A new look at diabetes

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Diabetes is currently one of the leading killers in America. It is also the primary cause of blindness in working-age adults, it causes a third of all kidney failures and half of all lower-extremity amputations, and it is a major factor contributing to the epidemic of cardiovascular disease in Western society. The incidence of heart disease among diabetics is a dramatic three to eight times that of the general population and is particularly prevalent among the 14 million Americans with type 2 diabetes. This is due in part to their increased susceptibility to cardiovascular risk factors such as hyperglycemia, obesity, hypertension, and hyperlipidemia. But as much as 50% of the increased risk of heart disease is not accounted for by these traditional factors.

The major cause of diabetic complications is a series of chemical reactions that occur throughout the body between sugars and proteins, forming "glycation" products. The glycation reaction occurs when sugars spontaneously bond to proteins, forming products that are toxic to tissues and cells. Early products of this reaction eventually lead to the formation of more complex and irreversible products known as Advanced Glycation End Products (AGEs). My lab and others have shown that AGEs accumulate in the tissues of diabetics, leading to a hardening of blood vessel walls, malfunction and scarring of the vessels, and an increase in damaging immune reactions.

Cardiovascular implications: Several large studies have shown that controlling blood sugar can reduce damage at the microvascular level—in the tiny capillaries of the eye and kidney especially—but the impact of blood-sugar levels on cardiovascular disease is less clear. The landmark examination of this question in type 2 diabetes, called the United Kingdom Prospective Diabetes Study, evaluated the impact of carefully controlling blood-sugar levels in 5,000 patients over a 10-year period. The researchers found significant reductions in microvascular disease in patients treated with insulin or any of several drugs, including sulfonylureas and metformin; but only metformin was associated with a significant reduction in cardiovascular disease. This agent, which has been used to treat diabetes for 42 years, was associated with a 40% reduction in heart-attack rates, even though its ability to reduce blood sugar was no better than the other treatment regimens. Using these clinical observations, and a theoretical chemical hypothesis, my lab has performed a series of studies to address this important question.

We have recently focused on highly toxic glycation products called alpha-dicarbonyls. They produce direct tissue damage by several different mechanisms and also lead to the formation of damaging AGEs. Among the most toxic of these is a compound called methylglyoxal (MG). To determine the role of alpha-dicarbonyls in producing diabetic complications, we have developed sophisticated laboratory methods to measure them and have performed extensive studies demonstrating that they are elevated in diabetics and that their levels relate to the degree of blood-sugar control.

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Hypothesis: An especially exciting area of diabetes research has been the effort to identify drugs that reduce diabetic complications. One of the most promising is an agent called aminoguanidine, which inhibits the glycation reaction by chemically binding MG and other alpha-dicarbonyl compounds. This reduces their toxicity by forming inert products. In the course of our research, I and my colleague Dr. Ben Szwergold observed that metformin closely resembles the chemical structure of aminoguanidine. We then performed some test-tube studies which showed that metformin, like aminoguanidine, prevents MG-induced protein damage. Based on these results, we hypothesized that aminoguanidine could lower patients' MG levels and potentially reduce the incidence of diabetic complications.

Though other researchers might have noticed the similarity between metformin and aminoguanidine, our extensive experience measuring MG and doing clinical research placed us in an ideal position to test the hypothesis. We measured MG levels in type 2 diabetics who were taking metformin and compared them with those of patients on other standard treatment regimens, including sulfonylureas, thiozolidinediones, and insulin. These studies clearly showed that metformin therapy significantly reduced MG levels, while achieving similar blood-sugar control.

Potential: We next investigated the mechanism leading to MG-reduction and identified an inert condensation product called triazepinone, which is formed by a chemical interaction between MG and metformin. We have also developed an assay to measure triazepinone in the clinical setting. Our preliminary studies have shown that triazepinone accounts for as much as 70% of the reduction in MG levels. Further studies are ongoing, but metformin shows potential against the ravages of glucose toxicity.

The trend these days has been for scientific research to become ever more specialized and complex, while at the same time economic pressures on clinicians mount. But these studies demonstrate that it is still possible for clinicians with some scientific background, plus a good idea and a willingness to work extra hours, to explore an exciting scientific idea and follow it to its logical clinical conclusion. ■

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