Diabetes and Glycohemoglobin

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Introduction: Diabetes mellitus has long been recognized as a major cause of mortality and morbidity. The true frequency of the disorder is difficult to estimate because of differing diagnostic criteria but it is clearly the most common of the serious metabolic disorders occurring in roughly 1 to 4 percent of the U.S. population. It is a leading cause of mortality in this country, taking over 300,000 lives a year. Chronic complications of diabetes account for 50% of lower limb amputations, 20% of end-stage renal failure and diabetes has become the leading cause of blindness in the U.S. Diabetes also accounts for 10% of all in-patient hospital days in the U.S. and estimates of its annual contribution to the nation's health-care bill range from $5 to 10 billion.

Diabetics were once considered to be uninsurable by life insurers. Prior to the advances in diabetic therapy of this century, a juvenile diabetic could expect to live only a few months while the adult diabetic had only a slightly longer life expectancy. Today, most diabetics can be considered for both life and health insurance. Landmark studies by the Equitable and Lincoln National Life remain major sources of information about the mortality of diabetics. The 1983 Medical Impairment Study published jointly by ALIMDA and the Society of Actuaries is another source for insurers' experience with diabetics.

Diabetes mellitus is a genetically and clinically heterogenous group of disorders that have in common hyperglycemia and either a relative or absolute insulin deficiency. There is the well-known distinction between thin, ketosis-prone, insulin-dependent diabetics and obese, nonketotic, insulin-resistant diabetics. Some diabetic conditions inherited in a autosomal-dominant fashion while others are recessive with incomplete penetration and still others appear to be the result of environmental factors including diet and infections. Despite the heterogeneity, this diverse group called diabetes has in common the long-term complications of lens, retina, glomerulus, and the lesions of basement membranes that can be seen by electron microscopy.

However, the heterogeneity within the diabetic syndrome is problematic for clinicians, researchers and underwriters. Despite the shared predisposition towards complications, it is difficult to predict which diabetic will develop them and when. Changes in the diagnostic criteria for diabetes and the new classification of diabetes and glucose intolerance have added confusion and made long term studies difficult to compare. Even the tests used to diagnose diabetes are controversial. This review will concentrate on controversial issues in testing and screening for diabetes.

Definitions: The interpretation of diagnostic tests for diabetes has been hindered by a lack of uniformity in procedures and in the criteria of abnormality. In an attempt to establish uniformity the National Diabetes Data Group of the NIH published the following recommendations for non-pregnant adults in 1979.[1]

The diagnosis of diabetes should be based upon:

1) Unequivocal plasma glucose elevation (PG $\geq$ 200mg/dl) together with classic symptoms of osmotic diuresis,
or 2) Elevated fasting PG (>140mg/dl) on more than one occasion,
or 3) Elevated PG ($\geq$ 200mg/dl) after a glucose challenge (75gm) at ½ hr., 1 hr., or 1½ hr. and at 2 hr., more than once (2 OGTT's).

The diagnosis of impaired glucose tolerance should be based upon three criteria:

1) Fasting plasma glucose (FPG) <140mg/dl,
and 2) 2 hr. oral glucose tolerance test (OGTT) value between 140 and 200 mg/dl,
and 3) PG $\geq$ 200mg/dl at ½, 1, or 1½ hr. after a 75gm glucose challenge, only once.

Note the "plasma glucose." In most modern laboratories glucose is measured in plasma or serum. Plasma and serum values are identical, but both are 10-15% higher than what is obtained using whole blood. The medical direcator should note the lab's procedure to avoid an inappropriate decision due to methodological differences.

The NDDG recommendations were not arbitrary but were based upon years of experience and careful review of that experience. Previous guidelines promoted by the USPHS and the WHO clearly set the blood sugar levels too low and over-diagnosed diabetes. It has been estimated that as much as 40-50% of the general public would have been diagnosed as diabetic by the earlier criteria.

