Other drugs

Melissa P Ford looks at other drugs that may be used in the treatment of diabetes

The most recent research indicates that about 80% of cases of type 2 diabetes can be attributed to lifestyle factors, the most powerful of which is obesity. There is also a strong correlation between hyperglycemia (even if type 2 diabetes is not pre-existing) and cardiovascular disease. Obesity is highly genetic - there are specific gene defects that predispose some people to obesity compared to others - and the placement of excess fat (belly or all-over) is genetically programmed. It is becoming very clear to researchers who focus on diabetes and obesity that abdominal visceral fat, the kind that consitutues a "beer gut," is much worse than the all-over Michelin Man/Pillsbury Doughboy kind.

An Australian researcher has a motto: "Butt fat is good but gut fat is bad." The reason for abdominal visceral fat (also construed as an "apple" shape) to be considered worse is that the sort of fat that makes the abdomen disproportionately big compared to the rest of the body is also the kind that likes to grow around the internal organs. When the fat grows around the liver, insulin resistance results because the insulin from the pancreas cannot get into the liver properly. Triglycerides rise because of inadequate insulinization. Abdominal visceral fat also finds its way around the heart, contributing further to the development of heart disease. With the inadequate insulinization caused by the insulin resistance, glucose rises. It is now thought that glucotoxicity from chronic hyperglycemia before the diagnosis of type 2 diabetes contributes in a major way to beta-cell dysfunction in type 2s (the UKPDS showed that by the time they are diagnosed most type 2s have only 50% of their original insulin production capacity left). While the UKPDS did not show a reduction in cadiovascular disease deaths in patients taking insulin, the follow-up study to the DCCT has recently (I mean June 2005!) shown that type 1s on intensive therapy have a 57% reduction in risk for a heart attack or stroke after even 6.5 years of intensive therapy compared to type 1s on conventional therapy for the same timespan. This difference is attributed to better glycemic control: the same percentage of patients in both groups took statins so the statins didn't help. Those of us diagnosed in the 1960s/70s may have stories of people with type 1 dying of heart disease in their 30s or 40s... now we know why. The findings from the DCCT follow-up may lead to a more targeted examination of the impact of better glycemic control on type 2s' risk for cardiovascular disease; at the moment it is extrapolation to consider the DCCT follow-up findings as entirely relevant to type 2 but I can certainly get on that bandwagon!

In the remaining 20% of cases of type 2- those among people who are otherwise fit and healthy - genetics are usually cited. For instance, maturity onset diabetes of the young (MODY) can be caused by a defect in one of several genes and people may reach middle age before anyone ever checks whether they could be diabetic or not. Those people are likely to get treatment for type 2 even if they ought to be genetically typed - "the type 2 treatment works so why order an expensive test?" the physician thinks. Also, a lot of latent autoimmune diabtes in adults (LADA) patients are initially diagnosed as type 2 even though they are usually progressed to insulin rapidly. It has been estimated that 10% to 25% of type 2s could actally be LADAs. It is hard to tell because a lot of them will be put on insulin without their diagnosis code being changed from type 2.

The other emerging possible truth is that the symptoms that we classify as "type 2 diabetes" may be caused by heterogenous factors: that is, perhaps in one person the primary defect that led to insulin resistance was factor A, but for another person factor B (whatever it is) was more relevant. We just don't know yet because assays to discriminate between the causes of type 2 are not available yet. We can do genetic testing or we can check for insulin antibodies, that's about it.

So we have to start with where the insulin resistance comes from. How does a slim person become insulin resistant? The most likely causes are disproportionate abdominal visceral fat (Asians who look slim to us Westerners are very prone to this) and genetics. In either case, the insulin resistance per se does not cause them to gain more weight. Recall that in type 1s and late-stage (undiagnosed until there's no insulin production left) type 2s, insulin deficiency causes weight loss. Insulin resistance is like partial insulin deficiency: the cells are not getting all the insulin that they need and triglycerides rise because insulin does not suppress them. Many newly diagnosed type 1s have sky-high triglycerides. Endogenous insulin does not make people fat, eating too much and not exercising enough does. If someone has a genetic predisposition to obesity, it is only that much easier to get fat if one eats more/exercises less than one should. And metabolic rates/ideal activity levels vary person-to-person because of our genes. Of course losing weight on purpose is always harder than gaining it. There is a long list of hormones that can be

disordered when one is obese that make it harder to reverse the metabolic dysfunction. It is very weird that about 80% of type 2 diabetic patients who have Roux en Y gastric bypass procedures (not any other forms of bariatric surgery, just Roux en Y) do not need their diabetes meds anymore within 48 hours of having that surgery. There is something going on in the gut in type 2 diabetes that we do not understand and it is related to an endocrine factor that is triggered or at least exacerbated by obesity. Adiponectin, peptide YY ("PYY"), GLP-1, amylin, and several other hormones are being investigated for their roles in appetite regulation and metabolism. Amylin and GLP-1 are both deficient in type 2 diabetes. Amylin is deficient in type 1 too - that is why it is so hard for some of us to get rid of the last 10 lbs!!!

Another intriguing theory is that insulin resistance resulting in endogenous hyperinsulinemia leading to atherosclerosis (btw, exogenous insulin therapy does not cause atherosclerosis - that conventional wisdom has been binned) is actually not as simple as it sounds. Andreas Pfützner (IFKE, Mainz) has a very interesting theory that he talked about last year at the Diabetes Technology Society meeting in Philadelphia. He has used some sensitive blood insulin assays that can distinguish between the various kinds of insulin in a blood sample - preproinsulin, proinsulin, and insulin. Pfützner found that in insulin-resistant type 2 patients, there is a greater proportion of proinsulin in the blood than there is in non-insulin-resistant/non-diabetic patients (http://care.diabetesjournals.org/cgi/content/abstract/27/3/682). This is significant because proinsulin can do bad things when it gets out of hand. As general beta-cell function deteriorates in type 2, an increasing proportion of the insulin secreted is not truly insulin but proinsulin. Pfützner suggests that the increased risk of cardiovascular disease in patients taking sulfonylureas might originate in the stimulation of proinsulin, because exogenous proinsulin constitutes an independent risk factor for heart attack and cardiovascular disease. Pfützner claims pioglitazone (Actos) reduces intact endogenous proinsulin. He argues that measurement of fasting intact proinsulin secretion might be useful in deciding when to change therapies for type 2 patients.

If a slim type 1 becomes fat it's very possible for insulin resistance to arise from obesity. Now that type 1s are living long enough that we can get middle-aged and pudgy, type 1s who thought they were off the hook are getting the metabolic syndrome and becoming insulin resistant. Because the insulin sensitizer drugs thiazolidinediones (TZDs) appear to increase rates of congestive heart failure in patients taking insulin, an insulin-resistant type 1 is more likely to be prescribed metformin than any other agent. There is a new class of non-TZD insulin sensitizers in development, one of which is metaglidisen (made by Metabolex) that should go to the US FDA in the next couple of years. If this new class of non-TZD insulin sensitizers is safe in combination with insulin, then I can imagine insulin resistant type 1s taking such drugs someday.

Author: Melissa P Ford <mford@hotmail.com>. Melissa P Ford is not a medical professional. She has Type 1 diabetes and uses an insulin pump. The information given here is based on her own personal experience. More about Melissa P Ford...

Created: July 2005; Last updated: Thursday 28 July 2005