Genetics or Lifestyle – How Do We Prevent Diabetes?

a report by
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The prevalence of obesity and type 2 diabetes has increased rapidly over the last 20 years. This has occurred not only in affluent societies, but also in developing countries, e.g. China and India. The dramatic increase in the prevalence of type 2 diabetes is considered one of the largest health problems worldwide, and it also increases the healthcare costs of nations, mainly due to its long-term chronic complications, such as coronary heart disease, peripheral vascular diseases, renal disease, retinopathy and neurological damage. Therefore, over the last 10–15 years there has been increased interest in the prevention of type 2 diabetes by lifestyle changes or drugs.[1] Type 2 diabetes has been shown to be a strongly genetic disease, but lifestyle changes could modify the risk. Indeed, the increase in the prevalence of type 2 diabetes indicates that lifestyle plays a central role in the development of the disease. In the following article, the gene–lifestyle interaction in the pathogenesis of type 2 diabetes will be considered, with an emphasis on the prevention of this disease through changes in lifestyle.

Risk Factors for Type 2 Diabetes

Lifestyle, as well as genetic factors, has a role in the development of type 2 diabetes.[1–3] *Table 1* lists the main lifestyle and related factors that have been shown to be associated with risk of type 2 diabetes in cross-sectional or long-term cohort studies. There are two main strong risk factors for type 2 diabetes: physical inactivity and obesity and long-term weight-gain. In particular, central obesity increases the risk, and many studies suggest that it is visceral fat that is most detrimental in this regard. A high-fat diet, consumption of food that is rich in saturated fatty acids or low in dietary fibre and a diet with a high glycaemic index or load have also been connected to increased risk. Furthermore, drinking a lot of soft drinks containing sugar could increase the risk of both obesity and type 2 diabetes. In some studies, a low socioeconomic status has been shown to be associated with increased risk. Interestingly, intrauterine or early nutritional defects, i.e. low birthweight, have been connected to increased risk of many chronic diseases in middle-aged or elderly people, e.g. atherosclerotic vascular diseases and type 2 diabetes.

Pathogenesis of Type 2 Diabetes

Two main mechanisms have been linked with the development of type 2 diabetes: insulin-secretion defect and insulin resistance.[2,3] Opinions have varied with time regarding the significance of these two basic abnormalities. Currently, it is a common belief that insulin secretion deficiency is the fundamental disorder in the development of type 2 diabetes, but it is insulin resistance that modifies the risk. Since obesity and physical inactivity increase insulin resistance, they also increase the susceptibility to develop type 2 diabetes in the long term. There are many mechanisms that also link insulin secretion defect with insulin resistance at the β-cell level, including lipotoxicity, oxidative damage, chronic low-grade inflammation associated with obesity and β-cell exhaustion caused by an increased demand for insulin in obese persons, which is known to be an insulin-resistant and hyperinsulinaemic state.[2,3] Recently, high insulin responses after carbohydrate-rich, high-glycaemic-index meals, when used chronically, have also been linked with the risk of type 2 diabetes.[4]

Interestingly, almost all of the genetic variants that have been identified as type 2 diabetes risk genes are involved in the regulation of insulin secretion.[5] Of course, insulin resistance may also have a genetic background, but it is highly modifiable with lifestyle changes, as shown in our subgroup analysis from the Finnish Diabetes Prevention Study (DPS),[6] which showed a greater than 60% increase in insulin sensitivity after four years in persons who were able to lose at least 8% of bodyweight (see *Figure 1*). Insulin secretion capacity remained almost unchanged,[6] which indicates that the progression of the insulin-secretion defect may not be inevitable provided lifestyle are changed. The *Pro12Ala* variant of the *PPAR-gamma2* gene is an example of such genetic variations, which may increase diabetes risk through insulin resistance, although it may be associated with the regulation of insulin secretion as well.[2,7]

What Is the Evidence for the Prevention of Type 2 Diabetes Through Lifestyle?

