

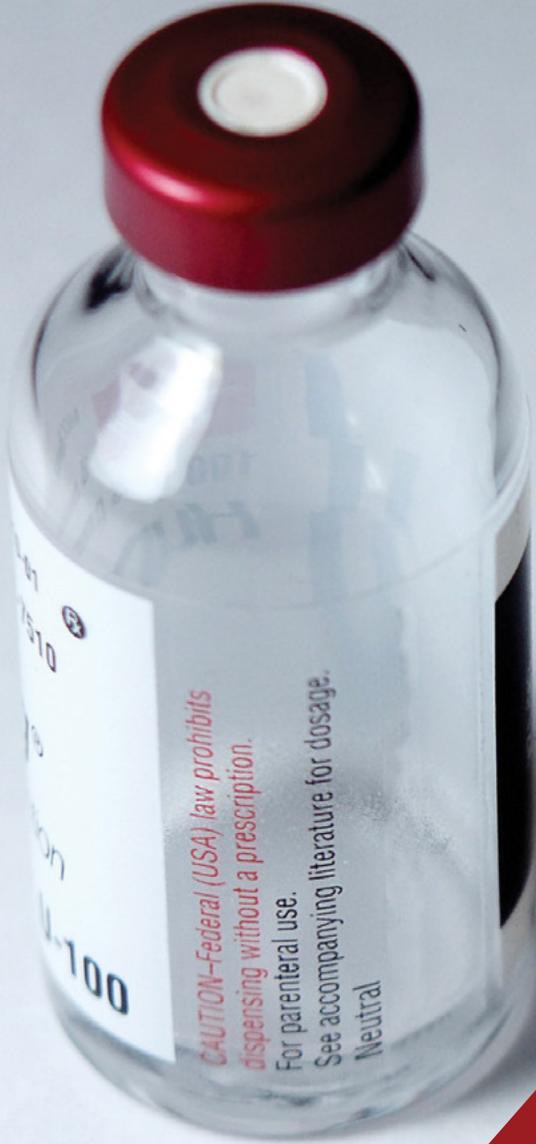
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LOOKING AT DIABETES MELLITUS & ITS COMPLICATIONS

From a Different Angle

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Researchers advance knowledge through discovery. There is often a significant time lag between when new findings are initially communicated in the scientific literature and when they become generally disseminated. Therefore, in order to provide the best treatment for those living with diabetes, I would like to encourage those working with diabetes to look at the bigger picture of diabetes and its complications by raising awareness of some newer research findings in the field.

Diabetes is known to result from lack of insulin action. Insulin is the primary hormone responsible for controlling the storage and utilization of cellular nutrients. Insulin decreases blood glucose, stimulates glucose transport into muscle and fat, promotes glucose storage as glycogen, inhibits hepatic glucose production, stimulates amino acid uptake and protein synthesis (in both muscle and liver), and inhibits breakdown of fat and protein. These actions of insulin are known as its short-term metabolic effects, and are the best known effects of insulin. Although the mechanisms by which insulin regulates the above metabolic events are still unknown, it is the deregulation of these functions that is believed to be the cause of insulin resistance in type 2 diabetes mellitus.

Along with its short-term metabolic effects, insulin acts on almost every cell and tissue in the body where it exerts important regulatory actions. It regulates gene transcription, thus affecting the synthesis of key enzymes, it has important effects on the cell cycle, and it protects cells from apoptosis (programmed cell death). In addition to its growth regulating effects, recent advances have shown that insulin plays an important role in the central nervous system (CNS). Insulin is involved in neuronal survival. It regulates neural proliferation, apoptosis and synaptic transmission, and it plays a role in memory and cognition. For example, insulin has been shown to protect synapses against Alzheimer's linked toxins. In short, insulin is a master hormone with multiple effects.

Diabetes mellitus (DM), a group of metabolic syndromes characterized by hyperglycemia, is due to lack of insulin action. In pre-diabetes and type 2 diabetes, cells develop resistance to the actions of insulin. As a result of decreased insulin action, blood sugar concentration increases. This increase in blood sugar occurs as a result of decreased glucose transport into fat and muscle, decreased use of glucose in the body, and increased conversion of amino acids into glucose (gluconeogenesis).

Conventional wisdom has been that diabetes complications are due to high circulating glucose levels. These complications include kidney failure, peripheral neuropathy, delayed wound healing which may lead to amputations (especially lower limb), risk of heart disease and stroke, hypertension, and sexual dysfunction. While this may be true for some of the complications of diabetes, the evidence suggests that the non-metabolic effects of insulin have a major role in the development of diabetic complications.

For example, periodontal disease and amputations may result from not only high glucose levels, but could also be the result of fibroblast (fibroblasts are the main cells that form connective tissue) changes in the body. It has been documented that fibroblasts isolated from people with diabetes have decreased proliferation and increased apoptosis, which could be the mechanism responsible for the delayed wound healing seen in those with periodontal disease and those requiring amputations.

A lack of insulin may be the cause of other complications as well. Insulin has been shown to relax blood vessels, and the loss of this effect could result in hypertension. People with diabetes are also more susceptible to infection and have reduced ability to deal with infection. This, too, is probably due to lack of insulin action. Additionally, it has been documented that type 2 diabetes mellitus and insulin resistance are associated with Alzheimer's. Research is showing that diabetes impairs hippocampus dependent memory, synaptic plasticity and adult neurogenesis. Evidence of insulin's protective role in the CNS, documented above, suggests that it is the lack of these actions of insulin that is responsible for these complications of diabetes.

In conclusion, several lines of evidence suggest that a decrease in the non-metabolic effects of insulin plays an important role in the development of diabetic complications. I believe that further study of insulin signaling, and increased understanding of how insulin causes its many and varied effects, will lead to a better understanding of the causes of diabetic complications. This in turn will lead to better ways to prevent or treat them. We are likely going to find that elevated blood sugar levels are only one facet of diabetes. We should be open-minded to new information, and be ready to widen our thinking about diabetes and its complications to include new directions. ■■