But these criteria are not without problems. Following the NDDG algorithm, it is possible for a diabetic to have a FPG, another FPG, and then two OGTT's before being categorized.[2] Even after that many steps, some patients are left in indeterminate categories by the NDDG algorithm. The second OGTT is necessary in part due to the lack of reproducibility of the OGTT even under ideal conditions.

In 1980 the World Health Organization published criteria for diabetes that do not require a second OGGT and in most

situations yield fewer indeterminate results. However, the WHO criteria result in a higher prevalence of diabetes in the test population. In actual practice, some researchers and clinicians do not strictly adhere to NDDG or WHO criteria but "base" their diagnostic strategies on the official guidelines. Even Harrison's *Principles of Internal Medicine* gives the NDDG criteria without mention of a second OGTT.[3]

Glycohemoglobin: The two most important recent innovations in diabetic care were not the high-tech insulin pump nor the recombinant-DNA production of human insulin. Instead the relatively low-tech home glucose monitoring and glycohemoglobin determinations have had wider impact on diabetic care and have allowed tight glucose control in a large number of patients. Glycohemoglobin is of particular significance to insurers, both as a screen for diabetes and as a measure of degree of control.

It was in 1971 that Trivelli *et al* reported their observation of an increase in a minor hemoglobin A_{1C}, in the blood of diabetic patients.[4] Hemoglobin A and hemoglobin A_{1C} have identical amino acid sequences, the only difference between the two being the presence of 1-deoxy fructose linked through its carbon number one to the NH2-terminus of the β chain. Hemoglobin A_{1C} comprises 5-7% of the hemoglobin in the blood of normals. In diabetics there can be a two to three-fold increase in this fraction.

Glycosylated hemoglobin fractions can be assayed by ion-exchange chromatography, isoelectric focusing, radioimmunoassay, or colorimetry. On a chromatographic column, the hemoglobins A_{1a}, A_{1b} and A_{1c} are eluted first and are thus dubbed the "fast" hemoglobins. Hemoglobins A_{1a} and A_{1b} are called minor hemoglobins but together they can comprise 5-8% of total hemoglobin. They are also more labile and their susceptibility to acute glucose changes *in vivo* and to improper specimen handling make their measurement a source of inconsistent glycohemoglobin measurements. Only assays that remove or do not measure the labile fractions should be used.[5]

Experience with high performance liquid chromatography (HPLC) indicate that this is a highly reliable assay for hemoglobin A_{1C}.[6] It gives a consistent range for non-diabetics of 4.0 to 6.0% and is less susceptible to the variance caused by measuring the minor glycohemoglobins, Hgb A_{1a} and Hgb A_{1b}. Methodologic differences have significant effects on the measured glycohemoglobin. It is the responsibility of the medical director to know the technique used and the normal range for a particular lab in question.

Hemoglobin A_{1C} is synthesized slowly and irreversibly during the life of the red cell. The total Hgb A_{1C} is a sum of contributions from young red cells with their relatively lower levels of Hgb A_{1C} and the relatively higher levels in older erythrocytes closer to the end of their 120 day lifespan. The glycosylation occurs non-enzymatically and at a rate determined by the ambient blood glucose concentration. The synthesis rate follows acute changes in blood sugar levels, the total Hgb A_{1C} percentage less rapidly and represents a dampened, integrated value for the previous 2-4 months of blood glucose levels.[7]

It is this integral effect that makes Hgb A_{1C} attractive for monitoring diabetic control in outpatients. Blood glucose determinations are only a snapshot of glycemic status at one point in time while the Hgb A_{1C} provides an indication of blood glucose levels for 24 hours a day for the previous 2-4 months. For long term prognosis it also makes sense to follow a value reflecting chronic non-enzymatic glycosylation of a protein since this is thought to be the way in which hyperglycemia causes end-organ damage. Glycohemoglobin levels can also be obtained in the non-fasting state.

