GLUCOSURIA AS A MORTALITY RISK PREDICTOR WHEN BLOOD IS NOT COLLECTED

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Executive Summary *A 12-year follow-up mortality study of 1,857,902 insurance applicants tested for urine glucose shows that increasing glucosuria is associated with increasing mortality risk, as well as increasing serum glucose and fructosamine levels. The mortality relationship is age-dependent but remains little changed when the analysis is limited to those who deny a history of diabetes. In situations where urine is the only body fluid obtained, urine glucose levels are an effective risk predictor.*

Currently, 3.6% of samples processed by Clinical Reference Laboratory (CRL) are urines collected without blood that are typically associated with lower face amount business (average face amount is $194,500). Such business rarely requires routine medical records; for-cause medical records or additional testing is uncommon. Though the underwriting of most urine tests (regardless of whether blood is or is not included) may not vary, urine glucose is an exception. When blood is available, serum glucose, glycated protein (such as fructosamine) or a reflexed HbA1c helps in making a decision. When blood results are absent, more reliance must be placed on the urine glucose results.

Glucose may appear in the urine as a result of episodic or chronic serum glucose elevation, or because that applicant's "renal threshold" for spilling sugar into the urine is exceeded. The average threshold for serum glucose spilling into the urine is around 160 mg/dL, but varies widely; it might be as low as 120 to 130 mg/dL or range much higher.[1]

How much mortality risk is actually associated with glucose in the urine, referred to as glucosuria or glycosuria? Do positive tests for urine glucose indicate chronically elevated serum glucose levels sufficient to elevate the HbA1c to 6% or higher (increasing mortality risk), or do most of these positive urine tests for glucose simply represent applicants with low renal thresholds for glucose (not increasing mortality risk)? At what level of glucosuria is mortality risk elevated? Such information is missing from the medical literature where glucosuria has long been an indication for evaluation of serum glucose, but is not further used for risk stratification.

How the Study Was Done

The authors conducted a study using CRL's data to answer these questions. In this study, 1,857,902 insurance applicants age 20 and up who were tested from 1993 to 1997 were followed up for mortality in 2007 using the Social Security Death Master File. There were 61,200 deaths, and median follow-up was 12 years (range 0 to 14 years).

Mortality ratios were calculated with Cox regression comparing those without glucosuria (the reference group) to those with various levels of glucosuria based on the 1993-1997 study population. Mortality ratios were calculated separately for men and for women; each group was further split into two age bands (20 to 59, 60+). The Cox regression analyses included age and level of glucosuria as variables. Analysis was also performed (not shown) using further age divisions but was not more informative than the two age bands reported in this study.

Unfortunately, no information regarding a self-disclosed history of diabetes was available for the 1993-1997 study population, so a second group of 3,072,274

applicants age 20 and up tested from 2003 to 2005 (when this history was obtained) and followed to 2008 was also studied. Because this second study population was tested more recently with a median follow-up of only 4 years, there were fewer deaths (19,624) contributing to the mortality ratio analysis.

We were unable to meaningfully split the 2003-2005 analysis into demographic subgroups because of the small number of deaths within some subgroups. Analysis split by history of diabetes was conducted using Cox regression including age, sex and level of glucosuria as variables. Because of fewer deaths and a shorter follow-up duration, results from this more recent study population should be considered only as a supplement (contributing information about history of diabetes) and confirmation of the earlier, larger 1993-1997 population study.

Finally, median values for both serum glucose and fructosamine were compared to urine glucose findings based on the 1993-1997 applicant population.

What the Study Found

Table 1 shows the relative mortality by urine glucose level obtained using Cox regression analysis split by the four demographic subgroups. It demonstrates that glucosuria presents a substantial extra mortality risk. The relative risk increases further as the urine glucose level increases, but at a slower rate for urine glucose values >.5 g/dL. Even for glucosuria <=.5 g/dL, the mortality ratio exceeded 150% for all demographic subgroups.

