Nonpharmacologic Therapy and Exercise in the Prevention of Type 2 Diabetes

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OBJECTIVE — To review the current knowledge about nonpharmacologic approaches in the prevention and early treatment of type 2 diabetes.

RESEARCH DESIGN AND METHODS — This study reviewed the research reports dealing with nonpharmacologic interventions aimed at preventing type 2 diabetes with early lifestyle interventions.

RESULTS — The results from the randomized controlled trials all show that people with impaired glucose tolerance who received enhanced lifestyle advice had significantly lower (on average ~50% reduced) incidence of type 2 diabetes compared with those allocated to receive "usual care." Individuals who were able to correct their lifestyle habits as recommended for usual healthy life patterns were mostly protected against type 2 diabetes. Thus, compelling evidence exists that most of the cases of type 2 diabetes can be prevented or at least the onset of the disease can be significantly delayed.

CONCLUSIONS — Randomized controlled trials have unequivocally demonstrated that lifestyle management is highly efficient in the prevention and also in the early management of type 2 diabetes. This evidence of lifestyle modification in diabetes prevention is stronger than for most other multifactorial diseases.

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It is well known that obesity, unbalanced diet, and physical inactivity are the major risk factors for diabetes. In people genetically predisposed to the disease, the probability to develop type 2 diabetes is high once exposed to "unhealthy" lifestyles. In understanding the potential for prevention of type 2 diabetes, it is important to understand the enormity of a preventive lifestyle intervention. The development of type 2 diabetes is a slow process that takes a long time and involves both genetic and environmental effects (1). It is commonly agreed that type 2 diabetes may develop only in subjects that carry a genetic predisposition to the disease. Based on epidemiological observations, about half of the people or even more in some populations will develop type 2 diabetes during their lifetime, and up to 30–35% will have impaired glucose tolerance (IGT) (2,3). Therefore, it is likely that more than half of the people carry genes that predispose the development of type 2 diabetes. Even though genetic effects are important for the development of the disease, it is not possible to modify them to prevent type 2 diabetes. Until recently, evidence regarding the prevention of type 2 diabetes based on proper randomized controlled trials has been virtually missing.

Type 2 diabetes is also a very expensive disease; ~10–15% of the total health care costs in developed countries are spent treating type 2 diabetes and, in particular, its complications (4). To avoid late complications of type 2 diabetes and related costs, primary prevention of type 2 diabetes itself and its early treatment are therefore necessary. The efficacy of prevention in subjects with IGT has been tested, and currently there is unequivocal and strong evidence that we can prevent or delay the progression of hyperglycemia to type 2 diabetes.

Data from certain population groups show that experiencing rapid westernization is accompanied by a rapid increase in the rates of obesity and type 2 diabetes (5). Can the situation be reversed by reversing these lifestyle changes? Yes, this has been demonstrated among Australian Aboriginals by O'Dea (6). In these studies, hyperglycemic subjects reverted to living naturally, in the traditional hunter-gatherer way of life. As a result, hyperglycemia was reversed.

The main risk factors for type 2 diabetes are obesity and sedentary lifestyle (7). A "westernized" dietary pattern with low fiber and high saturated and trans fats, refined carbohydrates, sweetened beverages, sodium, and red meat intake have been shown to be associated with increased type 2 diabetes risk (8). Another feature of modern lifestyle, sleep deprivation or irregularity, has also been shown to increase diabetes risk (9). Fortunately, there are also protective factors in modern lifestyle: data are being accumulated on the decreased type 2 diabetes risk associated with coffee and moderate alcohol intake, particularly wine consumption (10,11).

