CHAPTER 1

What have we learned from the number of clinical trials?

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Introduction

The primary prevention of type 2 diabetes (T2D) was originally proposed by Dr. E. Joslin in 1921 [1]. He commented on how obese people are more likely to have diabetes than their slimmer neighbors. Indeed, to be able to prevent a chronic disease such as T2D it is necessary to have knowledge about its modifiable risk factors and natural history. Furthermore, there should be a preclinical phase or a “window of opportunity” for intervention as well as a feasible screening tool to identify high-risk individuals. In addition, the efficacy of the intervention has to be proven in a clinical trial setting.

T2D is a very expensive disease – about 10–15% of the total health care costs in developed countries are spent to treat T2D and, in particular, its complications [2,3]. To avoid late complications of T2D and related costs, prevention of T2D itself is therefore desirable. There are some “natural” experiments in which ethnic groups have experienced rapid westernization and with it a rapid increase in the rates of obesity and T2D [4]. Therefore it is logical to assume that by reversing these lifestyle changes it would be possible to prevent the development of the disease. Such a potential for reversibility has been shown among Australian Aboriginals [5]. In these experiments hyperglycemic people returned to living in a traditional hunter–gatherer way of life – an ultimate lifestyle change not suitable for everybody.

T2D develops as a result of complex multifactorial process with both lifestyle and genetic origins. The main risk factors for T2D are obesity and
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A sedentary lifestyle [6]. A “westernized” dietary pattern with low fiber [7–9] and high saturated [10] and trans fats [11], refined carbohydrates [12], sweetened beverages [13], sodium [14], and red meat and processed meat products [15,16] intake has been shown to be associated with increased T2D risk. Another feature of modern lifestyle, voluntary sleep deprivation, also increases diabetes risk [17,18]. Protective lifestyle factors, in addition to those mentioned above, include coffee [19–21] and moderate alcohol, particularly wine consumption [22].

Impaired glucose tolerance (IGT) is a hyperglycemic state between normoglycemia and T2D, diagnosed by a 2-h oral glucose tolerance test (OGTT). Of the people with IGT, approximately half will develop T2D during a 10-year follow-up period [23,24]. In Asian populations the rate of progression seems to be even faster [25,26]. It is well known that the risk of complications begins in the prediabetic phase prior to glucose levels reaching diagnostic cut-points for T2D [27–29]. People with IGT would thus be the perfect subjects for preventive interventions.

Major lifestyle trials in prevention of T2D

Da-Qing Study

A large population-based screening program (110,660 persons screened with OGTT) to identify people with IGT was carried out in Da-Qing, China, in 1986 [25,30]. The randomization of study subjects was not random, but the 33 participating clinics (= cluster randomization) were randomized to carry out the intervention according to one of the four specified intervention protocols (diet alone, exercise alone, diet–exercise combined, or none). Altogether, 577 (312 men, 264 women + 1 undefined) subjects with IGT participated in the trial, and of these 533 participated in the measurements at the end of the intervention in 1992. The cumulative 6-year incidence of T2D was lower in the three intervention groups (diet alone, exercise alone, diet–exercise combined; 41–46%) than the control group (68%). Because no individual allocation of study subjects to the intervention and control groups was done, the results based on individual data analysis must be interpreted with caution. The study subjects were relatively lean, with a mean body mass index (BMI) of 25.8 kg/m², but, despite that, the progression from IGT to diabetes was high; more than 10% per year in the control group.

In clinics assigned to dietary intervention, the participants were encouraged to reduce weight if their BMI was >25 kg/m², aiming at <24 kg/m²,
otherwise a high carbohydrate (55–65 energy proportion (E%)) and moderate fat (25–30E%) diet was recommended. Participants were encouraged to consume more vegetables, reduce simple sugar intake, and control alcohol intake. Small group counseling sessions concerning diet and/or physical activity were organized weekly for the first month, monthly for 3 months, and every 3 months thereafter. Participants also received individual counseling by physicians. The participants were encouraged to increase their level of leisure time physical activity by at least 1–2 “units” per day, one unit corresponding to 30 minutes of slow walking, shopping, house cleaning, or traveling by bus, 20 minutes of cycling or ballroom dancing, 10 minutes of slow running, climbing stairs, or disco dancing, or 5 minutes of swimming, jumping rope, or playing basketball.

