



Diabetes Uncomplicated

Evan David Rosen, M.D., Ph.D.

Assistant Professor of Medicine, Harvard Medical School

Elevated glucose levels in all types of diabetes can cause damage to blood vessels, which is the root cause of the complications of diabetes. When the damage occurs in the tiny blood vessels of the eye, kidney, or nerves, the result is diabetic retinopathy, nephropathy, or neuropathy, respectively. Damage to the large blood vessels of the body leads to atherosclerosis, heart attack, and stroke. Despite decades of research on diabetic complications, we are only just beginning to understand the mechanisms by which hyperglycemia affects blood vessels. Even more frustrating is our inability to treat these complications once they occur. Specifically, we have very few efficacious therapies for diabetic retinopathy, neuropathy and nephropathy. The best advice we can give our patients is to take responsibility for keeping their sugar levels down, as this can prevent complications in the first place.

Slowly, however, researchers have chipped away at the problem of diabetic complications, and the result has been a better understanding of the basic processes involved. This improved understanding, in turn, has suggested some potentially useful therapies as well.

Studies on diabetic complications have pointed to four separate pathways activated by hyperglycemia leading to vascular damage. These pathways include increased polyol flux, increased advanced glycation endproduct (AGE) formation, protein kinase C (PKC) activation, and increased hexosamine flux. Without getting too bogged down in the biochemical details, suffice it to say that each pathway has had its adherents in the research community, and drug companies have spent a lot of time and money trying to halt diabetic complications by blocking one pathway or the other, with only modest success.

A major breakthrough in the field occurred a few years ago, when a group at the Albert Einstein College of Medicine unified the field by identifying a single glucose-induced mediator of all four pathways. This mediator is superoxide, a souped up form of oxygen with extra electrons attached that can cause great mischief when overproduced in cells. When glucose is metabolized, electrons are pushed down a chain of proteins that produce ATP, the currency for energy in cells. In the presence of too much glucose, electrons are pushed down the chain faster than these proteins can transfer them, allowing some electrons to “pop off” the chain where they can stick to oxygen and other similar molecules. Many

cells have the ability to regulate how much glucose they let in, but for some reason vascular cells can't do this. Thus, when blood sugar is high, there is high glucose inside vascular cells as well. The resulting elevated superoxide levels then block the metabolism of glucose, which increases the levels of intermediary compounds that are stuck behind the blockade. These compounds activate all four of the damaging pathways at once.

The Einstein researchers then postulated that if superoxide was causing glucose metabolism to get backed up, there might be benefit in unplugging the pipeline. They noted that an enzyme called transketolase could get rid of the troublesome intermediary compounds if it were sufficiently activated. They also noted that thiamine (also called vitamin B1) was necessary for the transketolase enzyme to have full activity. Perhaps elevating cellular thiamine levels could jack up transketolase and unblock the pipe, the reasoning went, but when the researchers added thiamine to cells in culture exposed to high concentrations of glucose, they found a measly 20% increase in activity, not enough to do any good.

The next revelation came from colleagues in Germany, who noted that a modified form of thiamine, called benfotiamine, had been used in that country for over a decade to treat diabetic nerve pain with some success, although nobody understood how or why it worked. When the Einstein researchers put benfotiamine on their cells, they found a whopping 300% increase in transketolase activity, enough to reduce the activation of at least three of the four offending pathways associated with vascular damage. Furthermore, benfotiamine could reduce hyperglycemia-induced damage to vascular cells in culture as well as in diabetic rats, which developed less retinopathy than did rats receiving placebo.

This study is nice because (a) it provides further "proof-of-principle" that superoxide-induced blockade of glucose metabolism is the root cause of diabetic complications, and (b) because it suggests a potential therapy for the prevention and treatment of those complications. As I mentioned earlier, benfotiamine has already been in use for a while in Europe for the control of diabetic nerve pain. As far as I have been able to discern, no one has systematically tested its use in humans to see if complications can be prevented in the first place, nor have they used it to treat other forms of diabetic complications such as retinopathy or nephropathy. Also, there is still controversy over the appropriate dose of benfotiamine to use even in neuropathy, its best studied indication. It seems likely that such detailed studies will now be performed, and we'll have a better sense of the utility of this agent. Fortunately, significant side effects have not been reported from the use of this agent, although that issue will also need to be more carefully studied in large controlled experiments.

Before you run out and buy jars of vitamin B1, remember that run-of-the-mill thiamine doesn't seem to have any beneficial effect on either transketolase

activity or diabetic complications. Hopefully, benfotiamine or a related compound will prove to be a valuable adjunct to the antidiabetic armamentarium, but for now, we'll have to wait for the appropriate studies to make that determination

References:

1. Hans-Peter Hammes, Xueliang Du, Diane Edelstein, Tetsuya Taguchi, Takeshi Matsumura, Qida Ju, Jihong Lin, Angelika Bierhaus, Peter Nawroth, Dieter Hannak, Michael Neumaier, Regine Bergfeld, Ida Giardino, Michael Brownlee. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. *Nature Medicine* 9, 294 - 299 (01 Mar 2003).

2. Michael Brownlee. Biochemistry and molecular cell biology of diabetic complications *Nature* 414, 813 - 820 (13 Dec 2001).

Written by Evan D. Rosen, M.D., Ph.D.