Translating "Nondiabetic" A1C Levels to Clinical Practice

The Art of Medicine

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It is well recognized that there is a significant delay from the time clinical research findings are first reported and when the results become an integral part of clinical care. With the understanding that the prevalence and incidence of diabetes is increasing worldwide, and that the resulting complications are a major contributor to morbidity and mortality, the need for more rapid clinical translation of research findings for diabetes could not be greater.

Specifically, a large amount of clinical research data has been reported in the recent past that is of great interest to the provider caring for individuals with diabetes. Much of the emphasis for research has been devoted to understanding the contribution of hyperglycemia and its treatment on macrovascular disease. For example, within the last decade, we have not only recognized the pivotal role that chronic hyperglycemia, as assessed with A1C levels, contributes to the development of microvascular complications, but we have recognized the importance of glycemia in contributing to cardiovascular disease (CVD) (1,2). Observations from large-scale prospective trials over the last couple of years have reported that in high-risk subjects, intensive therapy to lower A1C levels below suggested targets may not be beneficial or may increase mortality (3–5). However, as observed from these studies, we also learned that certain subsets of patients with type 2 diabetes may actually benefit from intensive glycemic control (3). The most recent analysis, reported in May 2010, has now suggested that mortality may actually be greater for those who maintain a higher A1C level despite attempts at intensive glycemic management (6). Interestingly, the excess mortality in the group randomized to intensive glycemic management was only seen at A1C levels greater than 7% (6). Thus, the findings regarding A1C targets for selected patient populations with type 2 diabetes continue to evolve to this day and remain important data for clinicians.

In addition to understanding the role of specific treatment of hyperglycemia, an equally important observation has been occurring with the recognition that nondiabetic hyperglycemia is associated with cardiovascular disease. Yet, this area of research does not appear to have been given as much attention as the high-profile prospective studies addressing intensive management of hyperglycemia for cardiovascular disease in individuals already diagnosed with type 2 diabetes. In this regard, it has been known for years that glycemia considered to be in the "nondiabetic" range, i.e., 2-h postprandial glucose levels defined as impaired glucose tolerance, has significant clinical implications related to increased CVD mortality (7–12). Of great interest, a very recent and additional analysis of the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study reported incredibly provocative data. Specifically, the investigators restricted the comparison to individuals with normoglycemia, i.e., mean 2-h glucose levels in one group of men and women of approximately 78 and 81 mg/dl, respectively, compared with a second group of men and women with 2-h values of approximately 112 and 113 mg/dl, respectively (13). Yet, even in this range of glycemia, elevated 2-h postprandial glucose conveyed increased mortality risk from CVD but not from non-CVD and suggests concern with nondiabetic hyperglycemia at postprandial levels considered in the normal range. With these observations, a relevant question would be: Why is 2-h glucose not routinely monitored by clinicians in an effort to stratify CVD risk? Clearly, this is a complicated question for which opinions vary widely and one for which there is no single right or wrong answer. But, as elegantly reviewed, it is known that the performance and interpretation of the oral glucose tolerance test has been shown to be inconsistent (14).

Given these concerns with oral glucose tolerance testing, and with the recent recommendation that the A1C test (as an objective test for chronic glycemia) can serve to diagnose diabetes, the next logical question is whether A1C can serve to stratify CVD risk in individuals with "nondiabetic" hyperglycemia. This is an important question and could potentially signal a paradigm shift in how we screen for the increasing number of individuals felt to be at great risk for CVD. Furthermore, having a reliable and stable clinical marker for disease risk would allow for more aggressive clinical interventions to prevent progression of the underlying pathologies relevant to glycemia. With the publication of the EPIC-Norfolk data, we had one of the first reports associating A1C levels considered to be in the normal range with disease outcomes. A1C level was continuously related to subsequent all-cause, cardiovascular, and ischemic heart disease mortality through the whole population distribution, with lowest rates in those with A1C concentrations below 5% (15). These observations from over 9 years ago are considerably expanded by

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a report in this issue of *Diabetes*. Specifically, Matsushita et al. (16) report on the continuous association of A1C in the nondiabetic range and progression of heart failure. The authors evaluated A1C levels in a very large cohort of over 11,000 individuals as part of the Atherosclerosis Risk in Communities Study. After adjustment for covariates, the hazard ratio of incident heart failure was increased in the cohort with A1C levels of 5.5–6.0% and even further in the cohort represented by A1C levels of 6.0–6.4%. Additional studies reported recently for this cohort demonstrated that the A1C level obtained at baseline was associated with adverse cardiovascular outcomes (17). For A1C values of <5.0%, 5.0 to <5.5%, 5.5 to <6.0%, 6.0 to <6.5%, and 6.5% or greater, the multivariable-adjusted hazard ratios for coronary heart disease were 0.96, 1.00 (reference), 1.23, 1.78, and 1.95, respectively. As an A1C level of ≥6.5% has been suggested for diagnosis for type 2 diabetes, the increased risk noted in individuals observed to have an A1C value of <6.5% clearly emphasizes the increased risk attributed to glycemia considered in the "nondiabetic" range. Thus, the recent observations strongly support the association of nondiabetic hyperglycemia to an increased risk for CVD.

With the above data outlining the clinical significance of "nondiabetic" hyperglycemia and that the A1C level appears to be a reasonable marker at this stage, is it time to make firm recommendations for clinicians to initiate interventions for A1C in this range? If that happens, it would clearly represent a huge leap in clinical translation of research data. The problem, as clearly understood, is that we have no evidence suggesting that treatment of nondiabetic glycemia based on a single A1C level <6.5% will ultimately have benefits on CVD. To gather such evidence, prospective studies will need to be done that will take years to complete, will involve a large number of subjects, and will take significant resources. However, for now, we can't ignore the recent data that an A1C level in the high-normal nondiabetic range may indeed serve as a simple clinical marker that heightens our awareness of individuals at increased CVD risk.

With knowledge of this information, shouldn't providers now be encouraged to provide a comprehensive evaluation for other comorbidities, i.e., hypertension, obesity, and dyslipidemia, that are present in individuals at levels of A1C suggestive of increased risk? Would it not make sense to strongly encourage providers to aggressively treat these risk factors based on intervention trials that have demonstrated effectiveness? At this stage, shouldn't the A1C in the high-normal nondiabetic range also signal the need for comprehensive education of the patient regarding CVD risk and allow for initiation of effective lifestyle modification? Such a strategy appears to be an extremely reasonable and rational approach, and, based on known evidence, such clinical translation of current A1C data in the "nondiabetic" range to clinical practice will be truly representative of the "art of medicine."

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