The dual personality of hemoglobin A_{1c}: precision medicine biomarker and population mortality predictor for both adult and geriatric patients

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The rapid rise in prevalence of diabetes and the upward shift of population age distributions are coincident demographic changes that explain why older adults have become the fastest growing diabetic population. In 2017 what do we know about diabetes in older adults? The initial clinical trials that elucidated the associations between glycemic control, hemoglobin A_{1c} (HbA_{1c}) as well as onset and development of diabetic complications focused on adults but often excluded ≥65 year olds (1,2). Subsequent trials found that geriatric patients had heterogeneous results (some benefit and some harm) from intensive glucose lower therapy (3-5). Compared to young adults, older adults have different onsets of symptoms, different outcomes as well as different co-morbidities and risks of hypoglycemia. The consensus panel recommendations from the American Diabetes Association (ADA), American Association of Clinical Endocrinologists, and European Association for the Study of Diabetes guidelines emphasized the importance of individualizing treatment recommendations of older adults, a call that is consistent with the aims of precision medicine (6-8). Precision medicine is an emerging approach for disease treatment and prevention that integrates individual variability in genes, environment, and lifestyle for each person. Given the clinical importance of managing diabetes in older adults and the ongoing emergence of new evidence, the April 2017 issue of *Diabetes Care* featured 11 articles to review the current state of knowledge. The 11 articles provide a comprehensive overview, expert perspectives on establishing the goals of care for individual geriatric patients in different settings as well as new insight into the association of diabetes and mortality among older adults.

Diabetes and mortality in older adults

Epidemiologic studies of observations can elucidate clinically and statistically important associations among variables that defy study by randomized control experiments. Epidemiologic studies of diabetes are often undermined by a large proportion of undiagnosed diabetes within the control group. To avoid that susceptibility, Palta *et al.* stratified patients into diabetic and non-diabetic groups and also created sub-categories by each patient's initial HbA_{1c} level (to enable the undiagnosed diabetics to be distinguished within the non-diabetic group by having HbA_{1c} ≥6.5%). Palta *et al.* created the dataset of people ≥65 years at recruitment from linked NHANES datasets [1988–2011] to test the associations between risk of mortality among populations of diabetic and non-diabetic older adults with initial HbA_{1c} level defined sub-groups (9). In this study design, only one HbA_{1c} level (obtained at the beginning of the study) was used per patient to establish the HbA_{1c} category for that patient. As a consequence, the HbA_{1c} variable was fixed or was time-insensitive in the Cox proportional hazard multivariate model analysis and the association between initial HbA_{1c} and mortality of older adults could be assessed.

The study was able to assess models for all cause mortality, cardiovascular disease mortality, cancer and non-cancer mortality and considered subgroups studies for age, sex, race/ethnicity, and treatments. There are several subtle findings, but overall Palta *et al.* demonstrated that among diabetic older adults as the HbA_{1c} level for each strata increased, the hazard ratios (HR) for all-cause mortality increased from 1.0 (at HbA_{1c} <6.5%) to 1.8 (at HbA_{1c} ≥9.0%). Among the non-diabetic patients defined by questionnaire, an HbA_{1c} ≥6.5% had a HR of 1.3 relative to the all-cause mortality compared to patients without diabetes with HbA_{1c} 5.0–5.6%. These observations support the association of good glycemic control and lower HbA_{1c} with lower risk of mortality for both diabetic and non-diabetics and this is the first study to use a nationally representative US population specifically that assesses older adults.

The ADA and American Geriatric Society (AGS) consensus statements of 2012 and 2014 that made recommendations of potentially less aggressive glycemic goals for older adults was largely based on expert opinion, a lower quality rank in evidence-based medicine scales (7,8,10). This epidemiologic study by Palta *et al.* shows that a general population of older US adults with diabetes, an HbA_{1c} >8.0% is associated with increased risk of mortality and supports the ADA and AGS consensus statements used in current clinical practice, a higher quality rank in evidence-based medicine scales.

Regardless of diabetic status, older adults are heterogeneous group that will continue to require individual treatment goals and priorities associated with the principles of precision medicine. In current practice, HbA_{1c} will be used as a biomarker to support diagnosis of diabetes and to assess treatment decisions and glycemic control in preceding weeks or months. This study by Palta *et al.* also revealed a seldom considered attribute that a single HbA_{1c} measurement among older adults can predict mortality risk for both diabetic and non-diabetic patients.

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