Use of Glycated Hemoglobin and Microalbuminuria in the Monitoring of Diabetes Mellitus

Summary

Overview

Clinical testing to assess levels of disease control and progression among persons with type 1 and type 2 diabetes mellitus is widely recommended to clinicians to improve patients' clinical outcomes. Two important foci of recommendations for the followup care of individuals with diabetes include monitoring of glycemic status by measurement of glycated hemoglobin (GHb) and screening for kidney disease with urine albumin to assess overall disease progression and to detect potential progression toward end-organ damage. According to the American Diabetes Association's Clinical Practice Recommendations, monitoring of glycemic status is considered a cornerstone of diabetes care and affects how physicians and patients adjust medical therapy as well as behavioral therapy (e.g., diet and exercise). Screening for urine albumin among persons with diabetes is also widely recommended for the detection and treatment of incipient diabetic nephropathy and affects the physician's implementation of therapy to slow progression of kidney disease.

Despite widespread recommendations for screening of persons with diabetes for both glycemic control and urine albumin, there has not been a systematic assembly of the literature to assess the risk relation between tests assessing long-term glycemic control or tests assessing the presence of microalbuminuria with cardiovascular, peripheral vascular, renal, and neurological outcomes (all of which represent end-organ effects of long-term diabetes). The report from which this summary was developed was commissioned by the American Association of Clinical Chemistry; it systematically reviews the literature identifying the risk relation between testing for glycemic control or urine albumin and these important clinical outcomes.

Glycemic Control

The advent of self-monitoring of blood glucose (SMBG) has allowed patients to attain glycemic goals more quickly and has revolutionized the care of individuals with diabetes mellitus; however, it does not provide information regarding glycemic control over an extended period of time. Measurement of glycated hemoglobin, which first began in the 1970s, has become the preferred method of assessing long-term glycemic control. Of the various GHb fractions, HbA1c is the preferred standard for measuring glycemic control over the previous 2-3 months. The American Diabetes Association began to make treatment recommendations based on HbA1c following publication of the results of the Diabetes Control and Complications Trial (DCCT) in the 1990s. The HbA1c has become the gold standard for the therapeutic management of diabetes mellitus in research and in the clinical setting.

Glycated hemoglobin testing gives an assessment of long-term glycemic control; but what other prognostic information does it provide in the management of individuals with diabetes mellitus? Several large, randomized clinical trials have demonstrated that intensive glycemic control prevents the development and progression of long-term diabetic microvascular complications. In these studies, glycemic goals were assessed using glycated hemoglobin as the measure of long-term control. Long-term hyperglycemia, as measured by glycated hemoglobin, is clearly related to the

development of diabetic microvascular complications; however, its relation to the development of macrovascular complications is less clear. The relation of glycemic control and cardiovascular disease (CVD) in individuals with diabetes remains controversial, with some studies demonstrating a positive association and others showing no association. Another important issue that is still an area of active investigation in the management of diabetes relates to whether there is a threshold effect of glycated hemoglobin for microvascular and/or macrovascular complications. The issue of a threshold effect of glycated hemoglobin has important implications for where the HbA1c treatment targets are set to prevent diabetic complications.

Urine Albumin

Screening tests for microalbuminuria are recommended annually for patients with type 1 diabetes of greater than 5 years duration and for all patients with type 2 diabetes from the time of diagnosis. Twenty-four hour collection of urine for quantitative assessment of urinary albumin excretion rate is currently considered the gold standard measurement of microalbuminuria. However, this method is frequently considered to be cumbersome and difficult to carry out in the outpatient clinical setting, and it is subject to timing and collection inaccuracies. Several other methods of testing, which are considered less difficult to perform in outpatient settings, have been studied and have been demonstrated to have varying degrees of correlation with 24 hour urine collection for the detection of urinary albumin. These include random or "spot" testing of a morning urine specimen for urine albumin concentration or albumin-to-creatinine ratio, overnight or "timed" urine collections for estimation of albumin excretion rates, and dipstick testing. While many experts now support the use of random or first morning tests for urinary albumin-to-creatinine ratio as a convenient and accurate approach to screening patients, there is currently no clear consensus on standardized testing methods.

