How Effective Are Lifestyle Changes in the Prevention of Type 2 Diabetes Mellitus?
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Obesity and impaired glucose tolerance are associated with a greater risk for a number of conditions, including insulin resistance, diabetes mellitus, hypertension, dyslipidemia, coagulation abnormalities, inflammatory markers, and coronary heart disease. Lifestyle changes can delay or prevent the development of type 2 diabetes in patients with obesity and impaired glucose tolerance. The risks improve with weight loss and increased physical activity. A decrease of 7% to 10% or more from baseline weight can have a significant effect. This has now been documented in a number of randomized, controlled studies.

Key words: diabetes prevention, lifestyle changes

INTRODUCTION

Impaired glucose tolerance (IGT) is a pathophysiological state that exists between normal glucose homeostasis and frank diabetes mellitus. It has been defined by the level of plasma glucose 2 hours after an oral glucose load. About one-third of people with IGT will develop diabetes within 2 years. Most will eventually go on to diabetes, but some will revert back to normal glucose tolerance or remain with IGT. The conversion rate to diabetes has varied in differing population groups, but is about 5% to 6% per year. IGT has been shown to be a risk factor for macrovascular disease and also increases cardiovascular mortality. Because diabetes is increasing rapidly around the globe and is predicted to continue to do so, it has become important to try to prevent it, and persons with IGT are obvious targets. It is not possible at the moment to clearly differentiate between people with IGT who will develop frank diabetes and those who will not. The most important predictors, however, are a higher 2-hour blood glucose and a greater weight. Another predictor is a low level of physical activity.

INCREASE IN PREVALENCE OF OBESITY

The National Health and Nutrition Examination Survey (NHANES) III, which was conducted from 1988 to 1994, showed that 59.4% of men and 50.7% of women in the United States are overweight or obese. In the period from the second NHANES survey and the third, the prevalence of obesity rose from 14.5% to 22.5%. Obesity is also increasing rapidly in other parts of the world. Global obesity increased from an estimated 200 million adults in 1995 to over 300 million in 2000. Childhood obesity has also increased. During the past 30 years, childhood obesity in the United States has more than doubled. As obesity increases, it leads to an increased disease burden, leading to an increased mortality and shortened life span. Obesity brings with it not only an increased incidence of type 2 diabetes, but also of dyslipidemia, hypertension, and cardiovascular disease.

ABNORMAL GLUCOSE METABOLISM AND TYPE 2 DIABETES

Excess weight is the most important modifiable risk factor for the development of type 2 diabetes. The incidence of diabetes rises as obesity prevalence increases. From 1990 to 1998, the prevalence of type 2 diabetes increased by 33%. There have been prospective studies describing this in Israel, Norway, and Sweden. In fact, over 85% of type 2 diabetic patients are overweight or obese.

Type 2 diabetes accounts for 90% to 95% of the 16 million cases of diabetes mellitus in the United States today. The prevalence of reported diabetes is 2.9 times higher in overweight than in non-overweight persons in the NHANES data. There is a strong cross-sectional correlation between the relative weight and the prevalence of diabetes in population groups. Obesity is associated with type 2 diabetes mellitus in both women and men. Excess weight is the most important modifiable
Risk factor for the development of type 2 diabetes. The US National Commission on Diabetes reported that the risk of developing type 2 diabetes was about 2-fold in mildly obese, 5-fold in moderately obese, and 10-fold in severely obese people. The British Regional Heart Study, which included 7735 middle-aged men followed for 12.8 years, found that the body mass index (BMI) was the most important risk factor for the development of type 2 diabetes. Men in the upper fifth of the BMI range (>27.9) had more than seven times the risk of type 2 diabetes compared with those in the lowest fifth. There is an increased risk of developing diabetes with increasing weight gain, and also an enhanced risk the higher the baseline BMI in an individual adult. Also, the longer a person remains obese, the higher the risk of his or her developing diabetes. Persons sustaining a BMI of over 30 for 10 years have twice the risk than persons who have sustained that weight for 5 years.

