

**The Royal Society of Edinburgh
Caledonian Research Foundation Prize Lecture**

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Fuelling the Fire: on how obesity fuels disease

The Western World is facing an obesity epidemic and a dramatic increase in rates of serious illness, including diabetes and cardiovascular disease. But why should weight gain be so unhealthy? Professor Shoelson looked at what is happening in our bodies at a molecular level as we pile on the pounds – and suggested that inflammation and our own immune systems could be contributing to the growing burden of ill health. In a fascinating lecture, he also suggested a remarkably simple possible solution.

Over the last two decades, obesity rates have rocketed. In the USA in 1985, only a small number of states had obesity levels of 10–14 per cent. By 2005, all states had surpassed that figure, with the majority showing rates of between 15 and 29 per cent. Shockingly, in three states more than 30 per cent of adults were obese. Hardly surprisingly, the states with the lowest rates of obesity also had the highest life expectancy.

Obesity is associated with a number of serious illnesses, including hypertension, dyslipidemia (high cholesterol), coronary heart disease, non-alcoholic fatty liver disease, insulin resistance and type 2 diabetes (T2D) as well as some cancers and other conditions including osteoarthritis. Many of these illnesses are characterised as being part of metabolic syndrome. As obesity rates have soared, so have numbers of individuals with diabetes, which is, in itself, a risk factor for atherosclerosis (where plaque builds up on the inside of the arteries), or cardiovascular events such as stroke or heart attacks. A combination of the Western diet, obesity and a sedentary lifestyle has consequences, leading to insulin resistance and metabolic syndrome. But what is it which causes insulin resistance in people who fall victim to obesity?

We know that individuals can take action so that their bodies are sensitive, rather than resistant to insulin. Weight loss, exercise and a healthy diet are known to improve health outcomes, but that doesn't mean people find it easy to do. So Professor Shoelson and colleagues have been exploring the molecular mechanisms which lead to insulin resistance – with varying success. They considered the insulin signalling pathways, but found little joy. "There are lots of pathways," said Professor Shoelson, showing a bewildering array on slide, "But they don't give us the answers." They considered genetics – fortuitously several genes have been discovered which are apparently implicated in T2D. But again, there was nothing to explain fully the recent upward swing in cases of diabetes and metabolic syndrome. "We knew that it couldn't be just genetics – we have the same genes as our parents and grandparents", he said. "the rise [in cases] has been too rapid."

He also considered lipid (fat) deposits in the liver and muscle, which causes insulin resistance. Again, however, it doesn't explain today's disease patterns. In wondering what else could be involved, thoughts turned to inflammation. There were a number of clues that this was involved. Epidemiologically, there were several markers in patients resistant to insulin which are commonly seen in inflammatory diseases. These include elevated white blood cell counts and CRP (C-reactive protein). Cell biology provided clues too. Proinflammatory cytokines such as TNF-alpha could create insulin resistance.

Interestingly – and this, said Professor Shoelson, was where the real breakthrough came in, there was also a history of old clinical literature which suggested that salicylates – anti-inflammatory drugs of the same type as aspirin – had an effect on patients with diabetes.

Professor Shoelson pointed to a paper from late 19th century Berlin which showed how high doses of salicylate were effective in reducing the blood sugar levels of a man with 'the lighter type' (what would now be called type 2) of diabetes. The man had not responded to the standard treatments of the time, which would have been a potatoes and milk diet. The doctor had reasoned that salicylic acid, which was similar to carbolic acid, might be used to treat diabetes. The initial treatment of 10g per day was cut by half when side-effects, including tinnitus, were intolerable. After 12 days the patient was discharged

That was in June 1876. Fast forward several decades to November 1957 and the BMJ published a paper based on research in Glasgow. It showed that aspirin reduced blood sugar levels in patients with *Diabetes mellitus*, but that levels rose again once the patients stopped taking the aspirin. The doctors had been inspired to do the research after a patient with diabetes, who was taking salicylate treatment for rheumatism, was found to have no sugar in his urine, despite taking nothing but aspirin.

Salicylic acid, originally derived from willow bark, had been suggested for centuries to be useful in treating pain and fever. By the beginning of the 20th century, the pharmaceutical company Bayer was marketing a form of salicylate, acetylsalicylic acid, which it called aspirin. By 1910, it was the most used drug in the world. Later in the 20th century it became popular as an anti-clotting agent and is used widely to prevent heart attacks and stroke.