The rapid increase in the incidence and prevalence of type 2 diabetes and its consequent long-term complications and the close link between the type 2 diabetes epidemic with our lifestyles make this disease a challenge for various preventative measures. Changing lifestyle, i.e. long-term weight reduction, increased physical activity and qualitative changes in diet, has been shown to correct insulin resistance in numerous clinical studies lasting for weeks to months. The effects on insulin secretion have been more variable due to different patient materials, but also insulin secretion may recover after lifestyle changes, weight loss and improved insulin sensitivity. Lifestyle changes also improve the level of cardiovascular risk factors and could reduce long-term atherosclerotic vascular diseases.[8]

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Table 1: Risk Factors for Type 2 Diabetes

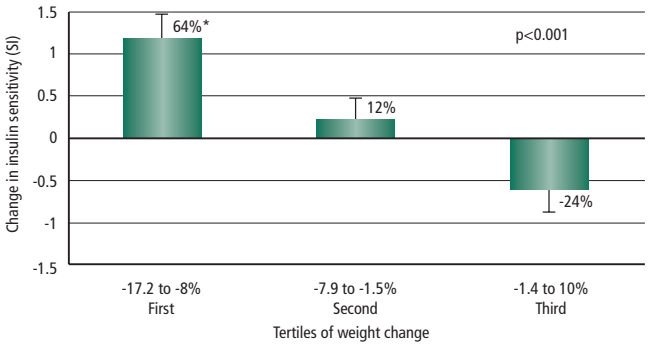
Sedentary lifestyle
Central obesity and weight gain
Diet rich in fat and saturated fatty acids
Diet low in fibre
High-glycaemic-index foods
High dietary energy density
Low socioeconomic status
Small size at birth and low birthweight

Table 2: Main Lifestyle Intervention Trials in Persons with Impaired Glucose Tolerance

Study	Intervention	Number of Persons	Risk Reduction (%)	Study Duration (years)
Eriksson and Lindgärde[9]	Lifestyle	181	63	6
Pan et al.[10]	Diet, physical activity, diet and physical activity	577	42	6, follow-up Da Qing data available 16
Tuomilehto et al.[11]	Lifestyle, weight loss, quality of diet, increased physical activity	522	58	3.2, follow-up data available 15
Knowler et al.[12]	Lifestyle, metformin	3,234	58 (31 with metformin)	3
Kosaka et al.[13]	Lifestyle	458	67	4
Ramachandran et al.[14]	Lifestyle, metformin, combined	531	28 (26 with metformin)	3

The impact of lifestyle on the risk of type 2 diabetes has provided the impetus to carry out long-term intervention trials with individuals at increased risk, i.e. those with impaired glucose tolerance (IGT), to discover whether type 2 diabetes is preventable by changing lifestyle. These trials have proved that it is, and the results are quite similar in different ethnic and patient groups. *Table 2* shows the major lifestyle intervention trials, which uniformly show that lifestyle changes in selected individuals with IGT result in a marked decline in the risk of type 2 diabetes. The risk reduction has been variable, and it is not so closely associated with the changes in lifestyle achieved in different studies. The Swedish Malmö feasibility study was not a randomised trial, but it gave suggestive evidence for the potential of lifestyle modification in relation to type 2 diabetes.[9] In the China Da Qing Diabetes Prevention Study, the risk reduction was 32–46%, and there were no significant differences across the three intervention arms: diet (31%), exercise (46%) and diet and exercise (42%). Interestingly, the diet and exercise group did not show any additional benefit.[10] There were no other studies comparing different lifestyle approaches. In the DPS[11] and the Diabetes Prevention Programme (DPP),[12] the risk reduction was similar: 58% in each. In the DPP, a metformin-treated group was also studied, which showed a 31% reduction in diabetes risk. In the Indian DPP (IDPP-1), the risk reduction by lifestyle was lower – only 29% – and no additional benefit was received by combining lifestyle changes with metformin.[13] In the metformin-treated group, the risk reduction was 26%, which confirmed the results from the DPP that the effect of this drug is not fully comparable to lifestyle changes for the prevention of diabetes. In a Japanese study of men with IGT, the risk reduction was marked – 67% – even if the weight-loss difference between the intervention and control groups was only 1.8kg.[14] In the DPS, we also analysed the risk reduction according to the success achieved in different lifestyle goals. The goals were weight loss of at least 5%, intake of fat <30% total energy intake, intake of saturated fatty acids <10% total energy intake, dietary fibre intake at least 15g/1,000kcal daily and physical activity of at least four hours a week. The risk reduction was four-fold in individuals who achieved four or five of these goals compared with those who were not able to change their lifestyle at all.[11,15]