We found differences in the magnitude of extra mortality associated with glucosuria between the sexes and by age. These differences are very similar to what we found in our analyses of mortality risk associated with HbA1c results.[2] The relative mortality impact is greater among those 20 to 59, and in this age group the impact is greater for women. The number of deaths and duration of follow-up were sufficient to provide relatively narrow 95% confidence intervals for all four demographic subgroups.

In the more recent 2003-2005 study population, we found that of all applicants with glucosuria, 34% also admitted a history of diabetes, 56% denied such history, and 10% did not answer the question. The median age of the total 2003-2005 study population was 42 years, with 41 years as the median age of those denying a history of diabetes, and 52 years the median age of those admitting a history of diabetes. Table 2 looks at those applicants with glucosuria who denied a history of diabetes relative to those in this group who did not have glucosuria.

Explanation of Cox Regression

The mortality analysis in this study was done by using Cox regression (Cox proportional hazards) which is the most commonly used outcome modeling tool in medical research. It is popular because it: (a) views the outcome of interest (death in this case) by duration so all entrants (i.e., insurance applicants who were tested over many years and might have died in the interim) can be included together; and (b) allows for entering multiple variables such as age, sex and laboratory results, creating proportional hazard ratios indicating the relative contribution of each variable to the outcome. It enables one to draw useful conclusions using limited numbers of lives who joined the study at various points, and who have multiple conditions that may also affect the outcome in addition to the variable in question.

Cox regression creates an average risk (hazard ratio) for death or other endpoint across all the lives studied. If the impact of the test actually varies by age and sex, unless the study is split into separate analyses, the differences will be lost. It also requires that the variables be independent of one another to correctly apportion risk. Obviously, many potential variables are not independent, such as age and average serum blood sugar; as age increases, so does average serum glucose. This can be overcome (but only if recognized) by splitting the analysis into different bands of sex, age, etc. Wide 95% confidence intervals for resulting hazard ratios (including mortality ratios) are the result of insufficient numbers of outcomes (i.e., deaths) occurring. Other limitations apply as well.

The Cox regression results shown in Table 2 included age and sex as variables in the analysis. The results are very similar in magnitude to the relative mortality seen at ages 60+ in Table 1, and only slightly less than those seen for ages 20 to 59. Applicants who deny a history of diabetes would presumably include all those who might have normal serum glucose levels and a low renal threshold for spilling glucose into the urine. Based on the mortality ratios, most of this group was likely to have had elevated serum glucose levels because excess risk was present, rather than a low renal threshold which would not likely be associated with excess mortality.

This 2003-2005 study population also allowed us to look at the mortality impact of glucosuria when a history of diabetes is admitted, using Cox regression analysis including urine glucose level, age and

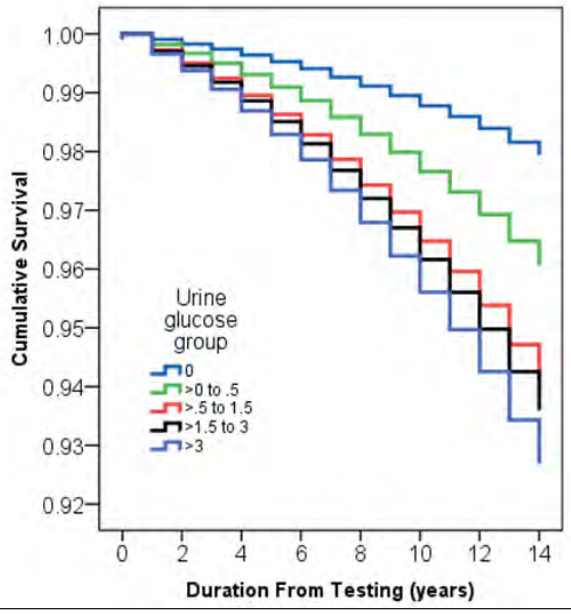
Table 1. Mortality Ratios for Urine Glucose Groups by Age and Sex, Using Cox Regression