For all these same reasons the test is also attractive to insurers. Underwriters can request a hemoglobin A_{1C} to evaluate control and likelihood of complications in a known diabetic. It has been shown that a single objective value for Hgb A_{1C} is superior to the subjective impression of "good control" versus "bad control" even when the clinical judgement is made by medical practitioners experienced in diabetic care.[8] Glycosylated hemoglobin tests can also be an effective screen for unadmitted or undetected diabetes.

Screening: Physicians order tests for reasons that can be grouped into three broad categories:
1) Diagnosis
2) Management
3) Screening

The insurance medical director or underwriter rarely has the opportunity to diagnose an impairment and must leave this to the attending physician who has the advantage of a candid interview, a complete physical and the time to follow a patient's course and pursue an open-ended branching workup.

Medical directors and underwriters do order tests for "management" reasons when they assess the extent and severity of a disease for prognostication. However, most insurance testing today is for screening.

Screening can be categorized as targeted or profiling. Despite the title of "Blood Chemistry Profile" and similar names, the chemistry panels used by the insurance labs are really a combination of targeted screening tests aimed at "case finding" of medical impairments of known significance to insurers.

There are four questions to ask when deciding to use a screen:
1) Is the condition significant? (Are the prevalence, morbidity and mortality significant to an insurer?)
2) Is effective intervention available? (Is there a basis for rating or declining a finding?)
3) Is the screening test effective? (Are the sensitivity, specificity and predictive values acceptable?)
4) Is the screening test effective in routine practice? (Is it practical?)

For an insurer considering whether to screen for diabetes the answer to the first question is obvious. The prevalence of asymptomatic or unadmitted diabetes and the associated mortality and morbidity are all significant.

At the present time, insurers are allowed to rate or decline for diabetes. However, an underwriting action based upon the results of a screen may be appealed and the insurer should be willing to consider the results of a more thorough diagnostic workup done to rule out diabetes. The NDDG recognized that other tests such as a postprandial or a random blood sugar could be used to screen for diabetes but recommended that their protocol be followed for confirmation.[1]

Both the OGTT and the fasting blood glucose can be eliminated as screens for practical reasons. The OGTT is uncomfortable, time-consuming and require special phlebotomy conditions. Fasting specimens also impose special blood drawing constraints and the fasting state is not reliably achieved ("Yes doctor, I skipped breakfast as you instructed. I just stopped for coffee and donuts on my way to your office").

Random glucose levels and glycohemoglobins are practical screens for diabetes. They can be drawn at any time of day without special preparation and without unusual handling requirements. One must then consider their sensitivity, specificity and predictive values.

Screening for Diabetes: The Hgb A_{1C} may actually be a better test for detecting diabetes and predicting its complications than the OGTT. Diabetes is a state of chronic hyperglycemia, what the Hgb A_{1C} measures. The OGTT is a test of physiologic reserve in response to an artificial glucose load, not a real life situation. The OGTT is known to be poorly reproducible and it is unable to predict diabetic complications.

Many studies have shown a strong correlation between Hgb A_{1C} and the degree of glucose tolerance. Most studies have shown considerable overlap in Hgb A_{1C} levels between diabetics, subjects with impaired glucose tolerance and normals. The overlap is especially great in the latter two groups. However, these studies were affected by the inherent difficulties in defining criteria and by less than satisfactory laboratory methods for measuring Hgb A_{1C}.

Dunn *et al* published a study of Hgb A_{1C} values for three groups of outpatients at the Joselin Clinic: 228 subjects referred for an OGTT who also had a Hgb A_{1C} done, 95 diabetic outpatients tested for Hgb A_{1C}, and 121 subjects with a recent normal OGTT had both a fasting glucose who had a Hgb A_{1C} done on two occasions 7 months apart. The older USPHS criteria were used for the OGTT's and they measured only the Hgb A_{1C} fraction of glycohemoglobin. Based on their results, they concluded that "Hgb A_{1C} is highly reproducible and responsive to minor degrees of abnormality of glucose tolerance and may provide an alternative method for defining carbohydrate tolerance or the degree of glucose control."[9]

In fact, their data from Group 1 indicates that Hgb A_{1C} has a poor sensitivity but a fairly high specificity. In 63 of Group 1 subjects the OGTT was abnormal while only 40 of these had an abnormal Hgb A_{1C}. On the other hand, of the 165 with normal OGTT's, 159 also had normal Hgb A_{1C}'s. Using the OGTT as the "gold standard" indicating diabetes, the calculated sensitivity for Hgb A_{1C} is 63% and the specificity s 96%. In this study group with a relatively high prevalence of diabetes, the predictive value of an elevated Hgb A_{1C} was also high at 87%.

