Type 2 diabetes in families and diabetes prevention

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Summary

Type 2 diabetes frequently clusters in families. Non-diabetic first-degree relatives (offspring and siblings) of patients with type 2 diabetes have a three-fold increased lifetime risk of developing diabetes compared with the background population. This increased diabetes risk results from the combined effects of shared genetic and lifestyle factors. Extensive studies of non-diabetic relatives of type 2 diabetic families show that impaired insulin secretion, insulin resistance and an adverse cardiovascular risk factor profile exist well before the development of frank diabetes. Despite this well-documented adverse metabolic predisposition, patients with type 2 diabetes and their non-diabetic relatives generally have a limited understanding of the risks. Several large-scale studies, such as the Finnish Diabetes Prevention and Diabetes Prevention Program studies, indicate unequivocally that lifestyle modification through dietary change and exercise can dramatically decrease risk of progression to diabetes in high-risk subjects. However, such individuals pursue lifestyle changes only if they understand their own risk of developing diabetes. Further work is therefore needed to investigate and develop optimal ways of improving knowledge of diabetes risk in families of patients with type 2 diabetes, so that they can appreciate the potential benefits of diabetes prevention strategies.

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Key Words

Offspring; siblings; prevention; education; cardiovascular risk

Introduction

There is general acceptance that we are in the midst of an inexorable increase in the prevalence of type 2 diabetes. The worldwide prevalence was estimated at around 150 million in 2000, but is predicted to double to over 300 million by 2025.[1] A major proportion of this increase is expected to occur in developing countries, as more people adopt aspects of a typical Western lifestyle. The clear concern is that this massive increase in the prevalence of type 2 diabetes will lead to an increased prevalence of diabetes-related complications, in particular large-vessel complications such as stroke and myocardial infarction, which will simply overwhelm future healthcare services.

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So, what can be done to avoid this situation? Strategies to limit the increase in prevalence of type 2 diabetes are clearly essential, and part of this will include the identification and management of individuals at high risk of the condition. This review aims to consider the non-diabetic relatives of patients with type 2 diabetes as a high-risk group of people who could be a focus for future preventative strategies.

Type 2 diabetes and familial risk

Type 2 diabetes frequently clusters within families. However, it is invariably difficult to discern a clear inheritance pattern, such as the autosomal inheritance pattern that is typical of maturity onset diabetes of the young (MODY). This is because type 2 diabetes is a complex trait in which multiple gene effects combine with lifestyle factors to predispose to diabetes (Figure 1). As a consequence, there is no single inheritance pattern for type 2 diabetes; in some families it can even appear to skip a generation.

Despite this complexity, it is well documented that non-diabetic relatives of patients with type 2 diabetes are at an increased risk of developing diabetes. The life-time risk of developing diabetes for non-diabetic first-degree relatives (siblings and offspring) of patients of North European ancestry with type 2 diabetes was reported to be over three times greater than that of the background population.[2] A similar increased risk has been found in other ethnic populations. Even though the prevalence of type 2 diabetes is high in the general Pima Indian population, the risk of

developing diabetes was found to be 2.3 and 3.9 times higher in offspring who had either one or two diabetic parents, respectively, compared with offspring who had two non-diabetic parents.[3] A comparable increased risk of type 2 diabetes has been reported in families of Mexican-American and South Indian Asian ancestry.[4,5] The key message is that, irrespective of ethnicity, if you are the first-degree relative of a patient with type 2 diabetes, your own risk of developing diabetes is around three-fold greater than that of an individual who does not have a family history of the condition.

Non-diabetic first-degree relatives: the metabolic phenotype

Once it was appreciated that the non-diabetic first-degree relatives of patients with type 2 diabetes are at an increased risk of developing diabetes, investigators set out to determine whether these relatives exhibited metabolic abnormalities that predisposed them to the condition.

Several studies established that at-risk non-diabetic relatives had defects of pancreatic beta-cell function, including decreased insulin secretion in response to glucose, increased proinsulin levels and altered pulsatility of insulin secretion.[6] Intriguingly, subtle abnormalities of pancreatic beta-cell function were identified in first-degree relatives with otherwise normal glucose tolerance, indicating that altered beta-cell function is an early and fundamental metabolic abnormality in these at-risk individuals.

