Individuals with no history of diabetes but with FPG ≥7.0 mmol/L (126 mg/dL) were classified as diabetics for this study; in a clinical situation, most of these individuals would require a second FPG or a glucose tolerance test to confirm that assessment. Prevalence of diabetes and prediabetes in the group was compared to national prevalence using a Chi-square Goodness of Fit test, and differences were considered to be statistically significant when $p \leq 0.05$.

The categories of risk factors were: family history of a first-degree relative with diabetes, body mass index ≥25 kg/m^2, age ≥45, history of hypertension, HDL ≤0.91 mmol/L (35 mg/dL) or triglycerides ≥2.82 mmol/L (250 mg/dL), history of gestational diabetes, or birth of a baby over nine pounds. No assessment was made for physical inactivity. Risk factors were assigned a value of 1 if they were present and a value of 0 if they were absent. The total number of risk factors was summed for all participants. The PPV of a risk factor was calculated by dividing the total number of diabetics in each risk factor total category (true positives) by the total number of individuals in each category (true positives + false positives). The PPV of a risk factor for determining impaired glucose metabolism was calculated by dividing the total number of individuals with a FPG ≥5.6 mmol/L (100 mg/dL) and/or a diagnosis of diabetes in each risk factor total category (true positives) by the total number of individuals in each category (true positives plus false positives).

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For the analysis of the euglycemics, all of the nondiabetics with FPG <5.6 mmol/L (100 mg/dL) were sorted by risk factor total category, and the means of the FPG were calculated for each category. Analysis of variance (ANOVA) was used to determine the probability that the difference in the means arose by chance, and was considered to be statistically significant if $p \leq 0.05$.

RESULTS

The participants were categorized as normal, prediabetic, or diabetic, and then sorted by risk factor total (Table 1). Forty-six individuals were classified as diabetics (6.9%); ten of these were unaware of their potential diabetic status. This compares well to the national prevalence of 6.3% (χ^2 = 0.610, p = 0.7371).[4] All of the diabetics had at least one risk factor: <1% of the participants with one risk factor were diabetic, and this increased to 4.3% with two risk factors, 8.1% with three risk factors, 20.3% with four risk factors, and 54.5% with five risk factors. Only one participant had six risk factors, and this person was diabetic. The sensitivity of risk factor total to predict diabetes in this population was 100% for ≥ one risk, and dropped to 97.8% for ≥ two risks. Low values of risk factor total were nonspecific for diabetes in this population, and gave a high false positive rate. The PPV is a statistic that correlates the number of true positives with the number of false positives, and is a better indicator of the success of risk factor total in identifying diabetics. The formulae for calculating sensitivity, specificity, PPV and PPN are shown in Figure 1. The PPV of risk factor total for identifying diabetics is depicted in Figure 2 as closed squares.

The number of prediabetics was similar to the national prevalence as well: 135 of the participants (20.4%) fell into the newly defined range for prediabetes. Participants with one risk factor (8.9%) were prediabetic, increasing to 18.8% with two factors, 32.9% with three factors, 31.1% with four factors and 9.1% with five factors. The sensitivity of risk factor total to predict prediabetes was 100% for ≥ one risk, and dropped to 88.9% for ≥ two risks. The PPV of risk factor total for identifying individuals that have impaired glucose metabolism, that is those who are either prediabetic or diabetic, is depicted in Figure 2 as closed triangles.

The proportion of euglycemics in each risk factor group steadily decreased as the risk total increased, yet 49% of the participants with four risk factors and 36% with five risk factors were euglycemic. Analysis of variance was performed to examine the FPG mean for each risk factor total. Figure 3 shows the mean FPG of the euglycemics sorted by risk factor total. The lowest FPG was found for individuals with no risk factors (4.5 mmol/L or 83 mg/dL). The FPG mean increased with the risk total to a high of 5.2 mmol/L (95 mg/dL) in individuals with a five total risk factors (p <0.0001).

Table 1. Risk factor total categories grouped by glycemic status

Risk factor total	0	1	2	3	4	5	6	Total
Normal	25	153	160	102	36	4	0	480
Prediabetic	0	15	39	57	23	1	0	135
Diabetic	0	1	9	14	15	6	1	46
Total	25	169	208	173	74	11	1	661

Figure 1. Formulae used for sensitivity and specificity

Sensitivity: % of the diabetics that are correctly identified by the criteria.

Sensitivity	TP/(TP + FN) * 100
Specificity	TN/(TN + FP) * 100
Sensitivity of ≥ 2 risk factors	45/(45 + 1) * 100 = **97.8%**

PPV: % of individuals in each category (risk factor total) that actually are diabetic

Positive Predictive Value	TP/(TP + FP) * 100
Negative Predictive Value	TN/(TN + FN) * 100
PPV of 2 risk factors	9/(9 + 199) * 100 = **4.3%**

DISCUSSION

This Caucasian population approximated the national trends for diabetes and prediabetes, and showed that risk factor total is a sensitive method to predict individuals at risk for diabetes. The use of the risk total, however, showed a poor PPV for diabetes because it is nonspecific (Figure 2). For individuals with as many as four risk factors only 20% were diabetic, and for individuals with five risk factors 55% were diabetic. Risk factor total showed a better PPV for impaired glucose metabolism, that is either a FPG >5.5 mmol/L (99 mg/dL) or history of diabetes. The

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PPV was lowest for a total of one factor (9.5%), and showed an almost linear increase up to 60% for individuals with five risk factors.

