Screening Insurance Applicants for Diabetes: A Korean Perspective

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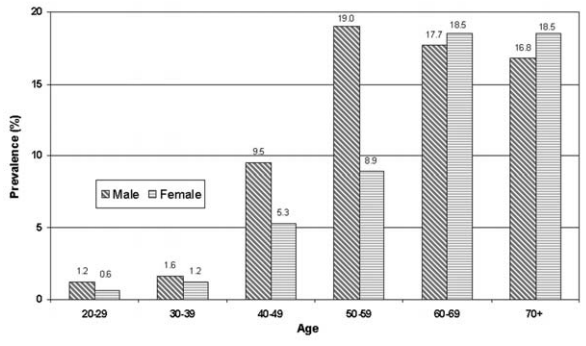
This article discusses the use of fasting blood glucose (FBG) and hemoglobin A1c (A1c) to identify insurance applicants who have diabetes or are at high risk for developing diabetes in the future. The conclusion is that the addition of A1c to insurers' underwriting requirements, either as a reflex or a routine (universal) test, may be a cost-effective strategy to manage the risk associated with impaired fasting glucose (IFG) and diabetes.

Increasing prevalence of diabetes in Korea

The age-specific prevalence of Type 2 diabetes continues to increase in South Korea.[1] According to the Third Korea National Health and Nutrition Examination Survey,[2] 9.5% of men and 5.3% of women aged 40-49 have diabetes, most of which are Type 2 (adult-onset) diabetes, and the prevalence is even higher at older ages (Figure 1).[3]

Figure 1. Age-and sex-specific prevalence of diabetes mellitus in Korea (2005 KNHANES)



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This issue is important from a public health perspective because diabetes is a major contributor to morbidity and mortality in Korea. It is also important from an insurance perspective because diabetics are at higher risk for many of the events that are covered by insurance. For this reason, insurers would like to identify applicants who have diabetes or are at high risk for developing diabetes in the future.

Urine glucose tests

A test for glucose in the urine was once commonly used by insurers to screen for diabetes, and an elevated urine glucose still has value for screening applicants who apply for small policies where it is not cost-effective to require blood tests. However, urine glucose tests are not sensitive enough to detect most diabetics.

Fasting blood glucose

Risk increases even within the normal range

As with other risk factors, such as blood pressure and cholesterol, risk of cardiovascular mortality increases continuously (not discretely) with blood glucose concentration, starting at levels well below the conventional threshold values used for the definition of diabetes.[4] Nichols et al. reported the incidence of diabetes in 46,578 members of a U.S. health maintenance organization who had a FBG of less than 100 mg/dl (5.6 mmol/l) and who did not previously have diabetes or IFG (Table 1).[5] As expected in a cohort with a normal FBG, the incidence of diabetes was low (less

than 1% per year), but the risk of diabetes still increased as FBG increased within the normal range (a 6% increase in diabetes incidence for each milligram per deciliter increase of FBG). For example, the relative risk of diabetes for a healthy person with a FBG of 95-99 mg/dl (5.3-5.5 mmol/l) was 2.3 times higher than for a person with a FBG of less than 85 mg/dl (4.7 mmol/l).

Table 1. Relative risk (RR) of diabetes, by level of fasting blood glucose*

Fasting blood glucose	RR
〈85 mg/dl (4.7 mmol/l)	1.0
85–89 mg/dl (4.7–4.9 mmol/l) †	1.2
90–94 mg/dl (5.0–5.2 mmol/l)	1.5
95–99 mg/dl (5.3–5.5 mmol/l)	2.3

* Nichols et al. Am J Med 2008;121:519–24.
† RR for 85–89 mg/dl was estimated from data in the abstract.

2003 ADA definition causes problems

In 2003, the American Diabetes Association (ADA) recommended that the threshold for IFG, a pre-diabetic condition, should be reduced from ≥110 mg/dl (6.1 mmol/l) to ≥100 mg/dl (5.6 mmol/l [Table 2]).[6] This decision was widely criticized as being too strict from a clinical perspective because it created a "pandemic" of IFG worldwide.[7] The 2003 ADA definition also caused problems for insurers because it effectively labeled more than half the population with the "impairment" of IFG.[9] This raised this question for underwriters, "Which cut-point should be used to classify the risk associated with IFG: 110 mg/dl (6.1 mmol/l) or 100 mg/dl (5.6 mmol/l)?