From a study of Hgb $A_1(a+b+c)$ levels in 107 normals and 112 patients with overt diabetes, Bolli *et al* concluded that Hgb A_{1C} was highly specific and had a sensitivity of 79%. Their conclusion that the OGTT seems more sensitive than the Hgb A_{1C} in detecting carbohydrate intolerance is an example of the basic difficulty with these studies.[10] If the OGTT is used to define carbohydrate intolerance, then of course it will seem more sensitive and more specific.

Early studies of the efficacy of Hgb A_{1C} were affected by the spectrum bias that resulted from comparing levels in known diabetics with values in known normals or from measuring Hgb A_{1C} in patients referred for OGTT testing. This narrows the spectrum of heterogeneity from individuals at different stages of different stages of developing glucose intolerance and those with comorbid impairments. Results from screening studies are also available.

Orchard *et al* reported on a study of Hgb $A_1(a+b+c)$ as a screen for diabetes in 450 close relatives of diabetic patients. NDDG criteria were used for OGTT's and 8.0% was the upper limit of normal for Hgb A_1. They found that the Hgb A_1 was elevated in only 37% of those with diabetic OGTT responses. Of those with either diabetes or impaired glucose tolerance by OGTT, 25% had elevated Hgb A_1's. Again the specificity for Hgb A_1 was high at 98%. They concluded that Hgb A_1 was too insensitive a measure to be used to screen for diabetes.[11]

Hgb $A_1(a+b+c)$, fasting plasma glucose, and a single post-load glucose were used to screen a large population for diabetes. Modan *et al* found that none of the shortcut methods fared very well. The subjects for Hgb A_1 evaluation were 1058 of the participants in the Israel Study of Glucose Intolerance, Obesity and Hypertension. Both NDDG and WHO criteria were used for OGTT's. The authors found that HbA_1 had no advantage over a fasting blood sugar alone in screening for diabetes. Their cost/benefit analysis indicated that a full OGTT was the best method for detecting diabetes or glucose intolerance (as defined by OGTT) in a general population.[12]

In considering the conclusions of the Bolli, Orchard and Modan studies, one should note that their lab methods measured the labile fractions of glycosylated hemoglobin, Hgb $A_1(a+b+c)$, as well as Hgb A_{1C}. Their data support the position of the American College of Physicians that only tests that remove or do not measure the labile glycohemoglobin fractions should be used.[5]

Hgb A_{1C} alone measured by low-pressure liquid chromatography (nl range 4.0 to 6.0%) and OGTT (WHO criteria) has been used to screen for diabetes in 333 volunteers. Simon *et al* found a sensitivity of 60% and a specificity of 91% for Hgb A_{1C} testing.[13]

Recently, Little *et al* published their experience with screening 381 Pima Indians for diabetes using both the OGTT and a Hgb A_{1C}. The Hgb A_{1C} was measured by high-performance liquid chromatography and the normal range was 4.07 to 6.03% based upon results from non-diabetic Caucasians. The WHO criteria were used to separate the study population into three groups: normal, impaired glucose tolerance and diabetes. They found the Hgb A_{1C} to have a specificity of 91% while the sensitivity was 85% for diabetes and 30% for impaired glucose tolerance.[14] While these results are excellent, it must be remembered that the Pima Indians not only have a high prevalence of diabetes but also are a unique population in terms of metabolic disorders.

