



## **Type 2 Diabetes; Take Two Aspirin and Call Me In The Morning?**

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

Assistant Professor of Medicine, Harvard Medical School

Acrp30 is a molecule that is produced by fat cells and which is deficient in the blood of people and animals with type 2 diabetes. When this protein is given back to diabetic mice, it seems to restore serum glucose and insulin levels, causes burning of fats accumulated inappropriately in muscle and liver, and leads to weight loss. One of the most interesting features of Acrp30 is that it looks very similar to molecules used by the body to ward off infection. In this edition of *Viewpoint*, I want to expand on this notion of immune molecules being produced by fat tissue, and the role these molecules may play in type 2 diabetes.

It turns out that adipose tissue (fat) is far more versatile than we once supposed. In addition to storing energy in the form of triglycerides, fat secretes a variety of hormones that have effects on a wide variety of bodily functions, ranging from bone density to blood pressure control. In the last three to five years, the list of factors known to be secreted by fat has swelled considerably, and at least one interesting theme has emerged: the fact that fat secretes a lot of things that are known to regulate the immune system. This was first seen with a protein called adipisin, which was identified as a fat cell product in 1986. Adipisin is also called complement factor D, and like other complement proteins it participates in a process that kills many forms of invading bacteria. A few weeks ago a paper was published about a family with many members carrying adipisin mutations; these unfortunate people are prone to devastating infections by meningitis-causing bacteria, among others.

But it's not just about adipisin. It turns out that many molecules known for their role in the immune system are produced by fat cells, including the inflammatory hormones tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), as well as a variety of proteins known to be a part of the "acute phase response," such as serum amyloid A, haptoglobin, and others. The acute-phase response is the name given to a phenomenon seen when the body is subjected to different kinds of stress, such as malignancy, infection, or tissue injury. It describes the appearance or disappearance of specific proteins in the blood, some of which I've just mentioned. Presumably, these proteins participate in the inflammatory process that helps the body deal with these events, although exactly what each individual protein does is still a bit murky. In many cases of

chronic inflammation, there is often what looks like a permanent state of acute-phase response (which points out the silliness of the name "acute-phase", but tradition dies hard in medicine and so the name has remained).

So what does all this have to do with diabetes? Well, one idea that is gaining currency is that type 2 diabetes is actually a form of chronic inflammation. Fat cells, overabundant in obese patients and cranking out lots of acute-phase proteins, may induce a state of persistent inflammation that manifests itself as type 2 diabetes.

This is not as crazy as it sounds, if you consider the following points:

- ?? Many inflammatory molecules, like TNF-alpha and IL-6, can induce a state of insulin resistance in muscle, fat, and liver. Blocking these molecules, at least in diabetic rats and mice, improves blood sugar levels.
- ?? It has been known for almost 100 years that high doses of salicylates, which include aspirin-like drugs and which have anti-inflammatory activity, can improve diabetes. These drugs block an enzyme called IKKbeta, and mice that lack this enzyme are resistant to obesity-induced diabetes.
- ?? Levels of many acute-phase proteins are higher in diabetics than non-diabetics.

Now, this last point can be interpreted two ways. On the one hand, I am obviously suggesting that these proteins may play a causative role in diabetes. On the other hand, you could just as well argue that these proteins rise *because* of the diabetes, rather than the other way round. A new study published in a recent *Journal of the American Medical Association* (JAMA) tends to support the former conclusion, however. In the Women's Health Study, physicians collected blood from thousands of women beginning almost a decade ago. They have followed these women over the ensuing years, and have kept up with them to record how they have fared. The results have been relevant to many diseases and conditions, but in this particular paper the authors chose hundreds of women who developed diabetes over the years and compared them to women who remained diabetes-free. They then went back to their freezers to look at the frozen blood samples collected *before the women developed diabetes*. Interestingly, they found that those women destined to have type 2 diabetes had higher levels of acute-phase proteins and other inflammatory markers than did those destined to remain healthy.

This observation, coupled with the sort of other data that I mentioned above, is certain to focus attention on inflammation as a way for diabetes to develop. This in turn will lead people to test new potent anti-inflammatory drugs in diabetes, a use that would not have been predicted even a few years ago. Another spin-off of this type of study might be the early identification of patients at risk for diabetes later in life--this would allow

doctors to focus their efforts to change diet and exercise patterns on those patients most likely to develop the disease. Many questions remain unanswered, such as how the inflammation is triggered in the first place. While these answers are being sought by scientists, practical interventions can still be tested that may benefit the millions of people that have or will soon have type 2 diabetes.

**References:**

1. Jason K. Kim, Yoon-Jung Kim, Jonathan J. Fillmore, Yan Chen, Irene Moore, Jongsoon Lee, Minsheng Yuan, Zhi Wei Li, Michael Karin, Pascale Perret, Steven E. Shoelson, and Gerald I. Shulman. Prevention of fat-induced insulin resistance by salicylate. *Journal of Clinical Investigation* 2001 108: 437-446.
2. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *Journal of the American Medical Association* 2001 Jul 18;286(3):327-34.
3. Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? *Diabetologia*. 1998 Oct;41(10):1241-8. Review.

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

Content created 8/14/01

Content last reviewed August 14, 2001