Figure 1: Long-term Weight Reduction Improves Insulin Sensitivity



*Changes in the insulin sensitivity index (SI) (10^{-4} x min^{-1} x μU^{-1} x ml^{-1}) by tertiles (n=16 in each tertile) of four-year bodyweight change (mean and standard error of the mean), both groups combined. The p value indicates the significance of the difference among the tertiles after adjustment for age, gender and study group. * Percentage change in the group mean. © 2008 American Diabetes Association. From Uusitapa et al., 2003.[6] Reprinted with permission from the American Diabetes Association.*

Are the Effects of Lifestyle Changes Sustained?

Both the DPS[11] and the China Da Qing Diabetes Prevention Study[10] have now provided new information about the effects of lifestyle changes after active intervention. In the DPS, the risk reduction after three years of active intervention was 43%, possibly due to permanent lifestyle changes made by intervention persons and/or permanent effects of intervention on glucose metabolism.[15] A similar magnitude of risk reduction was observed in the Da Qing Diabetes Prevention Study: persons belonging to the combined lifestyle intervention group (diet, exercise or diet plus exercise) showed 51% reduction in the diabetes risk during the active intervention and a 43% lower risk over the 20-year period. However, the incidence figures were high in both groups: 80% in the intervention and 93% in the control group. It is also of note that lifestyle changes actually achieved little in this study.[16] There was a trend towards lower cardiovascular mortality (17%) in the intervention group, but it did not receive statistical significance, perhaps due to limited power of the study.

To summarise: type 2 diabetes is in part preventable by lifestyle changes provided these changes are sustained, and improved glycaemia in the long term can be beneficial. At the very least, lifestyle changes may delay the development of type 2 diabetes for years. When it comes to the prevention of cardiovascular diseases (CVDs) by lifestyle in IGT persons, the results from the Da Qing Diabetes Prevention Study remain inconclusive,[16] and similar analyses from other studies are not yet available.

Does Genetic Predisposition Matter?

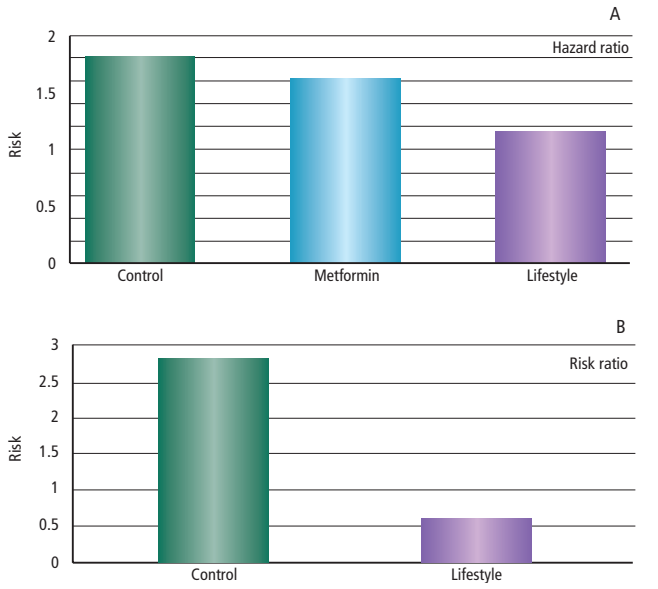
Long-term studies applying different lifestyle interventions have increased our understanding about how much can be achieved even with modest lifestyle changes in the prevention of type 2 diabetes in persons with IGT. Although type 2 diabetes is a heritable disease, only a few genetic variations have been described that have been consistently associated with an increased risk.[5] Furthermore, except for those genes leading to monogenetic maturity-onset diabetes of the young (MODY) types, the impact of risk genes has been modest. In genome-wide association (GWA)

studies the risk ratios for single-nucleotide polymorphisms (SNIPs) have been rather low.[5] Furthermore, both short-term clinical studies and large lifestyle intervention trials show that insulin resistance in particular is highly modifiable. Recent interest has focused on the question of how much genetic predisposition – i.e. known genetic variations – change the risk associated with risk genes.[17] From the clinical point of view, this question is of importance: what can be achieved with lifestyle changes if a patient has a known genetic variation connected to type 2 diabetes?

