Keep it in the family: the influence of genetics on microvascular disease

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Let's face it – some people are much cleverer than the rest of us. Whoever had the idea to look at insulin resistance in the relatives of patients with type 1 diabetes (T1DM) was very clever indeed, and yet now the idea seems blindingly obvious.

Why is it that some of our patients seem to develop nephropathy or retinopathy early on in their disease, when their glycaemic control has seemed little worse than their complication-free fellow patients? Familial clustering of complications such as nephropathy has long been observed within people with T1DM, and, several decades ago, Harry Keen noticed that patients with nephropathy were more likely to have a family history of hypertension.

This study has confirmed some of these previous clinical observations by investigating the relatives of patients with T1DM with and without microvascular complications. They found there was a greater likelihood of the features of the metabolic syndrome (described as an insulin resistance score) occurring in first-degree relatives of probands with nephropathy and retinopathy.

Although not conclusive it does suggest that genetic factors influence the risk of microvascular disease. The importance of this lies not only in understanding the nature of diabetic complications, but in identifying higher risk patients. A detailed family history may be helpful in targeting these individuals and at least ensuring they receive annual screening for microvascular complications from an early age. In the future it may of course be possible to identify the genes that increase those risks and allow early intervention with the appropriate drugs. *GATTACA* here we come...

DIABETOLOGIA

Progression to type 1 diabetes affected by insulin

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The role of insulin resistance in the development of type 1 diabetes has so far received little attention. This study explored insulin resistance as a potential risk factor for the progression to type 1 diabetes.

2 First-degree relatives of type 1 diabetes probands who were islet-antibody-positive were monitored during the study. The median duration was 4.0 years.

3 First-phase insulin response (FPIR) to intravenous glucose was used as a measure of insulin secretion. Homeostasis model assessment of insulin resistance (HOMA-R) was used to estimate insulin resistance.

4 The investigators compared these variables in people who progressed to type 1 diabetes (n=43) and those who did not (n=61).

5 In a matched comparison analysis, those participants who progressed to type 1 diabetes exhibited higher fasting glucose and fasting insulin levels. They also had higher HOMA-R and HOMA-R:FPIR ratios.

6 The study concluded that first-degree relatives positive for islet antibodies who progress to type 1 diabetes exhibit mildly disturbed insulin-glucose metabolism years before diagnosis.

Fourlanos S, Narendran P, Byrnes GB, Colman PG, Harrison LC (2004) Insulin resistance is a risk factor for progression to type 1 diabetes. *Diabetologia* **47**: 1661–67

DIABETES CARE

Microangiopathy linked with familial insulin resistance

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Insulin resistance is a risk factor for the development of diabetic retinopathy and nephropathy. Furthermore, a familial predisposition to these diabetes complications has previously been established.

2 This large, family-based study investigated whether insulin resistance in first-degree relatives of people with type 1 diabetes is associated with nephropathy and retinopathy.

3 Probands had type 1 diabetes and retinopathy (classified as proliferative, preproliferative or background). They possibly also exhibited diabetic nephropathy (classified as advanced, established, incipient or absent). Insulin resistance scores were calculated for their relatives, according to WHO recommendations.

4 The insulin resistance scores calculated for the relatives correlated positively (p=0.0009) with their albumin excretion rate, HbA_{1c} level (p<0.0001) and fasting plasma glucose concentrations (p=0.0003).

5 The insulin resistance score was also higher in the relatives of probands with diabetic retinopathy or diabetic nephropathy compared to those without the respective conditions.

6 The obesity and history of arterial hypertension components of the insulin resistance score were most common in relatives of probands with retinopathy. In contrast, obesity and history of lipid disorders were more common in relatives of those with nephropathy.

Hadjadj S, Péan F, Gallois Y, Passa P, Aubert R, Weekers L et al (2004) Different patterns of insulin resistance in relatives of type 1 diabetic patients with retinopathy or nephropathy: The Genesis France-Belgium Study. *Diabetes Care* **27**: 2661–68