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MORTALITY

Relationship of Hemoglobin A1c to Mortality in Nonsmoking Insurance Applicants

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Objective.—Determine the relationship between hemoglobin A1c value and 5-year, all-cause mortality in nonsmoking life insurance applicants.

Method.—By use of the Social Security Master Death Index, mortality was examined in 286,443 non-smoking insurance applicants aged 40 and up for whom blood samples for hemoglobin A1c were submitted to the Clinical Reference Laboratory. Results were stratified by hemoglobin A1c value, gender and age bands 40 to 59, 60 to 69 and 70 and up.

Results.—Increased mortality is apparent at hemoglobin A1c values of 6% and above, is linear, and on a percentage basis decreases with age. Hemoglobin A1c values less than 5% also are associated with increased mortality. Absolute mortality rates for females with elevated hemoglobin A1c are generally lower than rates for males, although mortality relative to the gender-specific reference group with hemoglobin A1c of 5% to 5.9% is generally the same for both.

Conclusion.—The importance of even small elevations of hemoglobin A1c above 5.9% is apparent. For screening, it is the degree of blood sugar elevation as measured by hemoglobin A1c rather than any diagnostic label that is critical in risk assessment.

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INTRODUCTION

Elevated values of blood glucose are associated not only with excess mortality among diabetics, but also those with no diagnosis of diabetes.[1] Hemoglobin A1c (glycosylated hemoglobin) is a sensitive and quantifiable measure of long-term elevation of blood glucose values.[2–4] In addition to the longer term risk of microvascular complications, a more immediate increased risk of death from cardiovascular disease and stroke associated with elevated hemoglobin A1c and diabetes has been found in many population studies.[5–11]

There are few opportunities to assess the relationship of hemoglobin A1c with long-term mortality in a large adult population;

fewer yet have sufficient data and participants to stratify by gender, age and a wide range of hemoglobin A1c values. Applicants for individual life and disability insurance are a self-selected group of relatively healthy adults, typically employed or retired with access to health care.

A blood sample is usually obtained as part of the application process, except for those at younger ages and lower amounts of insurance. This sample is then sent by overnight mail to one of a small number of laboratories serving the industry including Clinical Reference Laboratory (CRL). Hemoglobin A1c is typically performed as a reflex test if random blood sugar, fructosamine or other screen for abnormal blood sugar or history suggests possible elevation.

The all-cause mortality impact of different hemoglobin A1c values for insurance applicants or those issued coverage is not well studied. Both the point where mortality begins to increase and the amount of increase at various values and ages have been debated. Attempts to ascertain the mortality impact of elevated blood sugar in insured lives have been hampered by the lack of sufficient usable industry data and in selecting a reference group. Insurance applicants provide a useful, if not perfect, surrogate for insured lives. They also are representative of that portion of the general adult population seen regularly for preventive care screening, providing insights for this group, as well.

METHODS

We examined available hemoglobin A1c results for blood samples processed by CRL between 1993 and 2004. CRL performs testing on a substantial proportion of North American insurance applicants; all of the authors are either employees of CRL or have a consulting relationship with CRL.

This study includes 286,443 applicants aged 40 years and up who were tested for hemoglobin A1c and were also known to be negative for urine cotinine (<250 ng/mL), a metabolite of nicotine, indicating they were non-smokers. The cotinine-positive applicants were excluded from this study because their mortality was substantially higher (data not shown), and will be studied in a separate, later report.

Approximately 85% of the cases were applicants for life insurance; the rest were applicants for individual health or disability insurance. The type of insurance product applied for did not affect the handling or testing. Mortality follow-up to 2006 was done by use of the Social Security Administration's Master Death Index service. The mean duration of follow-up was 5.6 years, with a median of 5 years. Results were stratified by hemoglobin A1c value (2% to 4.9%, 5% to 5.9%, 6% to 6.9%, 7% to 7.9%, 8% to 8.9%, 9% to 9.9%, 10% to 10.9%, and 11% and up), gender and age group (40 to 59 years, 60 to 69 years, 70 years and up).

From 1988 to mid-2004, hemoglobin A1c was determined by high pressure liquid chromatography using assays developed by Bio-Rad Laboratories on their Variant instrument. Currently, the assays used by CRL for hemoglobin A1c and cotinine are immunoassays. Analysis for hemoglobin A1c is performed on the Roche Cobas Integra 800; the cotinine analysis is performed on a Hitachi Modular system. A comparison of the Roche Cobas Integra and Bio-Rad methods has a correlation coefficient greater than 98% (data not shown).