In the DPS, we analysed this question with regard to a number of gene variants.[17] Furthermore, there are some reports from DPP that indicate that lifestyle changes are relevant even if a person has a genetic variation associated with increase of type 2 diabetes risk. In the DPS, the known *Pro12Ala* polymorphism of *PPAR-gamma2* gene was associated with an increased risk of type 2 diabetes, and paradoxically the *Ala12* allele was a risk allele. Persons in the control group showed an increased risk of type 2 diabetes if they had the *Pro12Ala* or *Alal12Ala* genotype, but in the intervention group none of the persons with *Ala12Ala* developed diabetes. What made this happen? These persons were able to lose more weight than others, and therefore their risk of diabetes was reduced.[18] In the DPP, the results were different with regard to the risk allele: it was the *Pro12* allele that increased the risk of type 2 diabetes, but, interestingly, with increasing obesity persons with the *Ala* allele lost the preventative effect when the body mass index (BMI) reached 35kg/m^2.[7] This finding confirms our observation that people with the *Ala12* allele are more prone to weight gain, but they also may lose weight more easily than those people with *Pro12Pro* carriers. Another example regarding gene–lifestyle intervention is the findings from the *TCF7L2* gene variants published by both the DPS[19] and the DPP.[20] In both studies, the risk SNIP (rs12255372 in the DPS, rs79903146 in the DPP) was associated with the diabetes incidence in the control group only, but the intervention group showed the same risk as those without the risk genotype (see *Figure 2*). In the DPP, the intervention group also performed better than the group treated with metformin. Now *TCF7L2* has shown to be most consistently associated with diabetes, and it affects insulin secretion in a complex way.[21] Interestingly, the expression of *TCF7L2* in adipose tissue can be modulated by dietary modification, and we have shown that a diet with a low glycaemic index downregulates the expression of *TCF7L2* in adipose tissue.[4]

The *FTO* gene has been connected to obesity in many studies concerning adults and children. It also may increase type 2 diabetes risk, but this increased risk is due to obesity *per se*.[22] We have analysed the impact of *FTO* on diabetes risk and long-term weight changes in DPS. The risk SNIP was associated with an increased BMI, particularly in women, but persons with or without this SNIP lost weight at a similar rate (unpublished data). Recently, this finding was published from another study,[23] but the follow-up period was markedly shorter compared with the DPS follow-up period of four years.

Figure 2: Lifestyle Change Decreases the Genetic Risk



Risk reduction by lifestyle in the Diabetes Prevention Programme (DPP) (upper panel) and the Finnish Diabetes Prevention Study (DPS) (lower panel), according to the risk (TT-genotype for each) single nucleotide polymorphisms (SNIP) of the TCF7L2 *gene, rs 12255372 in the DPS[19] and rs 79903146 in the DPP.[20]*

Concluding Remarks

GWA studies have revealed some gene variants, which have consistently been associated with an increased risk of diabetes in large study cohorts of different origins. Lifestyle interventions even with modest changes in lifestyle can reduce the type 2 diabetes risk in high-risk groups with IGT. The Finnish DPS and China Da Qing Diabetes Prevention Study have yielded new evidence that lifestyle changes could lead to a permanent reduction in the risk of diabetes. Moreover, there is a strong lifestyle–gene interaction regarding the increased risk, and the available data suggest that lifestyle could reduce the increased risk to a lower level among those persons carrying the risk gene variants. Interestingly, lifestyle changes seem to work better than metformin in the prevention of diabetes. When it comes to the prevention of CVD in IGT persons, lifestyle changes should be more aggressive than achieved in intervention trials (see *Table 2*), and perhaps already started for high-risk persons with normal or nearly normal glucose metabolism. As individuals who are susceptible to type 2 diabetes also have a high risk of CVD, they need special attention in healthcare systems and their risk should also be decreased by pharmacological agents according to recommendations. Finally, for the risk reduction of type 2 diabetes, lifestyle changes can be considered as the first-line approach because they are well-documented, safe, efficient and cost-effective. ■

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