Table 2. American Diabetes Association (ADA) criteria for normal glucose, impaired fasting glucose, and diabetes*

Criteria	Normal	Impaired fasting glucose	Diabetes
ADA 1997	〈110 mg/dl (6.1 mmol/l)	110–125 mg/dl (6.1–6.9 mmol/l)	≥126 mg/dl (7.0 mmol/l)
ADA 2003	〈100 mg/dl (5.6 mmol/l)	100–125 mg/dl (5.6–6.9 mmol/l)	≥126 mg/dl (7.0 mmol/l)

* American Diabetes Association. Diabetes Care 2006;29:S4–S42.

Rate of progression from IFG to diabetes

Two recent reports estimated the rate of progression from IFG to Type 2 diabetes according to the 1997 and 2003 ADA criteria. Nichols et al. studied 5,452 Americans with newly acquired IFG (mean follow-up, 5 years),[8] and Forouhi et al. followed 633 subjects with IFG (the date of onset of IFG was not known) who were registered with a single medical practice (median follow-up, 10 years) in the UK.[9] Table 3 shows that the rate of progression from IFG to diabetes was 3 to 4 times faster with the 1997 criteria. The reason is because subjects who had IFG by the 1997 criteria had higher baseline FBG levels, i.e., they were already farther along the path toward diabetes.

Table 3. Annual rate of progression (%) from impaired fasting glucose (IFG) to Type 2 diabetes

IFG criteria	Nichols et al.*(U.S.)	Forouhi et al.†(UK)
ADA 1997 110–125 mg/dl (6.1–6.9 mmol/l)	5.6	1.8
ADA 2003 100–125 mg/dl (5.6–6.9 mmol/l)	1.3	0.6

* Nicholas et al. Diabetes Care 2007;30:228–33.
† Forouhi et al. Diabet Med 2007;24,200–7.

Rate of progression from IFG to cardiovascular disease

Rijkelijkhuizen et al. reported the likelihood of cardiovascular mortality in 1,428 Dutch subjects according to the 1997 and the 2003 ADA criteria.[10] Those with a FBG of 110 mg/dl (6.1 mmol/l), but not 100 mg/dl (5.6 mmol/l), were at higher risk of cardiovascular mortality, i.e., the 2003 criteria added people who were not at high risk for cardiovascular death.

Hemoglobin A1c

Clinical studies have shown that the sensitivity of FBG for diagnosing diabetes is not as high as expected, with up to one-third of individuals with diabetes remaining undetected.[11] Insurers who order FBG tests face the additional problem that underwriters don't know if the applicant was fasting. For these reasons, both clinicians and insurers are exploring strategies that use A1c as an alternative screening test for diabetes.

As with FBG, there is a continuous (not discrete) relationship between A1c level and risk. Khaw et al. reported the association between A1c and cardiovascular morbidity and mortality in 10,232 subjects aged 45 to 79 who lived in the UK.[12] As indicated in Table 4, the relative risk (compared to a baseline risk of 1.0 for A1c levels of less than 5%) for cardiovascular events and all-cause mortality increased steadily with higher A1c levels, even for values within the normal range. For example, the relative risk of a cardiovascular event or all-cause mortality was 1.8 times

higher for men and 1.6 times higher for women with an A1c of 6.0% to 6.4%. These associations were independent of blood pressure, cholesterol, body mass index, smoking, and history of heart disease or stroke.

Table 4. Relative risk of cardiovascular disease (CVD) events and all-cause mortality, by hemoglobin A1c level*

	Relative risk by hemoglobin A1c level					
	<5.0	5.0–5.4	5.5–5.9	6.0–6.4	6.5–6.9	≥7.0
Men						
CVD events	1.0	1.2	1.6	1.8	3.0	5.0
All-cause mortality	1.0	1.3	1.6	1.8	3.5	3.4
Women						
CVD events	1.0	0.9	1.0	1.6	2.4	8.0
All-cause mortality	1.0	1.0	1.3	1.6	1.7	6.9

* Khaw et al. Ann Intern Med 2004:141:413–20.

A broader analysis was done by Bennett et al. in a review of nine studies [U.S. (1), UK (1), Australia (2), Italy (1), Poland (1), Japan (1), Singapore (1), and Hong Kong (1)] that examined the use of A1c as a screen for diabetes.[11] The authors concluded that A1c was an effective way to screen for diabetes based on a cut-point of greater than 6.1% (which yielded a sensitivity of 78% to 81%, and a specificity of 79% to 84%).