The overall changes in risk factor patterns were relatively small. Body weight did not change in lean subjects, and there was a modest, <1 kg, reduction in subjects with baseline BMI >25 kg/m². The estimated changes in habitual dietary nutrient intakes were small and nonsignificant between groups. Within the exercise and diet plus exercise groups, physical activity increased modestly but statistically significantly (+ 0.6–0.8 activity units per day on average). Thus, it is not easy to determine the factors responsible for the beneficial effects on the risk of T2D. In this population, weight control obviously was not the key issue. Physical activity and qualitative changes in diet that are difficult to measure on individual level probably played a key part.

The 20-year follow-up of the original study cohort [30] showed that the reduction in diabetes incidence persisted in the combined intervention group compared with control participants with no intervention, and, furthermore, the risk reduction remained essentially the same during the post-intervention period. It should be noted that diabetes incidence during the follow-up was high: in the final analyses 80% of the intervention participants and 93% of the control participants had developed diabetes. The follow-up analyses showed no statistically significant differences in cardiovascular disease (CVD) events, CVD mortality, or total mortality between the control group and the combined intervention groups. A non-significant 17% reduction in CVD death was observed, which can be seen to be at least suggestively in favor of the lifestyle intervention.

**Finnish Diabetes Prevention Study**

The intervention of the Finnish Diabetes Prevention Study (DPS) was carried out during 1993–2001 in five clinics in Finland, aiming to prevent T2D with lifestyle modification alone [24,31–33]. A total of 522 individuals
at high risk of developing diabetes were recruited into the study, mainly by screening for IGT in middle-aged (age 40–64 years) overweight (BMI >25 kg/m²) subjects. The presence of IGT before randomization was confirmed in two successive 75-g OGTT; the mean of the two values had to be within the IGT range to qualify for the study. The participants were randomly allocated either into the control group or the intensive intervention group. The subjects in the intervention group had frequent consultation visits with a nutritionist (seven times during the first year and every 3 months thereafter). They received individual advice about how to achieve the intervention goals which were reduction in weight of 5% or more, total fat intake <30% of energy consumed, saturated fat intake <10% of energy consumed, fiber intake of at least 15 g/1000 kcal, and moderate exercise for 30 minutes per day or more. Frequent consumption of wholegrain cereal products, vegetables, berries and fruit, low-fat milk and meat products, soft margarines, and vegetable oils rich in monounsaturated fatty acids were recommended. The dietary advice was based on 3-day food records completed four times per year. The participants were also individually guided to increase their level of physical activity. Endurance exercise (walking, jogging, swimming, aerobic ball games, skiing) was recommended to increase aerobic capacity and cardiorespiratory fitness. Supervised, progressive, individually tailored circuit-type resistance training sessions to improve the functional capacity and strength of the large muscle groups were also offered.

The control group participants were given only general advice about healthy lifestyle at baseline. An OGTT was carried out annually for all participants and if either fasting or 2-h glucose values reached diabetic levels a confirmatory OGTT was performed. The study end-point was only recorded if the second test also reached diabetic levels; otherwise the subjects continued with their randomized treatment.

Body weight reduction from baseline was on average 4.5 kg in the intervention group and 1.0 kg in the control group subjects (P<0.001) after the first year and at 3 years, weight reductions were 3.5 and 0.9 kg (P<0.001), respectively. Indicators of central adiposity and glucose tolerance improved significantly more in the intervention group than in the control group at both 1-year and 3-year follow-up examinations. At the 1-year and 3-year examinations intervention group subjects reported significantly more beneficial changes in their dietary and exercise habits, based on dietary and exercise diaries.

After 4 years the cumulative incidence of diabetes was 11% (95% CI 6–15%) in the intervention group and 23% (95% CI 17–29%) in the
control group. Based on life-table analysis, the risk of diabetes was reduced by 58% ($P < 0.001$) during the trial in the intervention group compared with the control group during a mean follow-up time of 3.2 years. The absolute risk reduction was 12% at that point and the number needed to treat (NNT) was 8. Both men and women benefited from lifestyle intervention: the incidence of diabetes was reduced by 63% and in women by 54% in the intervention group compared with the control group. None of the people (either in the intervention or control group) who had succeeded in achieving all five predefined lifestyle targets developed diabetes, while approximately one-third of the people who did not reach a single one of the targets developed T2D. This is direct empirical proof that the reduction of the diabetes risk was indeed mediated through the lifestyle changes. *Post hoc* analyses have also shown that both dietary changes – adopting a diet with moderate fat and high fiber content [34] – as well as increasing physical activity [35] were independently associated with diabetes risk reduction. Furthermore, a subgroup analysis with intravenous glucose tolerance testing ($n = 87$ at baseline and 52 at 4-year examination) showed improvement in insulin resistance which was highly correlated with achieved body weight reduction [36]. The effect of lifestyle intervention on diabetes incidence was shown to be the largest among the oldest age group and those with the highest baseline risk profile, as measured with the Finnish Diabetes Risk Score (FINDRISC) [37].