In a variety of prospective studies, elevated urinary albumin excretion has been shown to be associated with increased risk of progression of kidney disease toward end-stage renal disease (ESRD) as well as increased cardiovascular morbidity, cardiovascular mortality, and total mortality. However, few studies have systematically ascertained the magnitude of increase in both renal and cardiovascular risk associated with microalbuminuria among persons with type 1 and persons with type 2 diabetes. Moreover, although observations of renal and cardiovascular outcomes among persons classified as having microalbuminuria by currently accepted standards have been reported, it remains unclear whether current definitions of microalbuminuria are optimal in terms of predicting renal and cardiovascular outcomes. It is unclear as well whether there is a dose-relationship or threshold effect in prediction of outcomes

associated with urinary albumin excretion. Knowledge of the pooled magnitude of risk associated with current definitions of microalbuminuria in addition to an improved understanding of the risk relationship of varying levels of baseline albuminuria with cardiovascular and renal outcomes could have important implications in screening and treatment recommendations for persons with diabetes.

Reporting the Evidence

This report addresses the following key questions in persons with type 1 and type 2 diabetes mellitus:

Glycemic Control

1. *What is the risk relationship between glycated hemoglobin and the subsequent risk of microvascular diabetic complications (retinopathy, nephropathy, neuropathy)?*
2. *What is the risk relationship between glycated hemoglobin and the subsequent risk of macrovascular diabetic complications (coronary artery disease, cerebrovascular disease, peripheral arterial disease)?*

Urine Albumin

1. *What is the risk relationship between microalbuminuria and renal function?*
2. *What is the risk relationship between microalbuminuria and cardiovascular disease and death?*

Methodology

The Evidence-based Practice Center (EPC) recruited six technical and community experts to provide input into the definition of the key questions and to review a draft of the report. The EPC also recruited representatives from a range of other stakeholder organizations to serve as peer reviewers of the draft evidence report. These stakeholder organizations included organizations of physicians, allied health professionals, and third party health care payers in addition to consumer organizations.

Because of the divergent content of questions related to glycemic control and urine albumin, two separate teams of investigators systematically reviewed literature in these two areas. Investigators from each team executed systematic search strategies pertinent to each set of questions. Thus, search strategies and studies identified were different for questions on glycemic control and urine albumin.

Glycemic Control

Articles published in the English language from 1966, when MEDLINE® began indexing, to April 2002 were accessed through PubMed® using MESH and text words for glycated hemoglobin, diabetes, and individual diabetic complications,

including retinopathy, nephropathy, neuropathy, and cardiovascular disease.

Reviewed studies were restricted to prospective longitudinal cohort studies, non-concurrent prospective cohort studies, and clinical trials that had data on GHb exposure and outcome data on individual microvascular and macrovascular complications during at least 1 year of followup in at least 50 participants with type 1 and type 2 diabetes. Because the investigators were interested in determining the risk relationship between GHb exposure and microvascular and macrovascular complications and in re-examining whether a threshold exists for this relationship, only studies that reported prospective, quantitative risk data (i.e., incidence rates, regression coefficients with standard errors reported separately, relative hazards, relative odds, relative risk) were included. Retrospective case-control studies that reported and compared previous GHb values in individuals with a given outcome versus those without a given outcome were excluded. Articles that reported data in graphical form in which specific quantitative values could not be determined were excluded.

Other exclusion criteria included review articles, animal or in vitro studies, non-English language, and studies in which the design was unclear.

Exposure Variables

Glycated hemoglobin—Data were abstracted on the biochemical method of measurement, whether the method was traceable to the DCCT standard and/or whether the lab was certified by the National Glycohemoglobin Standardization Program (NGSP), and how glycated hemoglobin was reported (i.e. HbA1c, HbA1, total GHb).

Diabetes mellitus—Data were extracted on the type of diabetes that study participants had and the method of diagnosis/confirmation.

Outcome Variables

Microvascular Outcomes

- Retinopathy—Incident retinopathy was defined as new onset retinopathy, progression of pre-existing retinopathy, cataract extraction, incident macular edema, need for focal or scatter photocoagulation, blindness, or change in visual acuity.
- Nephropathy—Incident nephropathy was defined as development of microalbuminuria and progression of nephropathy as progression from microalbuminuria to macroalbuminuria or progression to ESRD requiring renal replacement therapy. Other nephropathy outcomes included change in glomerular filtration rate/creatinine clearance.
- Neuropathy—Data on peripheral and autonomic neuropathy were recorded. Peripheral neuropathy was

defined as an abnormal neurological exam, subjective symptoms, abnormal biothesiometry, or abnormal nerve conduction study. Autonomic neuropathy was defined as abnormal R-R interval, orthostatic hypotension, or resting tachycardia.