Insulin resistance is also a key feature of non-diabetic relatives. We recognised that this could be because non-diabetic relatives tended to be heavier than control subjects with no family history of diabetes.[7] We therefore pair-matched normal glucose-tolerant relatives and control subjects for age, sex and adiposity, and found that the relatives were still more insulin resistant. This demonstrated that, like impaired beta-cell function, insulin resistance is an early and characteristic feature of at-risk relatives.

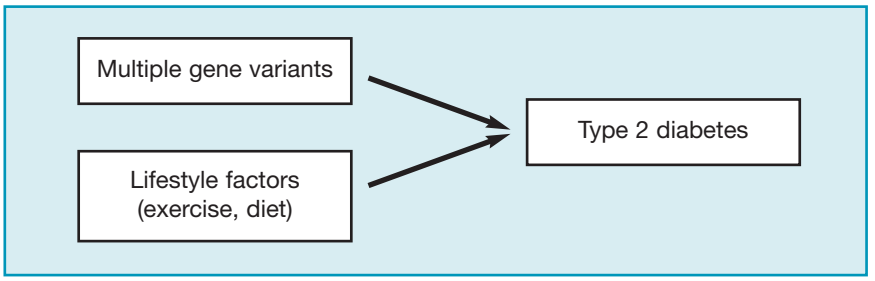

Figure 1. Schematic representation of type 2 diabetes as a complex trait

As part of our earlier studies of the relatives of people with type 2 diabetes, we also found that the prevalence of cardiovascular disease (CVD) risk factors that comprise the metabolic syndrome were more common in non-diabetic relatives. This implies that an increased risk of CVD was established well before the development of frank diabetes.[8] In summary, the non-diabetic first-degree relatives of patients with type 2 diabetes are at an increased risk of both diabetes and CVD.

Genetic factors

Remarkable progress has been made over the last few years in identifying genetic variants that increase the risk of type 2 diabetes.[9] Table 1 summarises those genes and their variants that are known to be associated with increased type 2 diabetes risk in replicated studies.

The susceptibility variants are generally common but functionally weak; for example, the *TCF7L2* variant is carried by around 50% of individuals, while the Pro allele of the *PPARG* gene is present in 87% of the background UK population. Clearly, 87% of the background population will not get diabetes! This is because these susceptibility variants do not *cause* diabetes, but simply impart a small increase in diabetes risk. The greater the number of these risk variants carried by an individual, the greater that person's risk of developing diabetes. It is anticipated that families with a history of type 2 diabetes carry more of these risk variants. The current problem is that while our knowledge of the genetic susceptibility to type 2 diabetes has increased, it remains incomplete. For this reason, and the fact that lifestyle factors are also important, we are some way off using genetic information to predict an individual's risk of type 2 diabetes.

On a positive note, it can be seen from Table 1 that some genes (*FTO*, *CDKN2B*, etc) are involved in unknown pathways or processes that do not seem immediately relevant to the pathogenesis of diabetes. These genes, therefore, hold the promise of identifying novel pathways and targets for the treatment and management of type 2 diabetes in the future.

Lifestyle factors

It is quite clear that the marked increase in the worldwide prevalence of type 2 diabetes is being driven by lifestyle factors such as changes in the quality and quantity of food intake and decreased physical activity. Are these relevant to the clustering of type 2 diabetes within families, or can this all be explained by shared genes? We are all aware that much of our early behaviour and attitudes are shaped by those of our immediate family members, particularly in relation to eating and exercise.

Is there evidence that lifestyle factors contribute to the increased

Susceptibility gene locus	Gene function	Risk variant	Odds ratio (per allele)
TCF7L2	Cell signalling	rs7901695	1.37
KCNJ11	K+ channel component	E23K	1.14
PPARG	Transcriptional regulator	Pro12Ala	1.14
FTO	Unknown	rs8050136	1.17
HHEX/IDE	Transcription/insulin degradation	rs1111875	1.15
CDKAL1	Cyclin-dependent kinase	rs10946398	1.14
CDKN2A/2B	Tumour suppressor	rs10811661	1.20
IGF2BP2	Binding protein	rs4402960	1.14
SLC30A8	Zinc transporter	rs13266634	1.15

