

Measuring the sweet smell of success in diabetes management

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Patients often bemoan about having to live with the daily disturbances and challenges required of diabetes self-management. Counting carbs, taking medications with names longer than Greek Gods none of which are covered by insurance, having to monitor blood glucose levels three to six times daily and even having to incorporate healthy foods and exercise into daily living can elicit a feeling of distress in most patients with diabetes. Those individuals who are suffering from diabetes are indeed living on the edge. When asked, “what is your biggest fear regarding your chronic disease” patients will universally respond that they do not want to lose their vision or their leg from a non-traumatic amputation. They want to live long enough to see their children graduate college or their grandchildren start a family. Thus, diabetes is considered by some patients to be a fatalistic disease which will result in devastating complications which are beyond their self-control.

A recently published manuscript by Gregg *et al.* in the *New England Journal of Medicine* (1), gives new hope to clinicians who manage patients with diabetes, as well as those who are facing the challenges associated with chronic disease self-management. Using data from a number of data systems, the authors determined the rates of lower-extremity amputations, end-stage renal disease, acute myocardial infarction, stroke and death from hyperglycemic crisis declined between 1990-2010. Could this mean that we as scientists, clinicians, educators, and patients are actually reversing the often anticipated effects of the dreadful glycaemic burden?

In 1920 (2 years before the discovery of insulin), diabetes was easy to diagnose, yet impossible to treat. Patients with diabetes suffered from malnutrition, cataracts, loss of vision, gangrene, impotence, and immune resistant often fatal diseases (pneumonia, tuberculosis, boils and carbuncles).

The average lifespan of a patient with diabetes was 6 to 12 months as patients often universally succumbed to diabetic ketoacidosis. Hospitals had the distinctive odor of acetonemia as described in *The Discovery Of Insulin* by Michael Bliss: “It was a sickish sweet smell, like rotten apples, that sometimes pervaded whole rooms or hospital wards.” (2). Surgeons recognized the futility of operating on patients with gangrene who were equally likely to die from hyperglycemia triggered postoperative infections. Women who were able to conceive were unable to carry their babies to term (2).

A dramatic change in death rates was observed immediately following the discovery of insulin in 1922. The all-cause mortality rates for patients with diabetes younger than age 10 between 1897-1914 was 824/1,000 patients. From 1950-1961 the mortality rate dropped to just 1/1,000 (3,4). In 1920, between 0.5% and 2% of the US population were estimated to have diabetes (5).

The discovery of insulin was perhaps the most impactful of all drug developments in human history. The work of Banting and Best clarified the role of the pancreas as the target organ for diabetes homeostasis. Following insulin's discovery, chemists began to develop more sensitive assays for urine and blood glucose testing, although self-blood glucose monitoring would not become available until 1970 with the Ames Reflectance meter. Drug purification and extraction methods were developed and perfected. Perhaps most revolutionary was the belief by patients that physicians could actually cure a disease. Prior to 1922, doctors would challenge patients to accept their treatments for different disease states while preaching from a side of a road. These remedies were no more beneficial than those hawked today on some popular TV shows! Clinical trials were initiated which gave birth to “evidence-based medicine.” Doctors

and scientists began to report their findings to their peers in medical journals rather than in the lay press. In 1923, Eli Lilly provided their pharmaceutical sales reps with something to actually sell-insulin, “Now gentlemen, we place in your hands for development the greatest advance in medicine for 50 years” (6).

Insulin changed the dynamics of the diabetes disease state. No longer were patients dying of acute complications (DKA). As life expectancies increased an average of 45 years with the use of insulin, so did their glycemic burden. Patients were unable to perform self-monitoring and were injecting insulin twice daily. Animal insulin was impure and not very safe; drug induced hypoglycemia was common. Glycemic variability fueled oxidative stress which activated microvascular and macrovascular complication pathways (7). Patients gained weight possibly due to hypoglycemia induced reactive eating. Hyperlipidemia was never addressed and statins were not marketed in the US until 1987 (mevacor). Diabetes has also become a costly epidemic in the US. Today, people with diabetes incur average annual medical expenditures of \$13,700 over twice the cost of care for patients without diabetes (8). Clearly, insulin did not answer all the prayers of everyone who lived with diabetes. So much more needed to be scrutinized about the pathogenesis of this complex disease state before patients lives could truly be impacted.

Individuals who have fasting glucose levels of 100-125 mg/dL, 2-hour postprandial glucose levels ranging from 140-199 mg/dL, and A1Cs from 5.7-6.4% are considered to have prediabetes (9). Approximately 10% of patients with prediabetes progress to clinical diabetes each year (9). Such individuals are at high risk for neuropathy, retinopathy, and cardiovascular disease. Conversion of impaired fasting glucose to clinical diabetes doubles one’s risk for cardiovascular mortality (10). Therefore, screening of high risk patients coupled with ambitious treatment of those individuals diagnosed in the earliest stages of prediabetes or clinical diabetes would be clinically and economically relevant.