Macrovascular Outcomes

- Coronary artery disease (CAD)—CAD morbidity was defined as non-fatal myocardial infarction, angina, ischemic heart disease, congestive heart failure secondary to ischemic heart disease, coronary artery bypass surgery, and angioplasty. CAD mortality was defined as fatal myocardial infarction or sudden cardiac death.
- Cerebrovascular disease—Cerebrovascular morbidity was defined as non-fatal stroke, transient ischemic attack, or need for carotid endarterectomy. Cerebrovascular mortality was defined as fatal stroke.
- Peripheral arterial disease (PAD)—PAD was defined as claudication, peripheral revascularization procedure (angioplasty, bypass surgery, stenting), gangrene, limb amputation, decreased ankle-brachial index, and decreased arm-toe gradient.
- Others—Outcome data were collected on congestive heart failure not related to ischemic heart disease and presence of atherosclerosis (i.e. carotid intimal-medial thickness, abdominal aortic aneurysm).

Urine Albumin

Articles published in the English language from 1966 to April 2002 were identified by searching PubMed® using MESH and text words for diabetes, proteinuria, and cardiovascular or renal outcomes. To obtain additional references not otherwise identified through the electronic search, the investigators searched bibliographies of relevant primary and review articles from the electronic search.

After identification of citations through PubMed®, all abstracts were reviewed for relevance by a single abstractor. All articles to be potentially included in the final review underwent double review by study authors for data abstraction. Differences in opinion were resolved through consensus adjudication. Data abstracted included the following: 1) study design, 2) study location, 3) numbers of study subjects enrolled, 4) study exclusion criteria, 5) type of diabetes studied and numbers of persons with each type of diabetes included in study, 6) measurement and definitions of microalbuminuria, 7) descriptive information about study participants (including age, gender, race, duration of diabetes, glycemic control, baseline diastolic and systolic blood pressure), 8) baseline and followup measures of urinary albumin excretion, and 9) baseline and followup measures of kidney function (e.g., serum creatinine, creatinine clearance, or direct measurement of glomerular filtration rates). For randomized controlled trials featuring

medication interventions (e.g., ACE inhibitors vs. other anti-hypertension agents), the type of medication, dose, and frequency were also recorded.

Exposure Variables

- Urine albumin—Data were abstracted on the biochemical method of urine measurement, including the timing of urine specimens and the cutoffs used to define different levels of urine albumin exposure at baseline. Microalbuminuria was classified according to the method of ascertainment in each study. Studies reporting only on persons with macroalbuminuria (levels greater than those defined above, unless authors defined microalbuminuria in some other fashion) were excluded from analysis.

- Diabetes mellitus—Data were extracted on study participants' type of diabetes and the reported method of diagnosis/confirmation of diabetes within each study.

Outcome Variables

- Renal outcomes—Outcomes reflecting decline in renal function over time were divided into eight categories: 1) change in glomerular filtration rate (GFR) at end of study, 2) rate of change in GFR, 3) change in creatinine clearance at end of study, 4) rate of change in creatinine clearance, 5) change in 1/serum creatinine at end of study, 6) rate of change in 1/serum creatinine, 7) doubling of serum creatinine, or 8) need for renal replacement therapy, including dialysis and transplantation.

- Cardiovascular outcomes—Cardiovascular outcomes were defined as: 1) incidence of all cause death, 2) incidence of composite CVD deaths, 3) incidence of death due to myocardial infarction, 4) incidence of death due to cerebrovascular accident, 5) incidence of CVD morbidity, and 6) incidence of composite CVD morbidity and mortality.

Coronary artery disease, cerebrovascular disease, peripheral arterial disease, and other outcome variables (congestive heart failure not related to ischemic heart disease and presence of atherosclerosis) are the same as described for glycemic control (see above).

Data Abstraction and Analysis

Two investigators reviewed titles and abstracts of identified articles and appropriate studies were selected for data abstraction. Articles chosen for abstraction were reviewed by two reviewers to ensure that all relevant data had been obtained and were correct.

Findings

Glycemic Control

1. What is the risk relationship between glycated hemoglobin and the subsequent risk of microvascular diabetic complications (retinopathy, nephropathy, neuropathy) in individuals with type 1 and type 2 diabetes?

- The evidence reported supports a strong, graded relation between GHb exposure and the risk of two major microvascular complications of type 1 and type 2 diabetes, retinopathy and nephropathy. These patterns are observed for various measures of glycated hemoglobin (i.e., HbA1c, HbA1, and total GHb).