Table 1. Replicated type 2 diabetes gene regions

risk of diabetes of the non-diabetic first-degree relatives of patients with type 2 diabetes? We asked this question in relation to diet. Using a validated food frequency questionnaire, we examined the dietary intake of non-diabetic first-degree relatives and compared it with that of control non-diabetic subjects with no family history of diabetes. Key findings were that the relatives reported a higher intake of total and saturated fat, and a lower intake of carbohydrate.[10] This finding was unexpected and worrying, primarily because we had expected that dietary advice given to people with type 2 diabetes to decrease fat intake would have been cascaded and pursued by their at-risk, non-diabetic, relatives. The finding indicates that the problem is not simply a matter of genetics: a higher fat intake may well contribute to an increased prevalence of obesity in non-diabetic first-degree relatives.[8] We also tried to compare levels of physical activity in our study using a questionnaire approach, which has since been recognised as an inaccurate way to assess physical activity compared with activity and movement monitors; this question still needs to be addressed using such monitors.

Knowledge of risk in type 2 diabetic families

Few recent studies have addressed knowledge or risk perceptions about the development of type 2 diabetes among either the general population or those with a family history of the disease. In a phone survey in the USA,[11] only 42% of those with a family history and 40% of those with three to six known risk factors for diabetes development considered themselves at risk. A Dutch study also reported low perceived risk despite the presence of risk factors such as higher age, obesity or taking anti-hypertensives.[12] In Britain, Pierce and colleagues asked parents with type 2 diabetes to estimate the risk to their offspring.[13] While the parents appreciated that the risk was increased compared with risk in the children of non-diabetic parents, they had little concept of the degree of risk. This is reflected in the surprising observation that 68% of the patients with type 2 diabetes thought that it was 'not very likely' or 'not at all likely' that their offspring would actually progress to develop diabetes. This underestimate of risk was also found in a study of non-diabetic adult siblings of patients with type 2 diabetes. Only 38% of the non-diabetic siblings appreciated that their own risk of developing diabetes was increased.[14]

Bearing in mind the limited work in this area, the evidence to date shows that diabetes risk is perceived to be low in families of people with type 2 diabetes. This has crucial implications for prevention, as prevention strategies are unlikely to be followed if the risk of diabetes is perceived to be low. Further work is clearly required to explore ways of improving knowledge of diabetes risk in families.

How can type 2 diabetes be prevented?

Studies of non-diabetic first-degree relatives show that impaired insulin secretion and insulin resistance are the key independent predictors for progression to type 2 diabetes.[15–17] The implication is that amelioration of these metabolic defects might delay and perhaps even halt the development of type 2 diabetes in these at-risk subjects. There are no large-scale studies of diabetes prevention in non-diabetic relatives to date, but studies of high-risk subjects with abnormal glucose tolerance that included subjects with a positive family history have been conducted. The Finnish Diabetes Prevention study group showed that the risk of diabetes decreased by 58% over three years in subjects with impaired glucose tolerance (IGT) undergoing lifestyle change, compared with a non-intervention control group.[18] The lifestyle change was quite challenging in that it comprised a weight-reducing dietary advice (decreased fat and increased fibre intake) and exercise programme