The availability of person years permitted the calculation of mortality density ratios and their 95% confidence intervals.[12] A mortality density rate is the number of deaths divided by the number of person years. We used this approach because not all our applicants have the same duration of follow up; while not meaningful on their own, mortality density rates allow comparison between each gender and age group. A mortality density ratio (MDR), which is the mortality density rate of the group of interest divided by the rate of a reference group can then be calculated. This is analogous to

Table 1. Mortality Density Rates and Ratios for Ages 40 to 59 Years

Hemoglobin A1c (%)	Deaths	Total Applicants	Person Years	Mortality Density Rate	Mortality Density Ratio (%)	95% CI
Males						
2–4.9	111	7807	56,110	0.0020	118	96–145
5–5.9 (reference)	552	58,496	329,232	0.0017	100	89–113
6–6.9	421	29,572	162,220	0.0026	155	136–176
7–7.9	314	16,886	93,397	0.0034	201	175–230
8–8.9	296	11,594	66,046	0.0045	267	232–308
9–9.9	244	8416	49,092	0.0050	296	255–345
10–10.9	194	6009	35,877	0.0054	323	274–380
11 up	353	9505	57,575	0.0061	366	320–418
Total	2485	148,285	849,549			
Females						
2–4.9	18	2906	18,246	0.0010	92	56–151
5–5.9 (reference)	125	22,407	116,601	0.0011	100	78–128
6–6.9	93	10,769	56,076	0.0017	155	118–202
7–7.9	90	6083	31,778	0.0028	264	201–346
8–8.9	61	4082	22,173	0.0028	257	189–349
9–9.9	61	2987	16,742	0.0036	340	250–462
10–10.9	65	2295	13,058	0.0050	464	344–627
11 up	150	4015	23,118	0.0065	605	477–767
Total	663	55,544	297,792			
Grand Total	3148	203,829	1,147,341			

a mortality ratio (MR) and is the metric likely of most interest.

Reference mortality was taken from the hemoglobin A1c band that represented the healthiest risks (5% to 5.9%). The resulting MDRs compare the mortality in the ''healthiest'' group of insurance applicants with the mortality of insurance applicants with higher values of hemoglobin A1c. No outside reference group is needed, because this internal group that is matched for all possible confounders provides the best reference to help identify the mortality risk attributable to elevated hemoglobin A1c levels.

Analyses were performed with SPSS for Windows, release 11.5.1 (SPSS, Inc.). The CRL Internal Review Board approved this study.

RESULTS

A total of 286,443 applicants aged 40 years and up who were processed by CRL between 1993 and 2004 were found to have urine cotinine values between 0 and 249 ng/mL, and also had a hemoglobin A1c performed either initially or as a reflex test. Mortality follow up in 2006 via the Social Security Master Death Index found 9235 deaths within 1,591,418 person years of experience.

As shown in Tables 1–3, sufficient person years and deaths are available for all values of hemoglobin A1c to support mortality analysis when divided by gender and the 3 age bands. Men represent 71.3% of the study population overall, with a higher percentage at the younger ages and lower at the older ages, in keeping with the relative percentage of men and women insurance applicants at various ages. Since hemoglobin A1c is usually performed based on a positive screening result or history of diabetes, hemoglobin A1c values of 5% to 5.9% (typically considered normal or optimal) comprised only 36.5% of the study's total person years of experience.