An analysis using the data collected during the extended follow-up of the DPS revealed that after a median of 7 years’ total follow-up a marked reduction in the cumulative incidence of diabetes was sustained [24]. The relative risk reduction during the total follow-up was 43%. The effect of intervention on diabetes risk was maintained among those who after the intervention period were without diabetes: after median post-intervention follow-up time of 3 years the corresponding incidence rates were 4.6 and 7.2 per 100 person-years, respectively (log-rank test $P = 0.0401$), that is, 36% relative risk reduction.

The 10-year follow-up results on the effect of DPS lifestyle intervention on total mortality and cardiovascular morbidity were published in 2009 [38], based on register linkage of the original study cohort to the national Hospital Discharge Register and Death Register. Among the DPS participants who consented for register linkage ($n = 505$), total mortality (2.2 vs. 3.8 per 1000 person-years) and cardiovascular morbidity (22.9 vs. 22.0 per 1000 person-years) were similar in the intervention and control groups. Interestingly, when the DPS intervention and control groups together were compared with a population-based cohort including people
with IGT, adjusted hazard ratios were 0.21 (95% CI 0.09–0.52) and 0.39 (95% CI 0.20–0.79) for total mortality and 0.89 (95% CI 0.62–1.27) and 0.87 (95% CI 0.60–1.27) for cardiovascular morbidity. Thus, the risk of death among the DPS participants was markedly lower than in a population-based IGT cohort.

**Diabetes Prevention Program**

The Diabetes Prevention Program (DPP) [39,40] was a multicenter randomized clinical trial carried out in the United States. It compared the efficacy and safety of three interventions: an intensive lifestyle intervention or standard lifestyle recommendations combined with metformin or placebo. The study focused on high-risk individuals (n = 3234) with IGT who also had slightly elevated fasting plasma glucose (>5.5 mmol/L). The main results were intensive lifestyle intervention reduced T2D risk after 2.8 years’ mean follow-up by 58% compared with the placebo control group. Lifestyle intervention was also shown to be superior to metformin treatment (850 mg twice daily) which led to T2D risk reduction of 31% compared with placebo [39].

The lifestyle intervention in DPP was primarily carried out by special educators, “case managers” and was relatively intense. The lifestyle intervention commenced with a 16-session structured core curriculum within the first 24 weeks after randomization, followed by individual sessions with the case manager every 2 months. The goals of the dietary intervention were to achieve and maintain a 7% weight reduction by consuming a healthy, low-calorie, low-fat diet and to engage in physical activities of moderate intensity (such as brisk walking) 150 minutes per week or more. Clinical centers (n = 27) also offered supervised activity sessions where attendance was voluntary. Of the DPP participants assigned to intensive lifestyle intervention, 74% achieved the study goal of ≥150 minutes of activity per week at 24 weeks. At 1-year visit the mean weight loss was 7 kg (about 7%).

The DPP investigators have also attempted to clarify the relative contributions of different components of the lifestyle intervention to the reduction in diabetes incidence in the intensive lifestyle intervention arm of the DPP [41]. Furthermore, they aimed to assess the contribution of diet and activity changes on weight loss. The main finding was that body weight at baseline and weight reduction during the intervention were the most important predictors of diabetes risk. Lower weight (10 kg) at baseline resulted in a 12% lower diabetes incidence, even when adjusted for demographics and changes in dietary fat intake and physical activity. For each
kilogram lost, the risk of developing diabetes was estimated to be reduced by 16%. In the model assessing one intervention characteristic at a time, the energy proportion of fat was a significant predictor of the incidence of diabetes, with a 5% reduction leading to a hazard ratio of 0.75 (0.63–0.88). However, in the multivariate models with predictors as continuous variables and with baseline body weight and weight reduction as covariates, neither physical activity nor energy proportion of dietary fat predicted diabetes. Nevertheless, among the participants not meeting the weight loss goal during the first year of the trial, those who achieved the physical activity goal had a 44% lower incidence of diabetes.