Urine Glucose (g/dL)	Number of Deaths	Total Population	Mortality Ratio (%)	Lower 95% CI (%)	Upper 95% CI (%)
Females 20 to 59					
0 (reference)	6,800	578,982	100	---	---
>0 to .5	362	13,651	217	195	241
>.5 to 1.5	86	1310	378	305	467
>1.5 to 3	80	850	528	423	659
>3	189	1,904	594	514	687
Males 20 to 59					
0 (reference)	20,989	1,041,406	100	---	---
>0 to .5	1,222	23,500	193	182	204
>.5 to 1.5	366	4,262	292	263	324
>1.5 to 3	281	3,035	318	283	358
>3	610	6,325	365	337	396
Females 60+					
0 (reference)	9,468	65,509	100	---	---
>0 to .5	540	2,160	181	166	197
>.5 to 1.5	118	406	237	198	284
>1.5 to 3	72	245	244	194	308
>3	110	366	249	206	300
Males 60+					
0 (reference)	17,256	104,714	100	---	---
>0 to .5	1,579	5,944	169	161	178
>.5 to 1.5	405	1347	203	184	224
>1.5 to 3	285	859	230	205	259
>3	382	1,127	244	221	271

Table 2. Mortality Ratios for Urine Glucose Groups Who Deny a History of Diabetes, Using Cox Regression

Urine Glucose (g/dL)	Number of Deaths	Total Population	Mortality Ratio (%)	Lower 95% CI (%)	Upper 95% CI (%)
0 (reference)	14,831	2,608,325	100	---	---
>0 to .5	374	29,269	184	166	204
>.5 to 1.5	55	3,031	213	163	277
>1.5 to 3	31	1,893	214	150	304
>3	73	3,756	295	235	372

Figure 1. Survival by Urine Glucose Group for Males 20 to 59



sex as variables. The relative risk compared to those admitting to diabetes but without glucosuria (3/4 of the group) was approximately 150% for those with urine glucose >0 to .5 g/dL, 200% for those >.5 to 3 g/dL, and 275% for those >3 g/dL.

Figure 1 above confirms that increased risk (as measured by survival over time) is stable from the first year through the 14th year of follow-up. Because each survival curve (representing a particular level of glucosuria) maintains a consistently proportional distance from other curves for each year of follow-up, a single mortality ratio adequately represents the risk for all durations after testing. Figure 1 also shows the large differences in survival between those without glucosuria, those with glucosuria in the range of >0 to .5 g/dL, and all those with higher levels where mortality is very similar.

Figure 2 (right) provides a comparison of urine glucose levels and corresponding median values for serum glucose and fructosamine, which increase in tandem. However, because of variability in factors affecting serum glucose levels (time of day, time of last meal, renal threshold, and time to separating off the serum), the association of these findings in any particular applicant may often be different.

The lowest level of glucosuria correlates with a fructosamine level of approximately 2 mmol/L and a serum glucose of around 100 mg/dL. This suggests that glycolysis associated with delayed centrifugation of the blood is common, which results in artifactually low serum glucose levels. Fructosamine standardization also varies by laboratory and may vary between that in use during the study and current results.

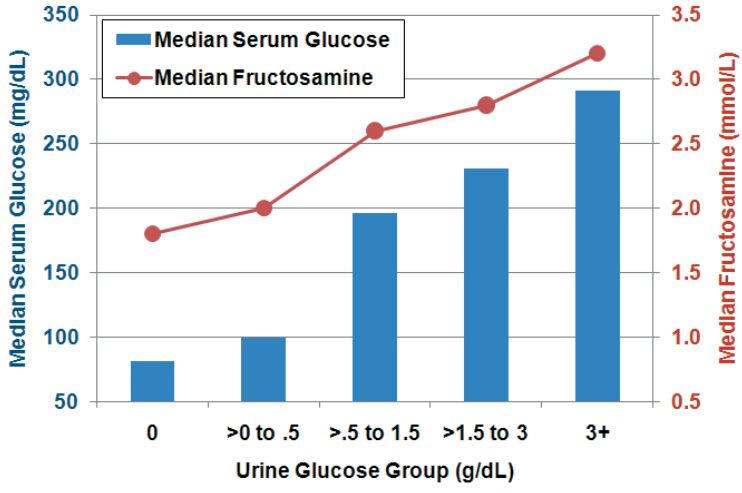
What Do the Study Results Contribute to Risk Assessment?