In both cross-sectional and longitudinal studies, fat distribution has also been found to be important in diabetes risk. Central or upper body fat deposition is independently associated with insulin resistance. The greater the amount of central or upper body or abdominal obesity, the greater the risk for diabetes and cardiovascular disease. Intra-abdominal or visceral obesity is strongly associated with insulin resistance, as well as with dyslipidemia, hypertension, and glucose intolerance. In Japanese-American men, intra-abdominal fat deposition was found to be closely correlated with type 2 diabetes, while subcutaneous fat deposits in the abdomen, thorax, or thigh were not statistically significant predictors.

Lack of physical activity is another important risk factor for the development of type 2 diabetes. The British Regional Heart Study found that men who habitually engaged in moderate levels of physical activity had a substantially reduced risk of diabetes compared with physically inactive men, even after adjustment for age, BMI, and other risk factors. It is known that physical training can reduce insulin resistance and that high physical activity can lower insulin levels. Adopting a regular exercise style will also improve lipids. This is related both to an independent effect of the exercise and to a loss of fat, particularly visceral fat.

PATHOGENESIS OF INSULIN RESISTANCE

How obesity leads to insulin resistance is the subject of much controversy. Increasing weight has been associated with increasing insulin resistance. The impact of obesity is independent of genetic factors, as illustrated by a study of 23 sets of identical twins who were discordant for weight. Within twin pairs (both male and female), the obese twin had higher fasting insulin levels and showed lower insulin sensitivity than the non-obese twin. These differences were particularly evident among those with high abdominal fat distribution.

Insulin resistance occurs in adipose tissue, liver, and muscle. There is decreased insulin-stimulated glucose uptake and less suppression of lipolysis. Both glucose transport and glucose oxidation are affected. Insulin signaling is defective. Insulin-stimulated protein kinase activity of the insulin receptor, which mediates tyrosine autophosphorylation, is reduced in obese subjects relative to non-obese ones, and is further reduced in patients with type 2 diabetes. There is impairment of the activation of tyrosine kinase after insulin locks to its receptor in insulin-sensitive cells. There is also impairment of other subsequent messengers, leading to diminished glucose transport and abnormalities in some critical enzymatic steps involved in glucose use. The net effect is a requirement for an increased insulin secretion by the beta cells of the pancreas and higher prevailing insulin levels. In those obese persons with the appropriate genetic make-up, the beta cell secretion eventually exhausts and carbohydrate tolerance becomes impaired. Eventually, frank diabetes supervenes.

The earliest detectable abnormality in subjects at risk for type 2 diabetes is insulin resistance in skeletal muscle. The ability of insulin to activate signal transduction events, alter gene expression of selected genes, and stimulate muscle glycogen synthesis is impaired. This reduced insulin-stimulated glucose disposal predicts the development of diabetes.

A “portal hypothesis” postulates that free fatty acids are actively released primarily from the visceral fat depot because the insulin does not shut off lipolysis appropriately. These fatty acids enter the portal vein, go to the liver, and there initiate a number of events. There is an increased production of VLDL, higher triglycerides, a drop in HDL-cholesterol, and an increase in small dense LDL particles. The increased free fatty acid flux leads to an inhibition of glucose utilization by skeletal muscle. This seems to be primarily due to a decrease of glucose transporters and a decrease in glycogen synthase activity.

THE ROLE OF ECTOPIC FAT

The relationship of appropriate glucose disposal in obese individuals may also be related to a widespread problem of ectopic fat in tissues important in insulin action. This ectopic fat may be related to the increased free fatty acid flux in these individuals. Intramyocellular lipid (IMCL) is increased in individuals with obesity and type 2 diabetes. There is now good evidence that fat in skeletal muscle can have a negative impact on glucose uptake. There is some evidence that an increase in
IMCL content in muscle induces insulin resistance by activation of inflammatory pathways and serine phosphorylation of the insulin receptor substrate-1. Boden et al. showed that infusion of lipid leading to an increase of muscle lipid led to activation of protein kinase. He et al. reported that in diabetes and obesity, skeletal muscle has both increased IMCL and diminished oxidative enzyme activity regardless of fiber type, suggesting that a proportionality between IMCL content and oxidative capacity is important in the production of insulin resistance.