Table 2. Mortality Density Rates and Ratios for Ages 60 to 69 Years

Hemoglobin A1c (%)	Deaths	Total Applicants	Person Years	Mortality Density Rate	Mortality Density Ratio (%)	95% CI
Males						
2–4.9	68	1019	7570	0.0090	124	96–160
5–5.9 (reference)	491	11,934	67,960	0.0072	100	88–113
6–6.9	491	10,984	58,483	0.0084	116	103–132
7–7.9	438	6787	36,762	0.0119	165	145–188
8–8.9	304	4199	23,286	0.0131	181	157–208
9–9.9	230	2500	14,700	0.0156	217	185–253
10–10.9	187	1517	8914	0.0210	290	245–344
11 up	230	1937	11,647	0.0197	273	234–320
Total	2439	40,877	229,322			
Females						
2–4.9	25	378	2764	0.0090	166	109–254
5–5.9 (reference)	150	5012	27,590	0.0054	100	80–125
6–6.9	188	4423	22,921	0.0082	151	122–187
7–7.9	120	2630	13,619	0.0088	162	127–206
8–8.9	112	1719	9295	0.0120	222	174–283
9–9.9	92	1079	6137	0.0150	276	213–357
10–10.9	39	663	3785	0.0103	190	133–270
11 up	110	1171	6945	0.0158	291	228–373
Total	836	17,075	93,056			
Grand Total	3275	57,952	322,378			

Figure 1 shows the 6 age/gender bands on a single graph expressed as mortality density rates. For each age group, female mortality rates are generally lower than male rates and younger ages have lower mortality as would be expected. Mortality increases as hemoglobin A1c increases in a linear fashion.

Figure 2 shows the 3 age bands on a single graph expressed as mortality density ratios instead of absolute rates, with hemoglobin A1c 5% to 5.9% values set at 100% for each age band. Genders were combined because when gender-specific relative mortality in the 5% to 5.9% group was set as the reference (100%), the differences between genders (but not ages) disappeared. For each age band, the gender-specific ratios (Tables 1–3) cross each other at various hemoglobin A1c values, and the 95% confidence intervals overlap for all but the most extreme hemoglobin A1c values.

Figures 1 and 2, and Tables 1–3 demonstrate increasing 5-year mortality risk with increasing hemoglobin A1c values at 6% and higher. This risk increases regardless of whether it is viewed as a mortality density rate, or as a ratio with the 5% to 5.9% group as the denominator.

The impact of increasing hemoglobin A1c on mortality is greatest at the youngest ages, and least within the oldest group. However, the impact on mortality is seen at all ages; each unit of increase in hemoglobin A1c is associated with a consistent percentage increase in mortality. Of note, hemoglobin A1c values less than 5% are also associated with increased mortality. This trend is even more dramatic as hemoglobin A1c values fall below 4% (data not shown as numbers are small).

DISCUSSION

Blood samples taken as part of an application for insurance that are combined with information from the Social Security Master Death Index provide a unique data base to

Table 3. Mortality Density Rates and Ratios for Ages 70 and Up Years

Hemoglobin A1c (%)	Deaths	Total Applicants	Person Years	Mortality Density Rate	Mortality Density Ratio (%)	95% CI
Males						
2–4.9	54	399	2688	0.0201	96	72–127
5–5.9 (reference)	495	4754	23,612	0.0210	100	88–113
6–6.9	503	4722	22,243	0.0226	108	95–122
7–7.9	352	2608	12,782	0.0275	131	115–151
8–8.9	207	1339	7074	0.0293	140	119–164
9–9.9	122	622	3357	0.0363	173	142–211
10–10.9	59	320	1781	0.0331	158	121–207
11 up	99	360	2036	0.0486	232	187–288
Total	1891	15,124	75,573			
Females						
2–4.9	32	175	1115	0.0287	181	125–261
5–5.9 (reference)	254	3376	15,988	0.0159	100	84–119
6–6.9	247	2908	13,328	0.0185	117	98–139
7–7.9	168	1412	6912	0.0243	153	126–186
8–8.9	78	733	3734	0.0209	131	102–169
9–9.9	64	399	2079	0.0308	194	147–255
10–10.9	37	241	1322	0.0280	176	125–249
11 up	41	294	1648	0.0249	157	113–218
Total	921	9538	46,126			
Grand Total	2812	24,662	121,699			

evaluate mortality, as is apparent here with hemoglobin A1c. Because of the large number of samples available, it was possible to obtain highly detailed and credible results as to the relationship of mortality risk to hemoglobin A1c values in insurance applicants. This has value both for the insurance industry in accurately assessing mortality risk, and for clinical medicine since individual insurance applicants are representative of that part of the adult population seen for preventative care.