- The preponderance of the evidence from cohort studies shows a strong relation between glycated hemoglobin and incident retinopathy, incident proliferative retinopathy and macular edema, and progression of retinopathy. Compared to the lowest categories of GHb exposure, the unadjusted relative risks for incident retinopathy were 4 to 7 times greater in the highest categories of GHb exposure for type 1 diabetes and 1.5 to 2.5 times greater in individuals with type 2 diabetes. The unadjusted relative risk for proliferative retinopathy was 6 to 7 times greater in individuals in the highest category of GHb exposure compared to the lowest category for individuals with type 1 diabetes, and the unadjusted relative risk was 3 to 13 times greater for individuals with type 2 diabetes although fewer studies examined this outcome in type 2 diabetes.

- This relation between GHb exposure and retinopathy is confirmed in several randomized clinical trials of individuals with type 1 and type 2 diabetes, which show comparable risk reductions in these outcomes in individuals randomized to intensive therapy, where the HbA1c levels were maintained at approximately 7 percent, compared to individuals randomized to conventional therapy, where the mean HbA1c levels were maintained at approximately 9 percent.

- Only a few studies address the relation between glycated hemoglobin and the risk of blindness; however, the majority suggest that increased glycated hemoglobin is a risk factor for blindness in individuals with type 1 diabetes. With the exception of one cohort study and one clinical trial, there are virtually no data on the relation between glycated hemoglobin and risk of blindness in individuals with type 2 diabetes.

- There are very few studies examining the relation between glycated hemoglobin and the incidence of cataracts.

- The majority of studies evaluating the relation between glycated hemoglobin and the risk of nephropathy have

evaluated the risk of developing microalbuminuria. These data show a strong and significant relation between glycated hemoglobin and the risk of microalbuminuria in individuals with type 1 and type 2 diabetes. Compared to individuals in the lowest category of GHb exposure, those in the highest category had an unadjusted increased risk of microalbuminuria that was 3 to 9 times greater for type 1 diabetes and an increased risk of microalbuminuria that was 1.4 to 8 times greater for type 2 diabetes. This is supported by clinical trial data that show significant risk reductions for incident microalbuminuria for individuals randomized to intensive glycemic control, where, as noted above, the mean HbA1c levels were maintained at approximately 7 percent, compared to those randomized to conventional glycemic control, where the mean HbA1c levels were maintained at approximately 9 percent. Among individuals with type 1 diabetes, the unadjusted relative risk reductions were 34 percent to 43 percent, compared to 60 percent to 74 percent for individuals with type 2 diabetes.

- Although fewer data exist on the relation between glycated hemoglobin and risk of macroalbuminuria and on the relation between glycated hemoglobin and the risk of nephropathy progression, several cohort studies and clinical trials support a strong and significant positive association in individuals with type 1 and type 2 diabetes.

- The only studies identified by the search strategy and inclusion criteria examining the effect of GHb exposure on GFR were cohort studies conducted in individuals with type 1 diabetes. All studies consistently demonstrated that increasing levels of glycated hemoglobin were associated with a decline in GFR. There are no clinical trial data examining the GFR outcomes and no data on the relation between glycated hemoglobin and GFR in individuals with type 2 diabetes.

- Very few studies examined the association between glycated hemoglobin and the risk of ESRD.

- Among individuals with type 1 diabetes, there appears to be a strong, positive association between glycated hemoglobin and the risk of peripheral neuropathy in both cohort studies and clinical trials; however, the evidence of an association between glycated hemoglobin and peripheral neuropathy in individuals with type 2 diabetes yields conflicting results.

- There are fewer data on the association between glycated hemoglobin and the risk of autonomic neuropathy. In individuals with type 1 diabetes, there appears to be a positive association. There are also very limited data on the relation between glycated hemoglobin and the risk of autonomic neuropathy in individuals with type 2 diabetes.

2. *What is the risk relationship between glycated hemoglobin and macrovascular diabetic complications (coronary artery disease, cerebrovascular disease, and peripheral arterial disease) in individuals with type 1 and type 2 diabetes?*

- In the cohort studies evaluating cardiovascular outcomes in individuals with diabetes, there was a positive association with GHb exposure; however, the risk estimates are much smaller compared to the risk estimates for the microvascular complications.