Combined use of fasting blood glucose and hemoglobin A1c

Combined use of FBG and A1c in a clinical context in Japan

Inoue et al. examined the value of using both FBG and A1c to predict future diabetes.[13] The cohort consisted of 10,042 Japanese subjects with a mean age of 53 years who had a routine health screen and were then followed for an average of 5.5 years. The study used the 2003 ADA cut-points for IFG. Table 5 shows a marked difference is the annual incidence of diabetes, with the extremes ranging from 0.07% per year (0.7 cases per 1000 people per year) in subjects with a normal fasting glucose and an A1c of less than 5.5%, to 4.3% per year (43 cases per 1000 people per year) in those with IFG and an A1c of 5.5% to 6.4% (which is 38 times greater than subjects in the most favorable category).

Combined use of FBG and A1c in a clinical context in Korea

Kim et al. studied the diagnostic value of A1c in patients at Bundang CHA General Hospital (Seoul) who were at high risk for diabetes because of an elevated random blood glucose, a BMI greater than 30 kg/m$^{(2)}$, or a history of gestational diabetes.[14] The primary goal was to determine if the combination of FBG and A1c was superior to FBG alone for diagnosing diabetes.

Table 6 shows five testing options. Option 1 was the least sensitive for detecting diabetes, but the most specific (by definition, a FBG of ≥126 mg/dl [7.0 mmol/l] on two separate occasions is diagnostic of diabetes). Options 2 and 3 were both more sensitive than option 1, but at the price of lower specificity (the false positive rate is calculated as "1 minus specificity"), i.e., more cases of diabetes would be found but there would be more false positives. Option 4 detected the most cases of diabetes, but this choice had the lowest specificity. The sensitivity of option 5 was higher than option 1, plus option 5 had a high specificity. The authors concluded that simultaneous measurement of FBG and A1c (Option 5) might be useful for screening people at high risk for diabetes.

Table 6. Sensitivity and specificity of different combinations of fasting blood glucose (FBG) and A1c for detecting diabetes in high risk Koreans*

Options	Sensitivity	Specificity
1. FBG ≥126 mg/dl (7.0 mmol/l)	55.7	100.0
2. FBG ≥110 mg/dl (6.1 mmol/l)	85.2	88.5
3. A1c ≥6.1%	81.8	84.9
4. FBG ≥110 mg/dl (6.1 mmol/l) or A1c ≥6.1%	95.5	77.6
5. FBG ≥110 mg/dl (6.1 mmol/l) and A1c ≥6.1%	71.6	95.7

* Kim et al. Diabet Med 2008:25:997–1000.

Table 5. Risk of developing diabetes in 10,042 Japanese subjects according to baseline categories of fasting blood glucose and A1c*

	% in each category	Cumulative incidence over 5.5 years (%)	Incidence per year (%)	Relative risk of diabetes†
Normal fasting glucose <100 mg/dl (5.6 mmol/l)				
A1c <5.5%	66.7	0.4	0.07	1
A1c 5.5–6.4%	6.0	2.5	0.4	7
Impaired fasting glucose 100–125 mg/dl (5.6–6.9 mmol/l)				
A1c <5.5%	20.4	7.6	1.4	14
A1c 5.5–6.4%	6.9	24.8	4.3	38

* Inoue et al. Diabet Med 2008:25:1157–63.

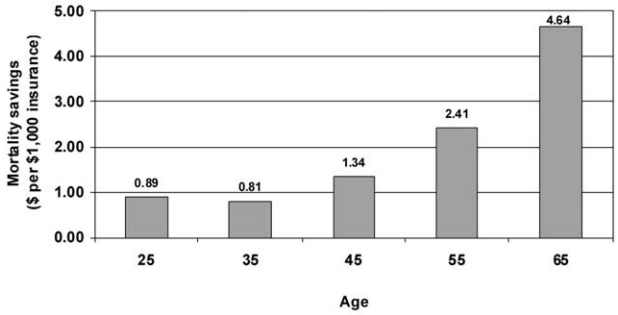
† Adjusted for age, sex, BMI, systolic blood pressure, triglycerides, ALT, and white blood cell count.

Reflex A1c tests as an underwriting requirement

Insurers may not want to order A1c tests on all applicants who have blood tests. One solution, known as "reflex" testing, is to ask the testing laboratory to do an A1c whenever the applicant's FBG reaches a certain level.