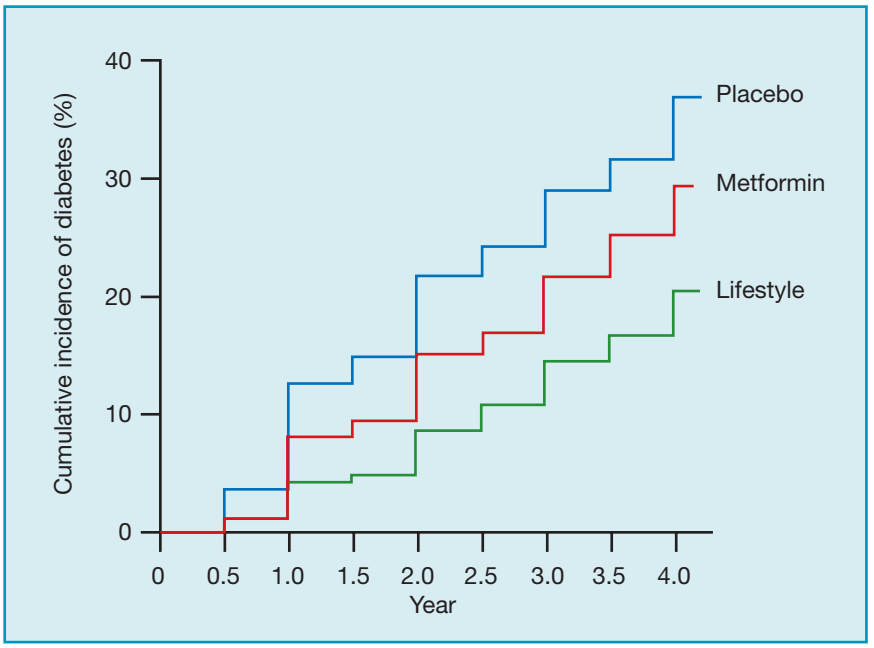

Figure 2. Cumulative incidence of type 2 diabetes in subjects with abnormal glucose tolerance randomised to placebo, metformin or lifestyle management in the Diabetes Prevention Program Research study. Reproduced from Knowler WC, Barrett-Connor E, Fowler SE, *et al*. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.[19] Copyright © 2002 Massachusetts Medical Society. All rights reserved

(≥30 minutes moderate exercise per day). The Diabetes Prevention Program Research Group conducted a similar study that recruited subjects with abnormal glucose tolerance (impaired fasting glucose and IGT) of whom around 70% had a positive family history of type 2 diabetes.[19] The study compared the effect of placebo, metformin therapy or lifestyle change on progression to diabetes. The lifestyle-modification programme aimed to generate weight loss of ≥7% body weight, through dietary change and exercise of ≥150 minutes per week. As shown in Figure 2, compared with placebo, the lifestyle programme decreased the incidence of diabetes by 58% over three years, which was considerably greater than the beneficial effect of metformin (31% risk reduction).[19]

Evidence to date therefore – from high-risk individuals including a high proportion of those with a positive family history of type 2 diabetes – indicates that the progression to diabetes can be delayed and that lifestyle change is an effective way to achieve this. However, whether such impressive health benefits can be replicated and sustained outside of a clinical trial structure, across different societies, remains to be seen.

What is needed?

From this brief overview, it is evident that non-diabetic relatives of patients with type 2 diabetes are at high risk of progressing to diabetes, and that lifestyle modification based on dietary changes and exercise can dramatically decrease the risk of diabetes. The challenge would appear to be transferring this knowledge to high-risk relatives so that they understand the potential benefits of prevention and can make informed decisions about lifestyle change. It would seem, therefore, that more work is needed to devise the optimal means of educating families about type 2 diabetes and the linked CVD risk, and also to look at different types of lifestyle change (for example, duration and type of exercise) to achieve the most efficient and effective risk reduction.

Acknowledgements

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Conflict of interest statement

None

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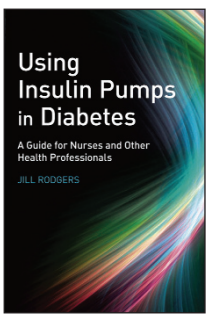
Book Review

Using insulin pumps in diabetes: a guide for nurses and other health professionals

Jill Rodgers



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Using insulin pumps in diabetes: a guide for nurses and other health professionals is an important contribution to the literature in the diabetes area and should be regarded as a valuable resource for nurses and other health professionals working with insulin pumps in the UK and other countries. It covers almost everything about insulin pump treatment. The specific pump therapy treatment is explained, and technical information about different features and functions of pumps and infusion sets is provided. The book presents experiences from pump users, which illustrate that this treatment can be a key to a more flexible life but that it requires hard work from the pump user and support from the diabetes team. It also discusses how to set up an insulin pump service. The importance of involving the whole diabetes team in the planning process and developing a common insulin pump service philosophy is highlighted. The effect of an empowerment education approach and the benefits of using group education when initiating pump therapy are also discussed. The book provides guidance on initiating pump therapy, adjusting insulin doses, optimising glycaemic control, and how to use carbohydrate counting. One chapter deals with insulin pumps in toddlers, children and teenagers. The rationale for using pump therapy at these ages and the differences when used by adults are discussed.

The risk of developing ketoacidosis with pump therapy could have been more highlighted. Education about how to prevent ketoacidosis is important both initially and in further consultations. It must be recommended to take a correction dose with a syringe or an insulin pen as soon as high blood glucose and ketones are detected, and then to check the pump and change the infusion site.

As the book is supposed to be read by nurses and other health professionals, more references might also have been useful.

Despite these criticisms, this book can be recommended for anyone who is interested in insulin pump treatment, although some parts are specifically written for UK users (e.g. funding). For those already involved in this treatment, it is always possible to learn or reflect on something new.

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