There is also growing evidence that fat in the liver can lead to increased insulin resistance and type 2 diabetes. Obese individuals with and without type 2 diabetes have increased fat in the liver. The prevalence may be as high as 75% of obese subjects. The amount of liver lipid correlates with insulin resistance of the liver leading to an impaired insulin suppression of hepatic glucose production. A fatty liver correlates with hepatic insulin resistance in those without type 2 diabetes. Further, Bugianesi et al. have shown that non-alcoholic fatty liver disease in non-diabetics is associated with whole-body insulin resistance, as measured by euglycemic insulin clamp.

The enlarged adipocytes in obesity play an important role in insulin resistance, with their increased production of fatty acids, leptin, and resistin and their decreased secretion of adiponectin. The large adipocytes are resistant to insulin-mediated suppression of lipolysis. This leads to elevated levels of free fatty acids, which enhance insulin resistance. Also, larger fat cells show an increased production of TNFα and interleukin-6. TNFα produces whole-body insulin resistance in rodents. It increases lipolysis and activates the potentially inflammatory MAP kinase isoforms JNK and p38 kinase. TNFα interferes with insulin signaling, interfering with IRS-1 activity by enhancing serine phosphorylation. IL-6 also enhances inflammatory response. Finally, there is also evidence for increased fat deposits in the beta cell, which may cause interference with insulin production and lead to beta cell apoptosis.

WEIGHT LOSS AND DIABETES

Weight loss can prevent or delay the progression to diabetes in obese patients. In the Nurses’ Health Study, women who lost more than 5 kg over a 10-year period reduced their risk of diabetes by 50% or more—a remarkable benefit for a relatively modest loss. In the Swedish Obese Subjects (SOS) study, there was a weight loss averaging 28 ± 15 kg at 2 years, and this was associated with an improvement of cardiovascular risk factors including glucose and insulin levels.

WEIGHT LOSS IN PERSONS WITH IMPAIRED GLUCOSE TOLERANCE AND THE PREVENTION OF DIABETES

Weight loss improves insulin sensitivity, leading to lower risk factors for diabetes and cardiovascular disease. There have been a number of trials that have tested the effect of lifestyle changes on the development of diabetes in persons with IGT. These have included generally both diet and exercise to effect weight loss and improve fitness. These trials are summarized below.

Diabetes Prevention Trials in Persons with Impaired Glucose Tolerance

There have been four longitudinal diabetes prevention trials that were long enough, large enough, and well conducted enough to be reviewed here as evidence for the proposition that weight loss helps to prevent the onset of type 2 diabetes.

The Malmö Study

In an early study in Sweden that was not randomized, 41 subjects with type 2 diabetes and 181 subjects with impaired glucose tolerance were followed. The intervention was a hypocaloric diet and increased physical activity. After 5 years, the intervention group showed a mean weight loss of 2.3 kg, whereas 79 control subjects with IGT showed a mean weight gain of 0.5 kg. In the intervention group, 75.8% showed improved glucose tolerance and 10.6% progressed to type 2 diabetes; in fact, more than 50% of patients with IGT returned to normal glucose tolerance. In contrast, 67.1% of the control group showed deterioration in glucose tolerance and 28.6% progressed to type 2 diabetes.

The Da Qing Trial

The Da Qing trial was conducted in 33 centers in one industrial city in China. It was unusual in that the cohort of 577 persons with impaired glucose tolerance was randomized by center, with some centers assigning their patients to dietary change, some to exercise change, some to both, and one (the control) to none. Control subjects received brochures on diet and increased leisure activity. In the intervention group, subjects attended counseling sessions weekly for 1 month, monthly for 3 months, and then once every 3 months. At 6 years, the cumulative incidence of diabetes was significantly lower in the diet group (43.8%), the exercise group (41.1%), and the diet-plus-exercise group (46%) than in the control group (67%). These results are presented in Table 1.
The Finnish Diabetes Prevention Study

