Why is hyperglycemia bad?

David W Moskowitz
GenoMed Inc., USA

Since the isolation of insulin from dog pancreases by banting and best almost a century ago, treatment of diabetes has focused on controlling glucose. It is generally assumed that glucose's effect is mediated through an increase in blood osmolality and viscosity (PMID: 12871609), as occurs in the lens of the eye. But blood viscosity increases only 5% when glucose increases from 100 to 300 mg/dl. First, the 300% increase must be divided by 18 for the molecular weight of glucose (180g/mole), and, second, osmolality is due mostly to sodium and chloride. Blood is essentially sea water, not lemonade. There must be an amplification step, something beyond mere osmolality/viscosity. One amplification step appears to be ACE, which is activated by viscosity, since ACE appears to be a mechanosensor (PMID: 12685804). But there's another way ACE is activated, even more strongly by glucose. ACE appears to be glucose's partner in a redox reaction (PMID: 15379656). Raising glucose to 300mg/dl may increase osmolality by only 5%, but it should increase ACE activity one-for-one: for every glucose molecule oxidized from an aldehyde to a carboxylic acid, one active site of ACE is revealed. This appears to have special importance for the kidney (PMID: 12396747) and lung (PMID: 16510756); both organs sense oxygen levels. A corollary is that a "normal" glucose level of 100 mg/dl is still chemically active. Perhaps aging is due to glucose activation of ACE as redox partners. Diabetes looks like accelerated aging because the glucose level, and the amount of ACE activation, is increased. In other tissues, like nerves, where ACE inhibitors have no effect, glucose may have unknown redox partners responsible for local complications. We are still in the early steps of exploring this hypothesis. My hope is that retinopathy will respond to high-dose quinapril as diabetic kidney disease has done for the past 24 years. In summary, blocking glucose's amplification partners may be just as important clinically as controlling glucose.

e: dwmoskowitz@genomed.com

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