Pokorski described the cost-effectiveness of this strategy in a 2006 review of the cost/benefit of laboratory tests in an insurance context.[15] Figure 2 shows the mortality savings for U.S. males who apply for a $250,000, 20-year term life insurance policy. For a 45-year-old, this reflex testing strategy would yield a mortality savings of $1.34 for each $1,000 of life insurance that is purchased. Reflex testing is cost-effective at all ages, but especially at ages 45 and older where there is a higher prevalence of diabetes. The mortality savings in other insurance markets would depend on variables such as the cost of underwriting requirements and the prevalence of IFG, impaired glucose tolerance, and diabetes.

Figure 2. Mortality savings for a reflex A1c test (U.S. male, nonsmoker, $250,000 20-Year term)



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Universal A1c tests as an underwriting requirement

Jackson National Life, a major U.S. life insurer, reported the results of a program to assess the cost-effectiveness of A1c as a screen for diabetes.[16] In this study, an A1c was ordered in all cases where a blood sample was obtained. An A1c greater than 6.0% was considered abnormal. Of 6,949 applicants who were screened with A1c, 737 (10.6%) had a level greater than 6.0%.

The authors made the following conclusions:

1. In 3% of cases where A1c screening was done, diabetes or impaired glucose tolerance was detected solely by an A1c of greater than 6.0% (based on an earlier pilot study in 2007).[17]
2. Screening with A1c was cost-effective. For policies with an elevated A1c that were accepted by the applicant (at a higher premium compared to applicants with a normal A1c), the sum of the additional first-year premiums due solely to A1c screening exceeded the cost of screening all applicants. The final value of screening would be even higher because this additional premium would continue for the life of the policy.
3. Elevated A1c levels sometimes generated a request for an attending physician's statement. This additional information revealed that a small number of applicants had grossly misrepresented their health status and were uninsurable.
4. For preferred risk products, an elevated A1c was sometimes the reason why applicants were placed in either a more or a less favorable mortality risk class.
5. The company did not see a decrease in sales due to an increase in the number of applicants who were placed in less favorable mortality classes. However, given the competitive nature of the U.S. market, it is likely that some sales would be lost to competitors because of screening with A1c. The competitors, who would be unaware of the higher expected mortality in these applicants, would be accepting business that was underpriced compared to the actual mortality risk.

Insurance issues

The current insurance screening strategies in Korea do not detect some applicants who are at higher morbidity and mortality risk because of IFG and diabetes.

Urine glucose

The primary use of a urine glucose test is to screen applicants who apply for small insurance policies where it is not cost-effective to request blood tests. These tests do not detect most cases of diabetes.

Fasting blood glucose alone

FBG is not a perfect test for detecting IFG and diabetes. Many applicants are not fasting (so underwriters cannot be sure about the accuracy of the test), there is no clear cut-point that defines the transition from low to high risk (risk increases continuously, even for FBG levels within the normal range), and FBG fails to detect some people with diabetes. For IFG, risk of diabetes and cardiovascular disease increases more

rapidly at FBG levels of 110 mg/dl (6.1 mmol/l) and higher. This would be a reasonable cut-point to define higher risk in an insurance context.

A1c alone

As with FBG, there is a continuous (not discrete) relationship between A1c level and risk. Risk of diabetes and cardiovascular disease is higher for A1c levels of 6.0% to 6.4%, and significantly higher for A1c levels of 6.5% to 6.9%. An A1c of 7.0% usually indicates diabetes.

Combined use of FBG and A1c in a clinical context in Japan and Korea

Studies from Japan and Korea show that the combined use of FBG and A1c predicts future diabetes more effectively than either test alone. In Korea, one of the best screening strategies was a FBG of 110 mg/dl (6.1 mmol/l) or greater and an A1c of greater than 6.1%. This yielded a reasonably high sensitivity (71.6%) and a high specificity (meaning, a low false positive rate) of 95.7%.

Reflex A1c tests as an underwriting requirement

Reflex testing (automatically performing an A1c test whenever the FBG reaches some predetermined value) can be a cost-effective screening strategy in some markets, such as the U.S. This may or may not be true in Korea where the insurance laboratory infrastructure is less developed, there are concerns about A1c test accuracy, and there is a different cost structure for underwriting requirements.

Universal A1c tests as an underwriting requirement

A U.S. study concluded that universal screening (whenever blood tests were done) with A1c was cost-effective when an A1c greater than 6.0% was considered abnormal. This strategy also helped classify applicants into different preferred risk classes. As with reflex A1c testing, this may or may not be true in Korea.

Conclusion

The addition of A1c to insurer's underwriting requirements, either as a reflex or a routine (universal) test, may be a cost-effective strategy to manage the risk associated with IFG and diabetes.

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