The Finnish Diabetes Prevention Study was carried out on 522 people with IGT in five centers in Finland. Their average age was 55 years, their BMI was 31, and all had impaired glucose tolerance by oral glucose tolerance test. Subjects were randomized into two arms: usual care and lifestyle intervention. The randomization was stratified according to clinic, sex, and baseline plasma glucose concentration at 2 hours post oral glucose challenge. The goals of the lifestyle intervention are listed in Table 2. The intervention group attended seven nutritionist sessions during the first year and one session every 3 months thereafter and received individualized instruction on weight loss. The mean follow-up was 3.2 years. At the end of 1 year, patients in the intervention group had lost 4.2 kg, while patients in the control group had lost 0.8 kg (P < 0.001). At the end of 2 years, weight loss was 3.5 kg in the intervention group and 0.8 kg in the control group (P < 0.001). Relative to baseline, decreases in waist circumference and systolic and diastolic blood pressure were statistically greater in the intervention group than in the control group. During this time interval, 86 subjects developed diabetes, 59 in the conventional treatment group and 27 in the intervention group. Thus, the cumulative incidence of diabetes was 11% in the intervention group and 23% in the control group. This was a 58% reduction in conversion to diabetes in the intervention group, a very significant difference (P < 0.001). It is also interesting that the risk of progression was directly proportional to the magnitude of the changes in lifestyle.

The Diabetes Prevention Program

The Diabetes Prevention Program was carried out to determine whether lifestyle intervention or treatment with metformin can prevent or delay the progression from IGT to diabetes, and if their effectiveness differs according to age, sex, race, or ethnic group. This randomized trial engaged 27 centers in the United States and included 3234 individuals. Subjects were selected who had impaired fasting glucose of 95 to 125 and/or postprandial glucose of 140 to 200. The mean BMI of this group was 34. These persons were therefore at high risk of developing diabetes. Individuals were randomized to an intensive lifestyle arm, a metformin arm (850 mg BID), a troglitazone arm, and a placebo usual care arm. The troglitazone arm was stopped after about a year because of hepatic toxicity.

The lifestyle intervention goals were very similar to those in the Finnish study: the weight loss goal was 7% from baseline and the physical activity at least 150 min/week. The study was terminated early by the Data Safety Monitoring Board because of the effectiveness of the lifestyle intervention. Patients had been followed for up to 4 years and the average length of follow-up was 2.8 years. The weight loss effects are shown in Figure 2 and the physical activity results in Figure 3. The goal of 7% weight loss from baseline was reached at 6 months. Thereafter, there was a gradual return to baseline weight. With this amount of weight loss in the lifestyle arm, there was a 58% reduction in the development of diabetes in the lifestyle intervention group compared with the usual care group. The metformin group had a 31% reduction of diabetes. The progression to diabetes in the three arms is shown in Figure 4. The incidence of diabetes was 11.0 cases per 100 person-years in the placebo group, 7.8 in

| Table 1. Data from Da Qing Impaired Glucose Tolerance and Diabetes Study97 |
|-----------------|-----------------|-----------------|
| Intervention    | 6-Year Incidence of NIDDM | Reduction from Control* |
| Control         | 67.7%            | –               |
| Diet            | 43.8%            | 31% (P < 0.03)  |
| Exercise        | 41.1%            | 46% (P < 0.0005) |
| Diet + Exercise | 46.0%            | 42% (P < 0.005)  |

* Adjusted for BMI and fasting glucose.
NIDDM, Non-insulin-dependent diabetes mellitus.

| Table 2. Goals of Finnish Diabetes Prevention Study98 |
|-----------------|-----------------|-----------------|
| • Weight reduction > 5% |
| • Fat intake < 30% of energy intake |
| • Saturated fat intake < 10% of energy intake |
| • Fiber intake > 15 g/1000 kcal |
| • Exercise > 4 hr/wk |

The progression results are shown in Figure 1. The changes in lifestyle not only improved glucose tolerance but also reduced the magnitude of several other cardiovascular risk factors.99

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| Figure 1. Results from the Finnish Impaired Glucose Tolerance Study showing the cumulative probability of remaining free of diabetes. (Data from Tuomilehto et al., 2001.98) |
the metformin group, and 4.8 in the lifestyle group. The results were highly significant for both metformin and lifestyle \((P < 0.001)\). These results did not differ by sex, race, or ethnic group. The lifestyle intervention was highly effective in all subgroups. Nearly half of the participants were from minority groups, who have an increased risk for developing type 2 diabetes. Also, it is interesting that preliminary data from the Diabetes Prevention Program suggest that weight loss rather than physical activity was most responsible for the reduction of the incidence of type 2 diabetes with the intensive lifestyle intervention.102