But at the start of the 21st century, Professor Shoelson and colleagues began looking seriously at the effect of salicylate treatment on inflammation. Their research has been both lab-based, in animal models, and on humans in clinical trials. One thing that has been discovered was that diet-induced obesity promotes inflammation in fat. Why should this be?

The team discovered that a pathway important to the immune system, NF-kappaB, was activated by obesity. This caused inflammation in fat and liver cells and led to insulin resistance. At a molecular level, the researchers found that while fatty tissue contains cells which are activated during the immune process (macrophages), the cells which generally regulate the immune response (Tregs) decrease where there is obesity. So there is a combination of obesity activating the immune response or inflammation, while the cells that would normally keep the immune system under control are diminished. The idea that insulin resistance can be caused by inflammation opens up the real possibility that anti-inflammatory agents might make good drugs for prevention and treatment of metabolic syndrome.

Back to salicylates. If they do lower blood glucose, does this provide clues to a better understanding of the molecular process which leads to insulin resistance, T2D and cardiovascular disease? Does it provide leads for new drug targets and, importantly, new drugs for T2D and CVD? Professor Shoelson described how mice on a Western diet would develop different aspects of metabolic syndrome, including atherosclerosis. This, however, was reversed by salicylate. There was, however, a problem with testing the theory in humans. High-dose aspirin has distressing and potentially fatal side-effects, including severe gastrointestinal upsets and bleeding – the latter could make a deadly combination with aspirin's clot-reducing activity.

Another salicylate compound, called salsalate (disalcid), does away with many of these side-effects, however, making it much safer. Small trials on patients have shown some signs of success and the results are due to be published soon. Professor Shoelson said, however, that much larger studies were needed. "The problem is that phase II and phase III trials are expensive – and pharmaceutical companies aren't interested in funding trials on generic drugs which are dirt cheap. So I approached the federal government."

His application for funding was eventually successful and larger scale trials have started. The first stage looks promising and suggests that the treatment is safe (although it did carry a risk of low blood sugar, which, as Professor Shoelson said, is remarkable in a diabetes trial). The second stage, due to start in September 2008, will involve 280 patients with diabetes, at 20 sites in the US, who will be randomly assigned to receive salsalate or placebo for six months. A separate study is being initiated this month to determine the effects of salsalate on coronary heart disease. 900

patients with metabolic syndrome and documented heart disease, at several centres, will be randomly assigned to receive salicylate, placebo or lifestyle modification for 30 months. They are being closely monitored with many tests including CT scans, to show whether they have atherosclerosis.

Professor Shoelson is optimistic. He has concluded that salicylate treatment inhibits obesity-induced inflammation and the activation of the immune response via NF-kappaB.

“We are hopeful that Salicylates represent a potential new method for treating patients with diabetes and the metabolic syndrome,” he said. “And they may decrease risk of other disease associated with obesity-induced inflammation, including CVD and possibly certain cancers.”

Questions

At the Edinburgh event, Professor Shoelson was asked several questions. These included whether salicylate treatment could be used for other inflammatory disease, such as rheumatoid arthritis. He said the problem was that rheumatologists followed the pack instructions and dosed at a maximum of 3g, which was ineffective. His personal feeling was that they would have more success if they dosed to the point that the patient developed side-effects. “If you’re dosing in the range where there are no side-effects then there won’t be efficacy either,” he said. “3g, no, 4g pretty good!”

He was asked about the culpability of the fast food industry on obesity. “It’s pretty easy to point fingers. The food industry is one culprit, but we’re culprits too. Society has to change”.

He was also asked about the importance of marketing such a simple and cheap solution – salicylate – when it wouldn’t make pharmaceutical companies any money. Professor Shoelson said that was a major challenge, but that getting physicians involved in trials was a good start.

Vote of Thanks

The vote of thanks was delivered by Professor Jonathan Seckl, who particularly praised Professor Shoelson’s focus on translational medicine – of taking the discoveries from bench to bedside and back again. His lecture was a “tour de force, full of novel thinking”, said Professor Seckl.

Jennifer Trueland

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