The American Diabetes Association recommends that individuals ≥45 years old be screened for diabetes every three years. Younger individuals should be considered for screening if they are obese or have any other 'risk factors'.[11] This leaves the decision to screen up to the physician. If the physician chose to screen all individuals with at least one risk factor, all of the diabetics in this study group would have been identified (100% sensitivity); that approach would have identified 100% of the subjects who were prediabetic as well. If, instead, the physician used the requirement of two or more risk factors before screening, he/she would miss 9.5% of the at-risk population.

Of the 25 individuals with no risk factors, all were euglycemic. This group had the lowest mean FPG, 4.5 mmol/L (83 mg/dL). It is interesting that the mean FPG increased as the risk factor total increased in the euglycemic subjects, and suggests that the individuals with a larger number of risk factors may be on the verge of becoming prediabetic. The recommendations for screening do support more frequent glucose testing in individuals who are high risk.[11] It appears from this study that more frequent screening of this group is indeed prudent.[11] It is possible that these individuals suffer from impaired glucose tolerance, and would be reclassified if they were tested by a two-hour glucose tolerance test.[7]

Figure 2. Positive predictive value of risk factor total

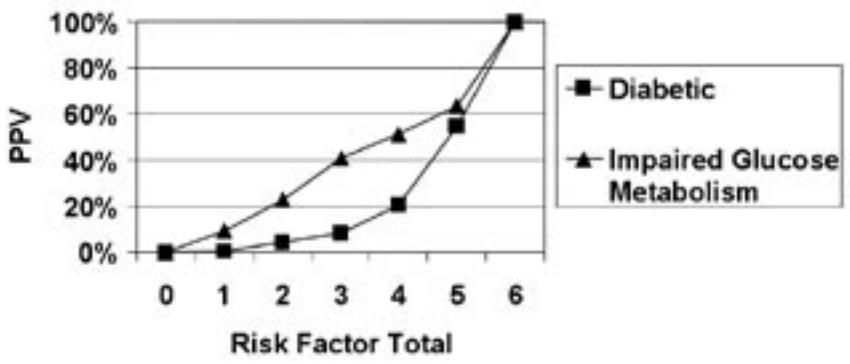
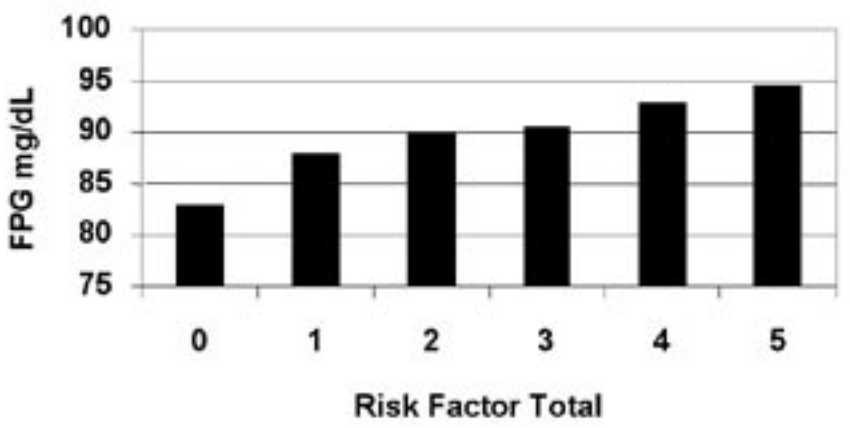


Figure 3. FPG increases with risk factor total in euglycemics



The American Diabetes Association Website offers a quiz to determine at-risk individuals, using weight, age, obesity, and physical activity as major predictors for diabetes.[4] The present study did not assess physical activity and treated all risk factors as equivalent, but it was nevertheless able to identify all subjects with impaired glucose metabolism. One limitation of this study is that there were relatively few subjects who had no risk factors. This study was performed on Caucasians only, and other race groups may show different results.

Many of the risk factors for diabetes are beyond the control of the individual, for example age, race, and family history. Other factors like hypertension, GDM, and dyslipidemias are in many instances linked to overweight and obesity. It is not surprising that there is a wave of increased diabetes in the U.S. that is concomitant with an increase in obesity.

Although the use of risk factor total showed a poor PPV for identifying diabetics in this study, it showed a good PPV for identifying individuals at risk for diabetes, both prediabetics and euglycemics. The current recommendation to screen all individuals for diabetes at age 45 or younger if they have one or more risk factors

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appears to be appropriate.[11] Based on this study, screening individuals with one or more risk factors would result in 100% sensitivity for identifying individuals early who are at risk for the microvascular and macrovascular complications that are associated with hyperglycemia, and allow education, intervention and follow-up.

ACKNOWLEDGEMENTS

This project was funded by a grant from the Scholarly and Creative Activities Committee at the University of West Florida (UWF). I thank Laura Stanko for technical support, Sam Raneri and the Westmoreland Regional Hospital Laboratory, Raid Amin and the Statistics Center at UWF, Frances Connolly for clerical support, and Swarna Krothapalli and the Medical Technology Program at UWF.

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