
Introductory Chapter: Diabetes, It is Always Something

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Additional information is available at the end of the chapter

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1. Where we are and how we got there

The diabetes world changed when Banting and Best reported on their success extracting insulin from a dog in 1922. Previous to that, the diagnosis of type 1 diabetes was a death sentence. In the 1800s, a 10-year-old diagnosed with type 1 diabetes would wither away and die within a year. When the two Canadians extracted insulin, a very dark cloud lifted.

6:00 AM, the alarm goes off. Time to get up and start another day. Shower, dress, and check blood glucose for the first time that day. A little low this morning. I will have to eat a little extra or cut back on the insulin some. Cereal, milk, and juice for breakfast. A bowl of cereal, 32 g of carbohydrate, 20 g of milk, and 30 g of juice. 82 g in total; ratios vary between patients, but let us use 1 unit of fast acting insulin for every 10 g of carbohydrate, so normally that would be 8.2 units of insulin to cover breakfast. Since we are starting a little low, let us just inject 6 units to cover the meal and the low. On and on all day. Every day. No time off just because it is Thanksgiving or your first date.

Diabetes is still no piece of cake. It is difficult, but doable. Today we even have a U.S. Supreme Court Justice with nearly life-long (diagnosis age 7) type 1 diabetes. Maintaining normal levels of blood glucose are a constant challenge to those with type 1 diabetes. In fact, achieving blood glucose levels equivalent to those considered normal for those without diabetes, may not even be a desirable goal. There are too many lows and then there is the Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) which told us those levels may not even be advisable.

Type 2 diabetes is at epidemic levels in both developed and developing countries. Still the battle to level the highs and lows is difficult, but manageable; however, many do not even know they have it and many do not have the resources or knowledge to deal with it.

With longer lives we found there could be complications such as eye, kidney, and extremity issues that did not show up when a diabetes life span was less than a year. The problems are present in those cells not requiring insulin as the gate keeper into the cell. Nearly every scientific paper written on diabetic retinopathy has an introduction telling the reader that diabetes is the leading cause of blindness in the working age population. Most of them maintain their vision, but some do not, even in countries with excellent health care systems.

2. Mechanisms, research, screening, and the future

Research into diabetes is also complicated by the lack of a good animal model. There are many animals which can simulate human diabetes, but none demonstrate the full blown aberrant retinal blood vessel development that can occur in someone with diabetes of many years duration. Perhaps the animal models do not live long enough to exhibit this type of damage.

Refractive changes may be one of the presenting signs of increased blood glucose; usually a move toward more myopia or less hyperopia. Cataract is also more likely to develop and does so earlier in poorly controlled diabetes. Diabetic retinopathy takes years to develop, although poorly controlled systemic factors and pregnancy can speed up the process. Blood glucose levels, especially A1c, blood pressure, lipid levels, and genetics all play a role in determining who will or will not develop retinopathy complications.

Diabetic retinopathy is a gradual process whose mechanism of action is not totally understood. It seems to start with damage to retinal ganglion cells and retinal capillaries. Hyperglycemia can result in the production of reactive oxygen species, hyperosmolarity of cells, production of advanced glycation products, activation of protein kinase C, retinal inflammation, and increased production of nitric oxide, which may individually or collectively play a role in the development of diabetic retinopathy. Retinal capillaries are lined with endothelial cells and pericytes which depend on each other for support. One of the initial steps occurring with hyperglycemia in the retina is the damage and loss of pericytes. Without the support supplied by pericytes, endothelial cells will eventually die leaving acellular capillaries or those damaged to the point where they no longer bring oxygen and remove carbon dioxide from retinal cells. It should be pointed out that the oxygen demand of retinal cells greatly exceeds than that of other cells in the body. As a response, cells starved for oxygen accumulate hypoxia inducible factor (HIF) which stimulates the production of vascular endothelial growth factor (VEGF) that initiates the formation of new blood vessels. One would think this might be a positive factor, except these poorly developed vessels leak, hemorrhage, and grow into the vitreous. When the vitreous shifts, this can pull the neural retina loose from its attachment to the retinal pigment epithelium (RPE) resulting in (a very difficult to fix) retinal detachment. At times, this can result in blindness.

Clinically, diabetic retinopathy is broken down into non-proliferative (NPDR) and proliferative retinopathy (PDR); proliferative indicating the development of new blood vessels. It is a continuum, from the initial hyperglycemia to damaged leaky vessels to the production of

new blood vessels in response to hypoxia. The early damage of these vessels is visible viewing the ocular fundus as the small dots of hemorrhages and microaneurysms. Later on the vessel damage progresses to a point where blood, fats, and other fluids from the retina leak into the retina. One possible complication of this is diabetic macular edema (DME). The fluid accumulating in the retina can damage an individual's central vision. For many years, macular laser has been the preferred treatment for DME, but newer trials have exhibited the effectiveness of anti-VEGF agents in helping control this complication. Sometimes anti-VEGFs are ineffective indicating that factors other than VEGF may play a role in the development of DME. DME can be a complication of both NPDR and PDR and can result in temporary, and in some cases, permanent vision impairment.

For many years, the primary procedure used to prevent blindness once PDR begins has been pan-retinal photocoagulation (PRP), which is a series of laser burns scattered over the retina. It is effective because it reduces oxygen demand of the retina by eliminating retinal neuronal elements and increases oxygen perfusion from the outer lying choroid. Unfortunately it reduces best corrected central vision as well as peripheral and night vision. Currently, the use of anti-VEGF injections is being investigated in an attempt to reduce or eliminate PDR, either in addition to, or in place of PRP, but many questions remain as to its long-term effects. Is this only a short-term treatment? Does the underlying causative hypoxia persist after treatment? Some studies have shown destruction of retinal components with long-term use of anti-VEGF injections. Are we causing degeneration of the retina in this relatively younger population of patients?

The Diabetes Control and Complications Trial (DCCT) told us that the higher the percentage of glycated hemoglobin, or A1c, the higher the risk of developing DR. This increase of DR with increasing A1c occurs not linearly, but in an exponential fashion. The United Kingdom Prospective Diabetes Study, done primarily on type 2 diabetes patients, found a positive effect of intensive blood pressure (BP) control. Further evaluation in the ACCORD study found no additional benefit of lowering BP below the long-standing limit of 140/90. However, more recently, the American College of Cardiology and the American Heart Association, in an effort to reduce the risk of heart attack and stroke, have reset the blood pressure desirable normal below this to 130/80. In addition, ACCORD demonstrated a decrease in the need for focal laser for DME with the use of fenofibrate to reduce triglycerides. Fenofibrate has been approved by Australian authorities to treat DR.

As previously mentioned, rates of type 2 diabetes have soared in both developed and developing countries outnumbering the number of professionals available to screen for DR. Many screening programs have been tried or are under investigation, but so far they have been inadequate in real world situations. Thus, the attempt to implement better screening modalities in underserved urban and rural areas is a much desired goal.

Patients with diabetes are living longer and are able to live full productive lives, but their paths are by no means easy. Maintenance of blood glucose levels, blood pressures, and lipids are a constant battle. When juggled with busy schedules, this can at times be overwhelming. Further fears of blindness, kidney disease and amputation remain definite prospects, espe-

cially for those whose control of systemic conditions is less than optimal. Genetics obviously also plays a role, but this is still not clearly understood. In this book, we review areas under investigation to help us better screen, predict, and understand some mechanisms relating to development of DR. Progress has been made, but much work remains because current treatments are available only near the endpoints of DR. Innovative and effective advances allowing the early detection and intervention of DR are especially relevant and urgently needed.

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