- The preponderance of the evidence from cohort studies shows a positive association between glycated hemoglobin and risk of fatal and non-fatal coronary artery disease, particularly among individuals with type 2 diabetes. Compared to those in the highest category of GHb exposure, the unadjusted risk of fatal and non-fatal coronary artery disease was 50 percent to 70 percent (relative risk, 1.5 to 1.7) greater than for those in the lowest category of exposure.

- There are few data on the relation between CAD and glycated hemoglobin among individuals with type 1 diabetes; however most studies have shown a positive association.

- The relation between glycated hemoglobin and the risk of PAD appears to be strong and positive in individuals with type 1 and type 2 diabetes. Compared to those in the lowest category of GHb exposure, the unadjusted risk of PAD was 5 to 6 time greater in individuals in the highest category of exposure among individuals with type 1 diabetes, and the risk was 2 to 4 times greater among individuals with type 2 diabetes.

- The risk relationship between cerebrovascular disease and glycated hemoglobin, which has only been examined among individuals with type 2 diabetes, is less clear.

- There are very few data on the relation between GHb exposure and congestive heart failure or subclinical atherosclerosis, assessed by carotid intimal-medial thickness, making it difficult to draw any conclusions regarding these outcomes.

- Only a few studies have examined the presence of a threshold effect of glycated hemoglobin on the risk of developing diabetic complications (i.e. a level of glycated hemoglobin above which there is a non-constant or exponential increase in risk of complications). The majority of these studies have not found a threshold effect for retinopathy and nephropathy outcomes but, rather, have demonstrated a continuous risk of complications with increasing GHb levels. There are very few studies that have attempted to examine the

presence of a threshold effect of glycated hemoglobin on neuropathy and macrovascular outcomes.

Urine Albumin

1. What is the risk relationship between microalbuminuria and renal function?

- Eleven studies reported on this question. The analyses had important limitations including broad variation in methods of assessing levels of urine albumin excretion as well as substantial heterogeneity in reporting of renal outcomes.
- The preponderance of evidence suggests that the presence of microalbuminuria at baseline is associated with progression of chronic kidney disease.
- The relation of urine albumin excretion at baseline to progression of chronic kidney disease appears graded; higher levels of urine albumin excretion at baseline are associated with a greater magnitude of decrease in renal function as well as a faster rate of decline in renal function over time.

2. What is the risk relationship between microalbuminuria, cardiovascular disease, and death?

- Nineteen studies reported on cardiovascular morbidity and mortality, and 24 reported on all-cause mortality. The analyses had important limitations including broad variation in methods of assessing levels of urine albumin excretion as well as few studies focusing on disease-specific cardiovascular morbidity or mortality.
- The preponderance of evidence from these studies demonstrates an association between microalbuminuria at baseline and increased risk of cardiovascular morbidity, cardiovascular mortality, and all-cause mortality.
- The relation of urine albumin excretion at baseline to cardiovascular morbidity, cardiovascular mortality, and all-cause mortality appears graded; greater levels of urine albumin excretion at baseline are independently associated with a greater magnitude of risk of cardiovascular morbidity, cardiovascular mortality, and all-cause mortality over time.

Future Research

For research on glycemic control, future cohort studies and clinical trials should focus on studying the relation between GHb exposure and the risk of macrovascular complications. Fewer data are available on these outcomes than on microvascular outcomes; however, more data are also needed on the relation between glycated hemoglobin and the risk of neuropathy, particularly the risk of peripheral and autonomic neuropathy in individuals with type 2 diabetes.

For research on urine albumin, future work should seek to define the optimal and most feasible tests for measuring microalbuminuria and to standardize measurement of microalbuminuria. Future research should also characterize the nature of the relation (e.g. threshold versus linear) between microalbuminuria and outcomes. In addition, further work is needed to understand whether currently accepted definitions of microalbuminuria are optimal in predicting future renal and cardiovascular outcomes.

Extension of research in both these areas has important future implications for gaining improved understanding of the role of glycemic control in the prevention of the cardiovascular sequelae as well as for future development of guidelines for screening practices among persons with type 1 and type 2 diabetes mellitus.

Ordering Information

The full evidence report from which this summary was taken was prepared for AHRQ by the Johns Hopkins Evidence-based Practice Center, Baltimore, MD, under contract No. 290-97-0006. It is expected to be available in late summer 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 84, *Use of Glycated Hemoglobin and Microalbuminuria in the Monitoring of Diabetes Mellitus.* Internet users will be able to access the report online through AHRQ's Web site at www.ahrq.gov.