The Puzzling Condition of Pre-diabetes

Dual citizenship in the "kingdom of the well" and in the "kingdom of the sick"

Post published by Sylvia R Karasu M.D. on Feb 26, 2014 in The Gravity of Weight

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Susan Sontag, in her essay, *Illness as Metaphor*, writes that we all hold "dual citizenship in the kingdom of the well and in the kingdom of the sick." Eventually, says Sontag, we will, "sooner or later," experience passage from one to the other. We can use Sontag's "dual citizenship" metaphor to call attention to type 2 diabetes and more specifically, that intermediate state of so-called "pre-diabetes."

Approximately 6.2 million people in the U.S. alone have undiagnosed type 2 diabetes (Cohen et al, *Journal Clinical Endocrinology and Metabolism*, 2010.) Apparently, by 2030 about 472 million people worldwide will have pre-diabetes. (Gosmanov and Wan, 2014). Pre-diabetes is a state of intermediate glucose metabolism not quite meeting the criteria for full-blown diabetes. Shaw, in his 2011 article in the *Medical Clinics of North America* writes that pre-diabetes is not a disease itself, but rather a "risk state." Eventually everyone who develops type 2 diabetes passes first through that state of pre-diabetes. One of the main reasons for diagnosing prediabetes is to identify those who may be at increased risk for developing not only diabetes but its many complications, such as cardiovascular disease, diabetic retinopathy, kidney disease, and neuropathy. Many studies suggest that proper blood glucose control has been associated with fewer long-term medical complications. Once identified, these patients can be better managed with the implementation of lifestyle changes and possible pharmacological interventions. Typically type 2 diabetes is diagnosed by measuring fasting blood glucose levels or assessing glucose levels by an oral glucose tolerance test.

It was Dr. Samuel Rahbar, in the late 1960s, who discovered, quite by accident, that those with diabetes had elevated levels of hemoglobin A1c (HbA1c), i.e., glycolated hemoglobin (glucose irreversibly attached to hemoglobin) in their blood. (Gebel, *Diabetes Care,* 2012) Hemoglobin A is the most abundant form of hemoglobin,

the substance that carries oxygen in human red blood cells from the lungs to the tissues, and there are five minor components of hemoglobin A, including HbA1c. The lifespan of a red blood cell is about 120 days; the HbA1c reflects the

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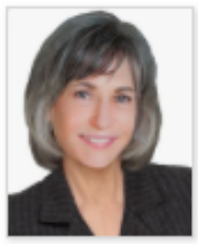

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average blood glucose level for the previous 8 to 12 weeks. Hemoglobin A1c accounts for about 3 percent of hemoglobin in normal adult red cells. In diabetes, though, this level may be two to three times higher than normal. Rahbar's discovery was not initially appreciated, but eventually has become an important clinical marker for those with both type 1 (insulin deficient, auto-immune disorder, more often seen in childhood) and type 2 diabetes (most closely associated with overweight or obesity and most often seen in adults, but with the spread of obesity, now seen in children and adolescents.) In 2010, the American Diabetes Association recommended using HbA1c to diagnose both pre-diabetes and diabetes. Currently someone with a percentage of HbA1c of 6 to 6.5% has a high risk for developing diabetes, while those with a percentage of 5.7 percent to 6.4 percent have "pre-diabetes."

Most recently, though, Gosmanov and Wan, in a 2014 *American Journal of the Medical Sciences,* have called into question the value of using HbA1c to diagnose pre-diabetes. Their prospective study of 66 patients found that the predictive value of HbA1c for the diagnosis of pre-diabetes is low and patients with values of HbA1c of 5.7 percent to 6.4 percent should undergo confirmation by an oral glucose tolerance test, the "gold standard" for diagnosing diabetes. In their study, those in this mid-range missed the diagnosis of diabetes, as assessed by an oral glucose tolerance test, in 12 percent of patients and only 39 percent had pre-diabetes based on the oral glucose test. In other words, the HbA1c can be misleading and over-diagnose pre-diabetes in more than half of the subjects. The HbA1c test, though, is convenient, does not require fasting or a two-hour time period, has international standardization, and less day-to day variability, though it is more expensive than a fasting blood glucose and may not be as accurate. Furthermore, race, age, and even medications may affect values, and there is just more "inter-individual physiological variability" than initially appreciated. Cohen et al, as a result recommends that the mid-level HbA1c range be called "impaired HbA1c" (rather than pre-diabetes), and they also recommend confirmation by a fasting blood glucose or oral glucose tolerance test.

For a systematic review of 16 prospective studies on HbA1c, involving over 44,000 patients, see the Zhang et al article in *Diabetes Care* (2010). Their review found that HbA1c values between 5.5 and 6.5 percent were associated with a "substantially increased risk" for developing diabetes but also concluded that errors could be reduced when done in combination with fasting blood glucose levels and an oral glucose tolerance test.

Bottom line: HbA1c is a screening blood test that reflects glucose levels over the past 8 to 12 weeks. It is most useful for identifying patients with a normal glucose tolerance if HbA1c is below 5.7 percent and has a high predictive value if the HbA1c is above 6.4 percent for diabetes. If your levels fall within that mid-range (i.e., neither completely normal nor overtly diabetic), consider asking your physician for an oral glucose tolerance test and/or a fasting blood glucose level to ensure a more accurate assessment.

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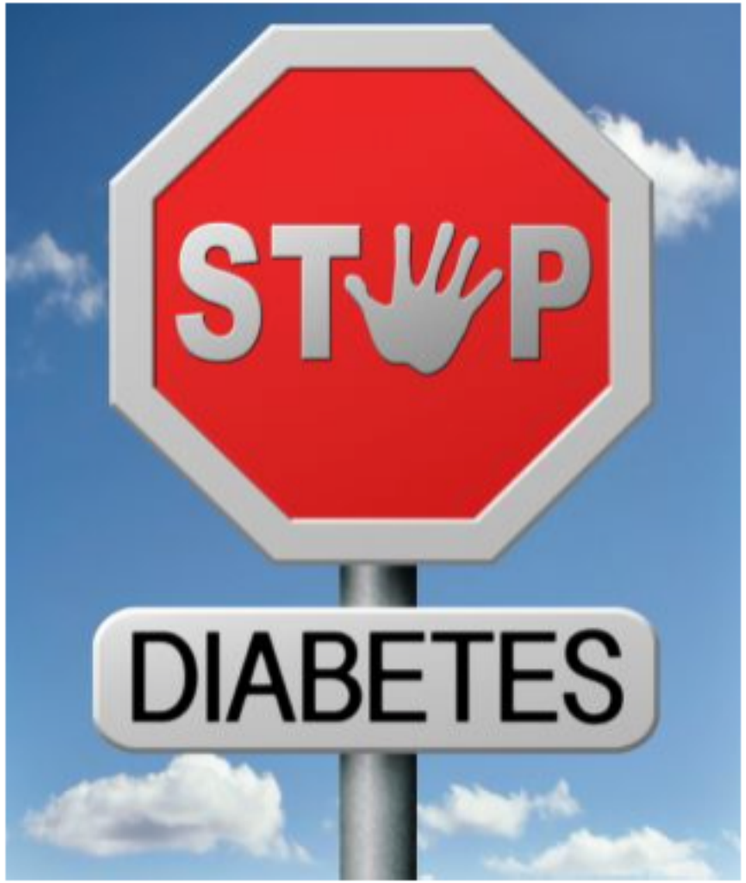

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