Hemoglobin A1c values of 6% and greater show a steady progressive increase in 5-year mortality risk which varies with age (Figures 1 and 2). In Figure 2, the highest percentage increase occurs in the youngest applicants, but the underlying pattern is similar at all ages. The percentage mortality ratio increase for each 1% increase in hemoglobin A1c beginning at a value of 6% is approximately 50% in the ages 40 to 59 group, 30% in the ages 60 to 69 group and 17% in the ages 70 and up group. Utilizing the ratio (Figure 2) rather than the rate (Figure 1) gives a better idea of the relative risk for an individual, although the total population impact of hemoglobin A1c values may be better assessed using the rate (Figure 1). Further splitting the 2 hemoglobin A1c bands between 5% and 6.9% into 4 bands showed that excess mortality does not begin until the hemoglobin A1c value of 6% is reached, and then climbs linearly (data not shown).

Diagnostic labels such as ''impaired glucose tolerance'' and ''pre-diabetes,'' though not based on hemoglobin A1c, most often include those individuals with hemoglobin A1c values in the 6% to 6.9% range; the diagnostic label of ''diabetes'' includes those with hemoglobin A1c values of 7% and higher. However, the increase in mortality risk is actually continuous and apparent by the time the hemoglobin A1c reaches 6%. It is the hemoglobin A1c value, and not the presence or absence of a diagnostic label,

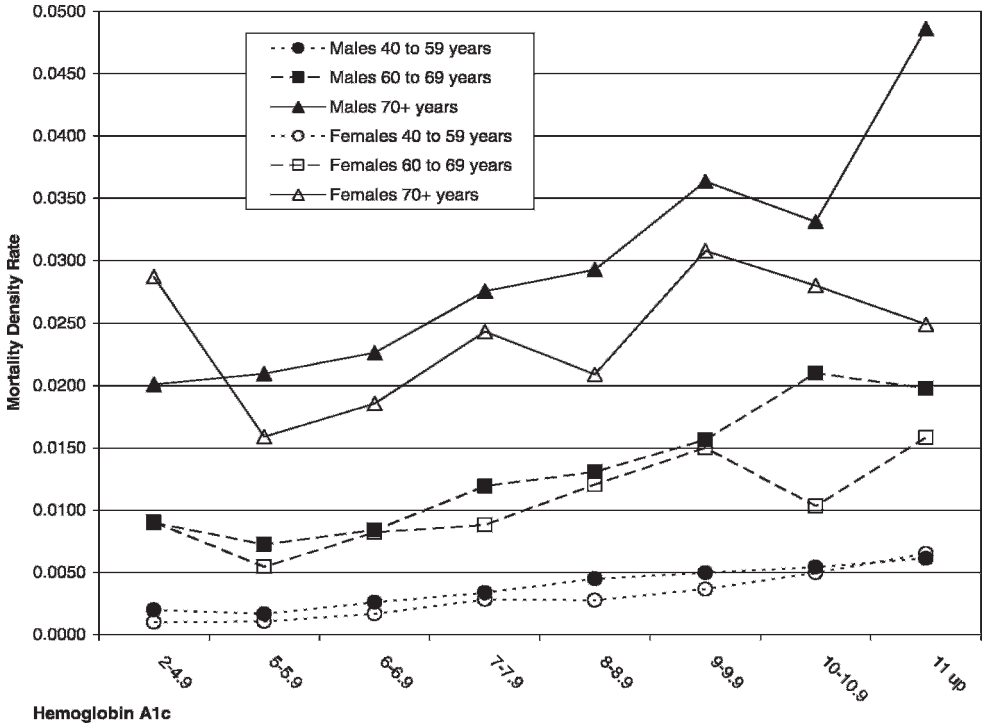

Figure 1. *Mortality density rates for hemoglobin A1c, by gender and age group.*

which seems important in establishing 5-year mortality risk.

Also noted is increased mortality within the small group of individuals with hemoglobin A1c values below 5%. This trend appears to accelerate for values below 4%, but our numbers are too small for firm conclusions. The common pathway here is likely to be shortened red blood cell (RBC) life, since hemoglobin contained within the RBC is glycated slowly over its lifespan. This group may include people with hemoglobinopathies or shortened RBC survival associated with blood loss, mechanical trauma, or disease.[13–14] Clearly, hemoglobin A1c values below 5% should prompt a health review when seen in a clinical or insurance applicant setting.

Potential limitations to the study are present. Individual insurance applicants are subject to additional evaluation (underwriting). The impact of this evaluation and the acceptance or refusal of any policy offered by the insurer on mortality within insured populations relative to applicants is uncertain. It may be that the insurance selection process reduces the 5-year mortality risk in those with elevated hemoglobin A1c more than the risk in those without, but evidence for this is lacking.