**Indian Diabetes Prevention Program**

The Indian Diabetes Prevention Program (IDPP) recruited 531 subjects with IGT (mean age 46 years, BMI 25.8 kg/m²) who were randomized into four groups (control, lifestyle modification, metformin, and combined lifestyle modification and metformin) [26,42]. Lifestyle modification included advice on physical activity (30 minutes of brisk walking per day) and reduction in total calories, refined carbohydrates and fats, avoidance of sugar, and inclusion of fiber-rich foods. The intervention included personal sessions at baseline and 6-monthly, and monthly telephone contacts. The intensity of the intervention thus was lower than in the DPP and DPS. After a median follow-up of 30 months, the relative risk reduction was 28.5% with lifestyle modification, 26.4% with metformin, and 28.2% with lifestyle modification and metformin, compared with the control group [26]. Thus, there was no added benefit from combining the drug and lifestyle interventions. In the control group, diabetes incidence was high (55% in 3 years) and comparable to the findings from the Chinese study [25].

**Japanese Prevention Trial**

The Japanese Prevention Trial included 458 men who were diagnosed with IGT in health screening and allocated randomly to receive either intensive lifestyle intervention (n = 102) or standard intervention (n = 356) [43]. The participants in the intensive intervention group visited hospital every 3–4 months where they were given detailed, repeated advice to reduce body weight if their BMI was ≥22 kg/m² (otherwise, to maintain their weight) by consuming large amount of vegetables and reducing the total amount of other food by 10%, for example, by using a smaller rice bowl. Intake of fat (<50g per day) and alcohol (<50g per day) were
limited, as was eating out (no more than once a day). Physical activity was recommended (30–40 min per day of walking, etc.). The participants in the control group visited hospital every 6 months and were given standard advice to eat smaller meals and increase their physical activity.

The cumulative 4-year incidence of diabetes was 3% in the intervention group and 9.3% in the control group, with 67.4% risk reduction ($P < 0.001$). BMI at baseline was 23.8 ± 2.1 in the intervention group and 24.0 ± 2.3 in the control group. Body weight decreased by 2.18 kg in the intervention group and 0.39 kg in the control group during the 4 years follow-up ($P < 0.001$). Thus, there was a remarkable reduction in diabetes risk despite the relatively modest weight reduction. Post hoc analyses in the control group revealed that diabetes incidence was positively correlated with change in body weight in this population; however, weight loss was not the sole explanator of diabetes risk reduction.

**Other trials**

Several more recent and/or smaller prevention trials have been completed, with very similar findings to the trials already presented. The SLIM Study [44,45] in the Netherlands aimed to determine the effect of diet and exercise intervention on glucose tolerance, insulin resistance, and CVD risk factors in individuals with IGT. At 3 years’ follow-up among those who completed the trial (n = 106) the cumulative incidence of T2DM was 18% in the intervention group and 38% in the control group, with relative risk 0.42 ($P = 0.025$); a 58% risk reduction.

The European Diabetes Prevention Study (EDIPS) extended the DPS to other European populations, using the same study design. In the Newcastle arm of this study (EDIPS–Newcastle) [46], among 102 participants with IGT (42 men and 60 women, mean age 57 years, mean BMI 34 kg/m²) the overall incidence of diabetes was reduced by 55% in the intervention group compared with the control group, with RR 0.45 (95% CI 0.2–1.2). These results contribute to the evidence that T2D can be prevented by lifestyle changes in adults with IGT.

The PREDIMED-Reus [47] was a substudy to a large nutrition intervention trial (the PREDIMED study) for primary cardiovascular disease prevention in persons at high risk. Altogether, 418 nondiabetic subjects aged 55–80 years were randomized to education on a low-fat diet (control group) or one of two Mediterranean diets, supplemented with either free virgin olive oil (1 L per week) or nuts (30 g per day). No advice on physical activity was given. After a median follow-up of 4.0 years, multivariable-adjusted hazard ratios of diabetes were 0.49 (0.25–0.97) and 0.48 (0.24–
0.96) in the Mediterranean diet groups supplemented with olive oil and nuts, respectively, compared with the control group. Diabetes risk reduction occurred in the absence of significant changes in body weight or physical activity.

**Clinical trial evidence of the effect of lifestyle components on T2D risk**

The results from clinical trials to prevent T2D have been surprisingly similar: a significant reduction in diabetes incidence has been observed following lifestyle modification. The intervention methods used to modify lifestyle have varied between the studies, because it is obvious that socio-cultural issues and the available facilities and personnel have dictated the application of the intervention. However, they have also several features in common. Lifestyle intervention in these clinical trials had a strong focus on increased physical activity (2.5–4 hours per week) and dietary modification (increased whole grain, fiber, vegetables, and fruit, reduced total and saturated fat, sugar and refined grain). Weight reduction among overweight participants was also an important goal and predictor of decreased diabetes risk in many of the studies [41]; however, beneficial changes in diabetes incidence were also achieved independently of weight reduction [25,26,47]. The interventions utilized behavior modification techniques such as motivational interviewing, self-monitoring, and individualized short and long-term goals.

