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EDITORIAL COMMENT

What is an Abnormal Blood Glucose Level?

Combining Lessons From Epidemiology and In Vivo Plaque Imaging*

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. . . the idea of a sharp distinction between health and disease is a medical artefact for which nature, if consulted, provides no support.

Geoffrey Rose (1)

Notions of what constitutes a normal blood glucose level have evolved rapidly over the last 2 decades. We have transitioned from a binary classification of glycemic disorders—individuals with and without diabetes—to a widely accepted concept that there is a continuous gradient of health risks across the range of blood glucose (2). This concept is important for several reasons. First, the mounting burden of obesity worldwide is fuelling a concomitant burden of impaired glucose homeostasis (IGH, a term that combines impaired fasting glucose and impaired glucose tolerance [IGT]) and diabetes. The global prevalence of diabetes will increase from 171 million in 2000 to 366 million by 2030 (3), whereas that of IGT will increase from 197 million to 420 million (4). Second, although diabetes accounts for nearly 1 million deaths worldwide every year, an additional 2.2 million cardiovascular (CVD) deaths are attributable to higher-than-optimal levels of blood glucose (5). In other words, diabetes is only the tip of the iceberg when it comes to burden of disease caused by suboptimal blood glucose. Third, the continuous gradient of health risks posed by blood glucose levels suggests that intervention at the onset of diabetes represents the failure of prevention, which is best begun much earlier along the disease continuum.

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Evidence for Continuous Gradient of Health Risks Across Blood Glucose Levels

Meta-analyses of epidemiologic studies suggest that there is a continuous gradient of risk across blood glucose levels (fasting and post-load) for the incidence of diabetes, CVD, and mortality (6,7). A 1-mmol/l lower fasting blood glucose level is associated with an approximately 20% lower risk of CVD (6). Whereas IGH increases the risk of diabetes, recent data suggest that such risk may begin at blood glucose levels considered normal (8), probably because beta cell dysfunction occurs early (2).

Why and How Does Impaired Glucose Homeostasis Pose Vascular Risk?

The continuous gradient of risk associated with blood glucose may have several explanations. First, mild elevations of blood glucose portend future tracking to higher levels, including diabetes. Second, risk factors cluster, and it may be the sum of risk factors that may cause and/or compound the hazard. Third, hyperglycemia and/or insulin resistance may both be atherogenic. Data from the Nurses Health Study (9) suggest that women destined to develop diabetes experienced a 3-fold increased risk of CVD 10 to 15 years before the onset of diabetes, corroborating the hypothesis that the "clock starts ticking" very early (10).

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Glycemia and Plaque Biology: Is There a Continuous Gradient of Risk?

In this issue of *JACC: Cardiovascular Imaging*, Amano et al. (11) use in vivo plaque characterization with intravascular ultrasound to study a group of older individuals with IGH. The study focused on target lesions in individuals undergoing percutaneous coronary interventions, one-quarter in the setting of an acute coronary syndrome. About 25% of the patients had a prior myocardial infarction, and nearly one-half had multivessel coronary disease. The investigators noted a 4-fold increased odds of lipid-rich plaques in individuals with IGH, a magnitude of association similar to that for diabetes. Of interest, a gradient of a higher prevalence of lipid-rich plaques was observed across insulin resistance tertiles.

On the face of it, the investigation provides striking support to the aforementioned epidemiologic data. But several caveats are worth noting. The investigators studied an elderly catheterization laboratory sample with a high burden of prevalent disease. The investigators acknowledge that they studied culprit plaques after their rupture. Thus, the study does not establish that average community-dwelling individuals with IGH have a greater burden of vulnerable plaques. However, the study is consistent with substantial experimental evidence.

Hyperglycemia adversely affects vascular cells and the cell–cell interactions that mediate atherogenesis (2,12). A greater leukocyte adhesion to endothelial cells occurs because of up-regulation of adhesion molecules and activation of protein kinase C and the transcriptional factor nuclear factor kappa B. Advanced glycation end products enhance monocyte migration, cytokine production, oxidant stress, and foam cell formation and increase vascular permeability and endothelial dysfunction. Nonenzymatic glycation can alter circulating lipoproteins and can modify proteins in the vascular basement membranes, thereby facilitating prolonged intimal contact of modified low-density lipoproteins and macrophages (the latter via scavenger receptor class A), which in turn enhances generation of oxidized low-density lipoprotein and lipid insudation into the plaque. Hyperglycemia also causes platelet dysfunction, promotes hypercoagulability, and reduces vascular distensibility.

Insulin resistance may be atherogenic via several mechanisms independent of hyperglycemia (12). Insulin receptors are present on the cells involved in atherogenesis, such as endothelial cells, macrophages, and vascular smooth cells, and T cells can express these receptors on antigen presentation (12). Insulin resistance impairs vascular nitric oxide production, is proinflammatory, impairs fibrinolysis, and increases endothelin production (12).

What Is an Abnormal Blood Glucose Level, and What Are the Implications for Prevention?

The data reviewed in the previous text suggest that an abnormal blood glucose level is best regarded as "a level for which there is scientific evidence that benefits of intervention outweigh potential harm," analogous to how Evans and Rose (13) defined hypertension. The implication is that an abnormal glucose level is not confined to those who meet the criteria for diabetes or IGH. Clinical trials have shown that diabetes is preventable by lifestyle interventions and by pharmacological means in individuals with IGH (14–16). Data are lacking, however, to show that such interventions reduce the increased CVD risk in IGH. Thresholds that define an abnormal blood glucose level and the choice of interventions are likely to be dictated by absolute risks, efficacy and cost-effectiveness of interventions at different thresholds, budgetary considerations, and constraints of health care delivery systems (17). Given the large segment of the population that falls into the IGH category, additional research is warranted to evaluate whether imaging and nonimaging tests can be used to further risk stratify this group to select a high-risk subgroup for intervention. Such tests should be simple, reproducible, validated, and cost effective.

The data presented herein argue also for considering fasting blood glucose level as a component of CVD risk prediction algorithms, as opposed to the currently available instruments that label diabetes as a risk equivalent but ignore lesser degrees of IGH.

A critical component to stemming the burgeoning global epidemic of IGH is tackling the problem of overweight and obesity (4). This requires initiatives both at the individual and at the societal levels (4). The latter must include policy directed at promoting affordable healthier foods, nonmotorized transportation and opportunities for exercise, health screening, and health education.

Conclusions

Accumulating evidence suggests that IGH is a life-course disease that evolves over a period of

decades, with excess adiposity, insulin resistance, and beta-cell failure as the underlying substrates. Therefore, prevention of diabetes and its precursors is best achieved by a long-term approach that combines lifestyle measures targeted at maintaining optimal body weight in all persons, with appropriate pharmacological measures being directed at high-risk individuals who are further along the spectrum of IGH.

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