This is the first study known to the authors that looks at mortality associated with various levels of glucosuria. Since some insurance products require only a urine sample (with no further evaluation possible because there is no subsequent blood draw), an understanding of this relationship is vital.

Glucosuria alone (without further investigation) is associated with substantial extra mortality across age and sex, with a greater impact at younger ages. The degree of excess mortality can be grouped by level of glucosuria (>0 to .5 vs. >.5 g/dL) and by age (20 to 59 vs. 60+) with small differences by sex. On an aggregate basis, there is a clear linkage to both serum glucose and fructosamine levels, with higher degrees of glucosuria being associated with higher levels of both.

Mortality associated with glucosuria when a history of diabetes is denied by the applicant is not much different than mortality with glucosuria when no history is taken; both are markedly elevated. Clearly the vast majority of those with glucosuria have elevated serum glucose on a recurrent basis, rather than a low renal threshold for glucose. For those who do admit to diabetes, the urine glucose can also be helpful in risk discrimination if no other data is available.

Figure 2. Median Serum Glucose and Fructosamine Values by Urine Glucose Group



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About the Authors

Vera F. Dolan, MSPH, FALU, Research Associate at Clinical Reference Laboratory, is a consultant specializing in underwriting research and product development. At CRL Vera assists with the analysis and publication of CRL's mortality study data. In her consulting practice, Vera develops risk assessment tools for underwriters, including underwriting manuals, as automated risk assessment systems and underwriter training. Vera provides litigation support for misrepresentation and other underwriting issues, as well as life expectancy calculations for use during litigation.

Vera has a BA in Public Health from the Johns Hopkins University, and a master's in Public Health in Epidemiology from the University of North Carolina at Chapel Hill. Vera was employed as an underwriting researcher at Lincoln Re and Transamerica Occidental Life before starting her consultancy in 1989. Vera is an Associate Editor of *ON THE RISK*, and regularly speaks to actuaries and underwriters on risk assessment topics.

Robert L. Stout, PhD, is President and Director of the Clinical Reference Laboratory based in Lenexa, Kansas. He completed undergraduate studies at California State University (Fullerton) and obtained a PhD in Biological Chemistry from UCLA School of Medicine. Since 1978 he has been directly responsible for introducing many of the new tests and procedures used in risk assessment such as urine and saliva HIV. Dr. Stout has produced nine patents over the last decade.

Dr. Stout has published numerous articles in the *Journal of Insurance Medicine* and *ON THE RISK*. He has made presentations to the Institute of Home Office Underwriters, the ACLI Medical Section, AAIM, the Home Office Life Underwriters Association, the Canadian Institute of Underwriters, the International Underwriting Congress, ICLAM, the Impaired Risk Group and numerous regional underwriters associations. Dr. Bob is grandfather of three and an avid golfer, fisherman and gardener.

Michael Fulks, MD, Consulting Medical Director, analyzes, interprets and writes up CRL's mortality study results. Dr. Fulks is a graduate of the University of California at Davis, completing his residency at the University of Wisconsin and practicing for 8 years before joining Allmerica in 1987. He became VP & Medical Director of Phoenix Life in 1989, working with its direct and reinsurance areas, group health and disability. Moving to Merrill Lynch in 1997, he developed an underwriting approach for its older age clientele. In 2001, he joined MassMutual, creating its first electronic underwriting manual and updating its requirements, preferred programs and ratings. He moved home to northern California in 2005 and now mixes ranch work with consulting, including ongoing research work for CRL.

Mike has contributed to articles in the *Journal of Insurance Medicine* and *ON THE RISK* on laboratory testing. He regularly speaks to medical directors and underwriters on various topics, including predictive value of testing and patterns of mortality in general and in relation to specific impairments ranging from coronary disease to hepatitis. Mike is board-certified in Insurance and Internal Medicine.