Screening high risk patients for pre-diabetes is certainly cost-effective (11). By spending less than \$200 per high risk screening those individuals who are subsequently diagnosed with prediabetes can be introduced to low-cost interventions such as lifestyle modifications, weight loss programs, and metformin. Such non-invasive therapies will result in a per quality adjusted life-year gained savings for screened individuals of over \$8,000 (12).

A total of 86 million Americans have prediabetes, an increase of 7 million individuals since 2010 (13). These

patients should be introduced to lifestyle intervention including weight loss and exercise at the time of diagnosis. The incorporation of healthy dietary practice and exercise into one’s daily routine appears to restore normal glucose regulation most efficiently if initiated within the first year of diagnosis (14). Under the direction and guidance of their health care provider, each patient with diabetes must be ambitiously managed towards customized metabolic targets in order to minimize the risk of long-term complications. Dietary changes targeting weight loss of 5-7% from baseline in patients with pre-diabetes in association with moderate intensity exercise of at least 150 minutes per results in a 58% reduction in progression towards clinical diabetes (15).

Diabetes is a complex disease state whose effective medical strategies are clearly dictated through several published expert guidelines (16,17). However, 90% of patients with patients are managed by primary care physicians (PCPs) many of whom are unaware of the existence of the vary guidelines designed to provide counsel in assessing effective therapeutic strategies for such busy clinicians. Government regulations such as the Sunshine Act, CME oversight, EMR certification and meaningful use incentive programs are minimizing the importance of becoming chronic disease state literate in diseases such as diabetes, peripheral vascular disease and asthma. Some clinicians fear that the government may be driving them away from their own personal learning objectives in an industry which is already highly regulated.

The report by Gregg *et al.* noted that the largest decline in diabetes-related complications was observed with acute myocardial infarction (-67.8% from 1990-2010) followed by death from hyperglycemic crisis (-64.4%) with stroke and amputations declining 52.7% and 51.4% respectively. Reduction rates were higher among adults with diabetes than among adults with normal glucose tolerance. Death due to hyperglycemic crisis now stood at 0.1 cases per 10,000 patients far below the incredulous rate of 824/1,000 observed prior to the discovery of insulin.

Before one declares that the war on diabetes has been beaten off at the pass and the victory is nearly at hand, let us examine some sobering facts about this devastating disease. Our medical personnel are now managing 29.1 million Americans with diagnosed diabetes, or 9.3% of the U.S. population. This represents an increase of 3.3 million patients with a rise in penetrance rate of 1% of our population since 2011 (18). Just when our medical team, though leaders, educators and patients thought they could

breathe a sigh of relief, the numbers of newly diagnosed patients heading to an office, clinic, research center or hospital near has become impressive. By 2050, one in three adults is predicted to have diabetes while the number of newly diagnosed cases of diabetes will increase from 8 per 1,000 people in 2008 to 15 per 1,000 in 2050 (19).

This is an exciting time for those of us who are living with and managing others with diabetes. Within the next 5 years we will experience a pharmacologic explosion of innovative therapies designed to intensify the treatment of patients with diabetes and minimize complication rates. Faster acting prandial insulins, inhaled insulins, new and improved basal insulins, low volume basal insulins, biosimilar insulins, implantable GLP-1 therapies, oral weekly GLP-1 receptor analogues, fixed dose combinations (SGLT2 inhibitors plus metformin or DPP-4 inhibitors, GLP-1 receptor agonists plus basal insulin), glucokinase activators, GLUT4 transport stimulants, and glucagon receptor agonists. Within 2 years patients may be able to perform “flash glucose testing” every 3-5 minutes by scanning a 2-week durable inexpensive glucose sensor placed on their arm. Finger sticks will become obsolete. The artificial pancreas is in development for patients with type-1 diabetes. This important technology will eventually “close the loop” between insulin delivery and glucose monitoring thereby minimizing one’s risk of hypoglycemia while maintaining ideal glucose regulation.

The road ahead remains littered with financial uncertainty, government regulation, and formulary concerns. Nevertheless, we have come such a long way since 1920, when starvation was the only treatment for diabetes. Patients with diabetes should be reassured that their disease may be a blessing in disguise. How can incorporation of healthy lifestyle practices ever be criticized? Early detection of impaired glucose tolerance allows clinicians to introduce therapies which may return the islet to normal glucose regulation and minimize one’s risk toward progression of diabetes. By mitigating glycemic variability, the pathways related to diabetes complications are less likely to become activated allowing patients to live a normal, healthy life.

PCPs should reassure our patients that well managed diabetes is the major cause of nothing! To that end, we should convince our patients that they should ambitiously follow the customized treatment plans which have been provided on their behalf. Our goals are to achieve the targeted lipid, glycemic and blood pressure goals as soon as possible, for as long as possible, as safely as possible, and as rationally as possible.

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