These four studies show that it is possible to significantly reduce the development of diabetes in persons with IGT with a program of a hypocaloric diet and exercise that will decrease weight by about 7% and be at least partially sustained for the next 4 years. To prevent one case of diabetes in the Finnish study, 5 persons need to be treated for 5 years; in the Diabetes Prevention Program, 7 persons need to be treated for 3 years. Metformin would prevent one case if 14 persons were treated for 3 years. This has caused the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Disease to put forth lifestyle intervention as the first line of treatment in attempting to prevent diabetes.103

It is not clear whether such an intervention of diet and exercise merely delays or can actually prevent the onset of diabetes. For this, continued follow-up is necessary, which is what is being done with the Diabetes Prevention Program cohort.

**WEIGHT LOSS STUDIES FOR THE PREVENTION OF DIABETES IN PERSONS WITHOUT IMPAIRED GLUCOSE TOLERANCE**

More recently, a study was conducted in Europe evaluating weight loss effects on the progression to diabetes in obese patients, both with and without IGT. The weight loss was induced with Orlistat in combination with lifestyle changes and compared with lifestyle changes alone over a period of 4 years. Orlistat is a lipase inhibitor that causes a dose-dependent reduction in dietary fat absorption in the gut, with a maximum 30% inhibition of fat absorption when utilizing a dosage of 120 mg TID.104-105 This action tends to counteract the excess fat intake that is characteristic of many obese individuals.106 The drug has been shown to be effective in large, long-term (1- and 2-year), randomized clinical trials in inducing and maintaining weight loss in both obese patients without107,108 and with109 diabetes. Orlistat significantly reduced the incidence of type 2 diabetes. The hazard ratio showed a 37.5% decrease with Orlistat compared with placebo over 4 years. Approxi-
mately 50% more Orlistat than placebo patients achieved weight loss of 5% and 10% from baseline. Waist circumference, LDL-cholesterol, and blood pressure decreased significantly more in the drug group. The adverse event profile in this study was not serious, and was equivalent to that previously reported in other long-term trials.107-109

Will et al.110 examined retrospectively the 13-year incidence of diabetes in a large cohort of subjects from the first Cancer Prevention Study. The authors also found that intentional weight loss was associated with a significant reduction in the rate of developing diabetes. Colditz et al.90 found in the Nurses Health Study that women who lost more than 5 kg reduced their risk for diabetes by more than 50%.

METABOLIC SYNDROME AND LIFESTYLE CHANGES

The metabolic syndrome has been defined by the National Cholesterol Education Program as shown in Table 3.111 It has been reported that the metabolic syndrome increases the risk of cardiovascular disease and the risk of cardiovascular disease mortality. In the Diabetes Prevention Program, 53% of the subjects had the metabolic syndrome.112 Of the components, an elevated waist circumference was the most common (73%) and high fasting glucose was the least common (33%). The prevalence of the metabolic syndrome between baseline and follow-up increased from 55% to 61% in the placebo group, remained unchanged in the metformin group (54% to 55%), and was reduced in the lifestyle group from 51% to 43%. The study showed that an intensive lifestyle intervention with weight loss and increased physical activity is more effective in reducing the onset of diabetes, but is also more effective in reducing the other components of the metabolic syndrome. This may mean that, in the long run, it is more effective in reducing the incidence of cardiovascular disease.

<table>
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<th>Measure*</th>
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| Elevated waist circumference | ≥ 102 cm (40 in) in men  
≥ 88 cm (35 in) in women |
| Elevated triglycerides | ≥ 150 mg/dL (1.7 mmol/L)  
or on drug treatment for elevated triglycerides |
| Reduced HDL-C | < 40 mg/dL (1.03 mmol/L) in men  
< 50 mg/dL (1.3 mmol/L) in women  
or on drug treatment for reduced HDL-C |
| Elevated blood pressure | ≥ 130 mmHg systolic BP  
or ≥ 85 mmHg diastolic BP  
or on antihypertensive drug treatment with a history of hypertension |
| Elevated fasting glucose | ≥ 100 mg/dL  
or on drug treatment for elevated glucose |

* Any three of these measures constitutes a diagnosis of metabolic syndrome. HDL-C, high-density lipoprotein cholesterol

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