Of special interest is a screening program based on a random glucose and glycohemoglobin reported by Ferrell *et al*. They used total glycohemoglobin, Hgb $A_1(a+b+c)$, measured by the less accurate microcolumn technique but their protocol was otherwise similar to that used by many insurers. Subjects were randomly selected from an area in Starr County, Texas as part of an ongoing study of adult onset diabetes among Mexican-Americans in the lower Rio Grande Valley. Demographic data, medication and diabetic history and a capillary blood sample were obtained from all subjects. If the casual blood glucose was greater than 130 mg/dl then a four-hour fasting blood glucose was obtained. If this was greater than 130mg/dl, then a formal OGTT was done using NDDG criteria. Hgb A_1 was obtained from all subjects. Thus the study protocol categorized subjects as known diabetics (by history), newly diagnosed diabetics (by OGTT), or non-diabetics. Diabetics with no history and a random blood glucose less than 130mg/dl were not detected.

The authors reported their sensitivity and specificity findings not as single parameters but graphically as continuous functions thus allowing the reader to evaluate the effect of using different cutpoints. For their study the optimal cutpoint for Hgb A_1 was 8.0% where the sensitivity and specificity curves intersected at 87%. The optimal cutpoint for using a casual blood glucose alone was at 130mg/dl where the sensitivity and specificity were 80%.[15]

However, the individual optimizing cutpoints could be replaced by different cutpoints to optimize a sequential protocol. From their data a cutpoint of 115mg/dl for the random blood glucose would result in a 93% sensitivity and a 50% specificity for that test. Choosing a 9.0% cutpoint for the Hgb A_1 would give a sensitivity of 74% and a specificity of 98% for glycohemoglobin testing. A screening protocol could consist of a random glucose followed by a Hgb A_1 for glucoses over 115mg/dl. If used to screen a group of 100,000 individuals with a diabetes prevalence of 5%, this protocol would yield the following results: 4,650 diabetics and 47,500 non-diabetics would be abnormal by the confirmatory Hgb A_1 resulting in a positive predictive value of 78%. The cost of this screening program would be extraordinarily high because over half of the population would be tested for Hgb A_1.

In actual practice such a protocol is likely to be a more efficient screen than the above scenario suggests. The laboratory used by the Mutual Life Insurance Company of New York measures only the Hgb A_{1C} fraction of the glycohemoglobin and the measurement is done by the highly accurate HPLC. Out of 9,150 consecutive glucoses done for MONY, 780 (8.5%) were over 115mg/dl. Of these 709 also had Hgb A_{1C}'s. Of the Hgb A_{1C}'s, 138 (19.5%) were greater than 6.0% (upper limit of normal) and 45 (6.3%) were greater than 9.0%. Considering the total cost of blood testing, the marginal increase attributable to diabetic screening is only 2%. Work is under way to determine the sensitivity of this testing for a large number applicants whose diabetic or glucose tolerance is known.

Conclusions: The various laboratory tests used to detect diabetes and predict its complications are still controversial. While the OGTT carries the force of tradition and official sanction, the Hgb A_{1C} may actually be the better test. In any case, the random blood glucose and the Hgb A_{1C} are the only practical tests available to insurers for large-scale screening. The prevalence, mortality and morbidity of diabetes are significant to insurers, enough to make diabetes screening a serious consideration. Hgb A_{1C} testing by accurate methods is highly reliable and an elevated result is highly specific for diabetes. A medical director can design a screening protocol that is cost effective and has a high predictive value by choosing appropriate cutpoints for the random glucose and the Hgb A_{1C}. Without our current understanding of Hgb A_{1C}, one must remain open to appeal from those who are normal by glucose tolerance testing.

An opportunity exists for life insurance medical directors to provide important data to our clinical colleagues. Over 500,000 blood tests are being performed by life insurers each year and this volume is not likely to drop in the near future. Most of these lab exams include a glucose and many also have a Hgb A_{1C}. Demographic data is available in all cases and many applications will include a detailed medical statement. Insureds will be followed to mortality and morbidity end-points. It is our responsibility to use this data to help answer some of the questions surrounding diabetes definition and detection.

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