Another consideration is the limited follow-up with a mean of 5.6 years and median of 5 years, especially from a general population risk perspective. Ideally, this follow-up should be longer, and this population can be re-examined in a future study, but 5 years exceeds the information that is currently available to the insurance industry. It covers the expected duration of many life and health insurance products.

Still another limitation of our study is that some deaths may have been incurred but not reported to the Social Security Master Death Index. We believe that this should have a neutral impact on the mortality density ratios. Finally, the study was limited to those with urine cotinine values below 250 ng/mL, which excludes almost all regular tobacco users. Mortality among life insurance applicants who use tobacco is substantially higher than for those who do not; the impact at various ages and hemoglobin A1c values

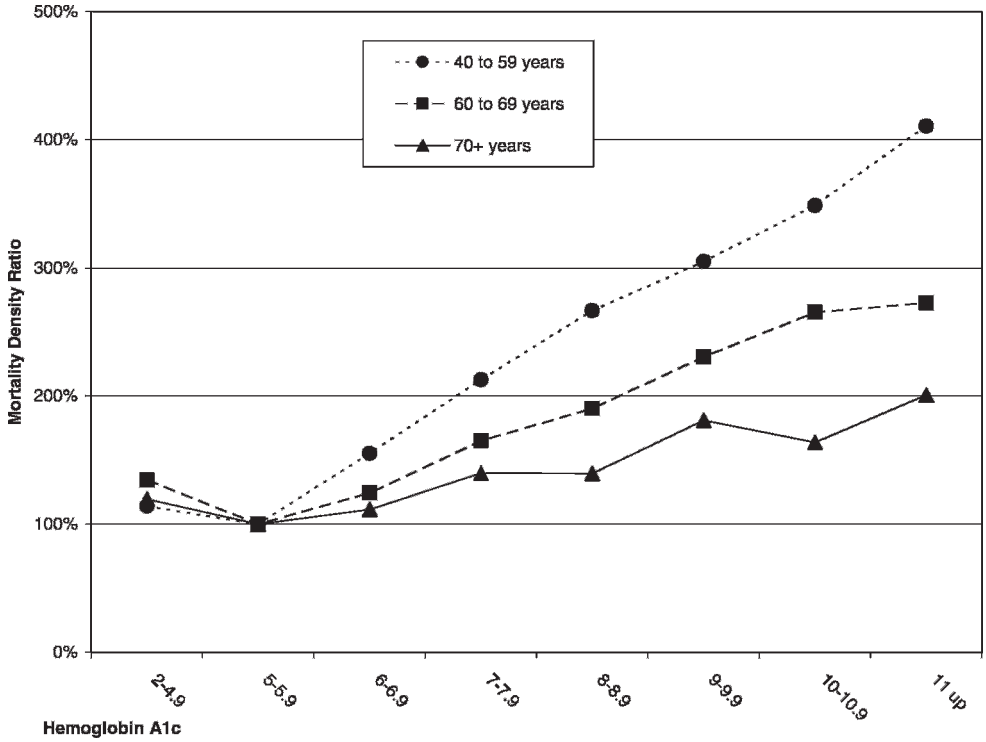

Figure 2. *Mortality density ratios for hemoglobin A1c, by age group.*

may well be different. This group will be considered separately in a later report.

CONCLUSIONS

Utilizing blood obtained as part of the application process and the Social Security Master Death Index, the relationship between hemoglobin A1c value and mortality over the subsequent 5 years is described in detail. This relationship is linear, with excess mortality beginning at the hemoglobin A1c value of 6%. When compared on a ratio basis to mortality in those with a hemoglobin A1c of 5% to 5.9%, mortality varies by age but not by gender. Hemoglobin A1c values less than 5% are also associated with increased mortality, presumably because this represents increased red blood cell turnover from a variety of conditions. Further evaluation of individuals with this finding is indicated.

Our results have implications both in evaluating risk in insurance applicants and for clinical medicine. The importance of even small elevations of hemoglobin A1c above 5.9% is apparent. It is suggested that for screening, it is the degree of blood sugar elevation as measured by hemoglobin A1c rather than the diagnostic label that is critical in mortality risk assessment.

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