In most of the published prevention trials the main aim was to explore the effect of comprehensive lifestyle intervention. In the Chinese prevention study [25] an attempt to determine whether a diet or exercise intervention is more effective revealed no difference in outcome between the two interventions.

In the DPS the risk of being diagnosed with diabetes was strongly associated with the number of lifestyle goals achieved [24]. Success in achieving the intervention goals in the DPS was estimated from the food records and exercise questionnaires. The success score (0–5) was calculated as the sum of achieved lifestyle goals. There was a strong inverse correlation between the success score and the incidence of diabetes during the total follow-up. This was especially apparent when the success in achieving the goals was assessed at year 3, which probably reflects the importance of sustained lifestyle changes. The independent effects of achieving the success score components at 3-year examination was assessed by including each of the
five lifestyle goal variables individually in a Cox model. Univariate hazard ratios for diabetes incidence (95% CI) were 0.45 (0.31–0.64) for weight reduction from baseline, 0.65 (0.45–0.95) for intake of fat, 0.59 (0.31–1.13) for intake of saturated fat, 0.69 (0.49–0.96) for intake of fiber, and 0.62 (0.46–0.84) for physical activity, comparing those who did or did not achieve the respective goal. When all the five success score components were simultaneously included in the Cox model, the multivariate adjusted hazard ratios for diabetes (95% CI) were 0.43 (0.30–0.61) for weight reduction, 0.80 (0.48–1.34) for intake of fat, 0.55 (0.26–1.16) for intake of saturated fat, 0.97 (0.63–1.51) for intake of fiber, and 0.80 (0.57–1.12) for physical activity. Furthermore, weight change was significantly associated with the achievement of each of the other four lifestyle goals, and consequently, success score was strongly and inversely correlated with weight reduction [24].

Correspondingly, the reduction in body weight was reported to be the main determinant of risk reduction in the US DPP [41]. After adjustment for other components of the intervention, there was a 16% reduction in diabetes risk per 1 kg weight lost during the first year of the intervention. Furthermore, lower percentage of calories from fat and increased physical activity predicted weight loss, and increased physical activity was important to help sustain weight loss. Achieving the physical activity goal of 150 min per week reduced diabetes risk especially among those participants who did not achieve the weight reduction goal.

The findings suggest that dietary composition and physical activity are important in diabetes prevention and their effect on diabetes risk is partly but not entirely mediated through resulting weight reduction. Due to multicollinearity, the results should be interpreted cautiously. In the Indian IDPP [26] and Chinese prevention study [25] the participants were relatively lean and there was no large change in body weight, but despite that a remarkable reduction in diabetes risk was apparent. Thus, in these studies other components of the intervention than weight control were responsible for the beneficial effects on diabetes risk. In the PREDIMED-Reus study diabetes risk reduction was associated with compliance with the Mediterranean diet [47] and especially with high intake of either nuts or extra virgin olive oil. So far there have been no studies comparing the “healthy diet” based on the DPS and DPP approach (reduced saturated fat, moderate total fat, increased fiber from cereal and vegetables) with the Mediterranean diet scheme of the PREDIMED-Reus. Possibly the best solution would be a combination of both: emphasis on quality of diet but simultaneous aim of moderate weight reduction.
A pragmatic way to prevent diabetes therefore would be to focus strongly on behavioral factors such as diet composition and physical activity. Dietary changes according to the intervention goals will reduce the energy density of the diet and lead to decreased total energy intake. Increased physical activity on the other hand will increase energy consumption. Together, these changes, even if relatively modest, can lead to weight reduction. A strict diet emphasizing dietary restriction and aiming solely at weight reduction may be more efficient for achieving weight loss in the short term, but typically does not lead to sustained behavioral change.

Diets may vary according to food culture, food availability, and personal preferences, and yet follow the same general principles, as shown by the clinical studies. Based on the range of different diets associated with diabetes prevention these principles are as follow [48]:

- Aim for a high intake of vegetables
- Consume mainly unrefined, wholegrain cereal products
- Choose vegetable oils such as olive or rapeseed oil for everyday use
- Opt for fish, dairy, or vegetable sources of proteins (e.g., nuts, legumes)
- Limit the intake of highly processed or energy-dense foods that are high in fat and/or refined sugar (e.g., processed meat, sweetened beverages, confectionery).

References


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