National Genetics Education and Development Centre

Genetics and common forms of Diabetes

Patient Scenario
Louise is a 51 year old woman with Type 2 diabetes, diagnosed when she was 35 years old. She is obese and is finding it hard to control her blood glucose levels with tablets. Her doctor has recommended she commences insulin therapy. Her mother, who came from a large Scottish-Irish family with 13 children, was one of 4 siblings with diabetes. Eleven of Louise's 27 cousins have diabetes, as well as both of Louise's adult children. She is fatalistic about the disease and says "it is in my genes" and although her doctor has referred her to the dietitian, she does not see how it can help.

Key points for dietitians

- Diabetes mellitus is a heterogeneous group of disorders characterised by persistent hyperglycaemia. The two most common forms of diabetes are Type 1 diabetes mellitus (T1DM, previously known as insulin-dependent diabetes) and Type 2 diabetes mellitus (T2DM, previously known as non-insulin-dependent diabetes). Both are caused by a combination of genetic and environmental risk factors.

- Gestational diabetes (GDM) occurs when a mother's production of insulin is not enough to overcome the blocking effect of placental hormones such as human placental lactogen. It usually begins at 20-24 weeks into the pregnancy and can disappear within hours of giving birth. However, a significant number of women with gestational diabetes go on to develop Type 2 diabetes mellitus. Both conditions feature insulin resistance and share risk factors such as obesity. It is possible that these two conditions may also share diabetes susceptibility genes.

- There are other rare forms of diabetes caused by single gene mutations (*see 'Genetics and Rare Forms of Diabetes Reference Guide'*). These are likely to be diagnosed before referral to a dietitian. Dietitians should be aware of their Regional Genetics Centre which can be found at **www.bshg.org.uk**, referral to which can be done only where a single-gene disorder is suspected.

- Asking about family history is a routine part of dietetic assessment for conditions such as diabetes and obesity. For advice about taking a family history visit **www.geneticseducation.nhs.uk**.

- By discussing family history information, a patient's feelings of negativity or guilt can be acknowledged, and a dietitian can explain that changes to diet and lifestyle can reduce the short and long-term complications of diabetes, even if people are genetically susceptible to it.

Genetics concepts underpinning diabetes

Candidate genes for diabetes genetic studies

Candidate genes for the risk of diabetes are selected because they are thought to be involved in pancreatic beta cell function, insulin action, glucose metabolism, or other metabolic conditions that increase diabetes risk such as energy intake or expenditure, and lipid metabolism.

Genetic factors in Type 1 diabetes

Type 1 diabetes is an autoimmune disorder in which the body attacks the pancreatic beta cells that produce insulin. The onset is attributed to both an inherited risk and external triggers, such as infection. First degree relatives have a 6% risk of developing T1DM compared with 1% in unrelated individuals (*Dorman & Bunker, 2000*).

There are more than 20 regions of the genome linked with influencing diabetes risk. The HLA class II genes which code for immune response proteins contribute approximately 40-50% of the heritable risk for T1DM. Two other genes, INS (the insulin gene) and CTLA-4 (which codes for a molecule that hinders the activation of immune cells) also influence T1DM risk.

Although variations in genes are an important risk factor for T1DM, they alone do not account for the disease. Environmental risk factors such as enteroviruses are thought to act as either 'initiators' or 'accelerators' of beta cell autoimmunity, or 'precipitators' of overt symptoms in individuals who already have evidence of beta cell destruction.

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Genetic factors in Type 2 Diabetes

Environmental factors such as obesity, distribution of body fat and physical inactivity may account for the dramatic increase in the prevalence of T2DM worldwide. Evidence shows that these are modifiable risk factors and lifestyle interventions can decrease the risk of progression from impaired glucose tolerance to T2DM by approximately 60% (*Pan et al., 1997; Tuomilehto et al., 2001*). However, genetic differences can mean that certain individuals are at greater risk of developing obesity (*see 'Genetics and Obesity Reference Guide'*) and T2DM.

Family studies have revealed that first degree relatives of people with T2DM are about 3 times more likely to develop the disease themselves than individuals without a positive family (*Florez et al., 2003*). Concordance rates for identical (monozygotic) twins are 60-90% and are significantly higher than those for non-identical (dizygotic) twins. All of this suggests that genetics play a fundamental role in the risk of T2DM.

More than 50 candidate genes have been studied in populations, however, results have been conflicting. Attention is now focused on a smaller number of T2DM susceptibility genes.

Other causes of diabetes

Numerous other causes of diabetes have been found, including injury to the exocrine pancreas, drug-induced damage, infection, and endocrine diseases, for example, Cushing's Syndrome.

Patient Scenario

The dietitian asked Louise about her family history. The family history was very complex, however, Louise's own case presented as Type 2 diabetes, and her doctor was considering changing her treatment from tablets to insulin, indicating a gradual loss of beta cell function combined with insulin resistance due to her obesity. Louise and her relatives could have certain variants of genes that predispose to developing obesity and insulin resistance.

The dietitian acknowledged Louise's feeling of negativity about diabetes in her family. However, the dietitian was able to identify that Louise's son had lost 4 stone and was managing his diabetes with diet and lifestyle. The dietitian was therefore able to use this to motivate weight loss in Louise as well.

Role of genetics in the treatment and prevention of diabetes

At the present time there is no way to prevent T1DM, lifelong insulin injections remains the only available treatment for the disease, although islet transplantation has been successful in a small number of patients.

T2DM can generally be prevented by maintaining an age-appropriate body weight and engaging in physical activity. Although many candidate genes have been investigated, the predictive value of genetic tests is low, and it is unclear whether knowledge of one's genetic risk increases motivation to engage in disease prevention. However, many of the current T2DM susceptibility genes of interest are drug targets.

In 2006, the Diabetes Prevention Program found that variants (called Single Nucleotide Polymorphisms, SNPs) in the gene TCF7L2 predisposed individuals to T2DM. Since then, many studies have replicated the findings in various populations (*Florez, 2007*). It has recently been found that carbohydrate quality (e.g. glycaemic index) and quantity (glycaemic load) modified risk of T2DM associated with TCF7L2 (*Cornelis et al., 2009*). This suggests that changes in risk attributable to the TT genotype are magnified under conditions of increased insulin demand, and suggests that dietitians' understanding of the interaction between TCF7L2 and diet is important in reducing the risk of developing T2DM.

For references and information please go to the Dietitians section at **www.geneticseducation.nhs.uk**