It is a well-known fact that antidiabetic drug treatment in type 2 diabetes has only a limited effect on glycemic control, which deteriorates in diabetic patients despite intensive treatment, as demonstrated in newly diagnosed type 2 diabetic patients in the U.K. Prospective Diabetes Study (12). Thus, it is obvious that interventions to prevent increase in blood glucose must start much earlier than when clinical symptoms of diabetes occur, ideally before glucose levels reach the values considered as diabetes or clinical symptoms due to the disease. In people with IGT, approximately half develop type 2 diabetes during a 10-year follow-up (13), and in Asian populations, the rate of progression seems to be even faster (14,15). It is well known that the risk of complications begins already in the pre-diabetic phase before blood glucose levels reach diagnostic cut points for type 2 diabetes (16). Thus, waiting until individuals attain the diagnostic criteria for type 2 diabetes will result in significant morbidity and mortality from cardiovascular disease (17,18). The vast majority of costs in type 2 diabetes are due to the secondary and tertiary care of type 2 dia-

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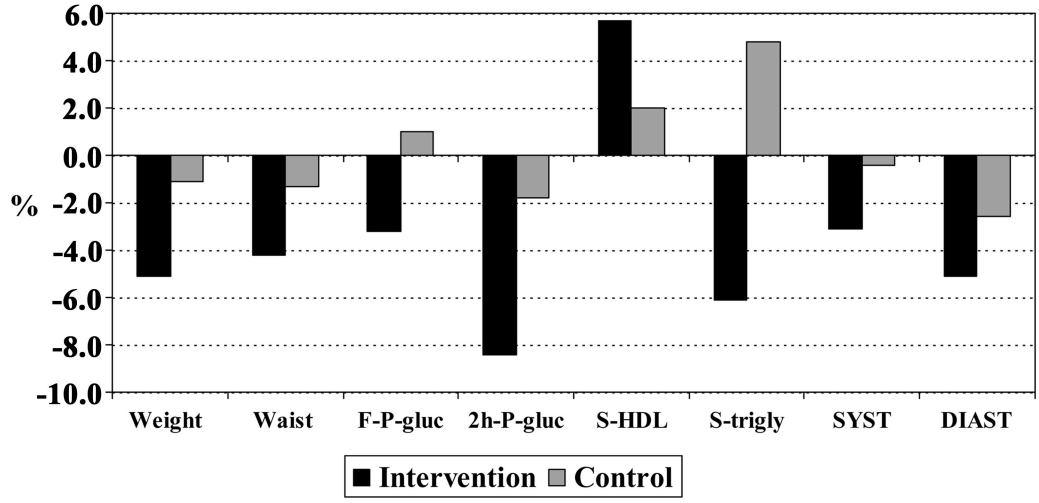

Figure 1—*Changes in clinical and metabolic characteristics among the intervention and control group participants of the DPS. 2h-P-gluc, 2-h plasma glucose; DIAST, diastolic blood pressure; F-P-gluc, fasting plasma glucose; S, serum; SYST, systolic blood pressure.*

betic patients who have late complications, primarily cardiovascular disease (CVD) (4). Up to 80% of type 2 diabetic patients will have CVD. With increasing number of type 2 diabetic patients worldwide, the number of patients with CVD will inevitably also rise. The only logical way to prevent this projected increase in health care costs is to prevent or postpone the onset of type 2 diabetes.

LIFESTYLE TRIALS IN PEOPLE WITH IGT TO PREVENT PROGRESSION TO TYPE 2 DIABETES

— In the early randomized intervention study in Malmöhus, Sweden (19), lower rates of type 2 diabetes was found in IGT men randomized to dietary intervention compared with those who received no therapy. More recently, several trials have tested the efficacy of lifestyle intervention in prevention of type 2 diabetes.

The feasibility of diet and exercise intervention in men with IGT was assessed in another study in Malmö, Sweden (20). Because the reference group comprised of men who did not want to join the intervention, the groups were not randomly assigned. The lifestyle intervention aimed at reducing the intake of refined sugar, simple carbohydrates, fat, saturated fat, energy, and alcohol and an increase in the intake of complex carbohydrates and vegetables. Physical activity training consisted of two weekly 60-min sessions with various dynamic activities. By the end of the 5-year study period, 11 and 29% of the men in the intervention group and reference group had developed type 2 diabetes, respectively. Overall, the progression to diabetes in these Swedish men was relatively low, even in the reference group compared with the data from the observational studies (1). The intervention resulted in significant changes in lifestyle and physiological parameters.

In another study, 577 subjects with IGT were assigned either to a control, exercise alone, diet alone, or exercise plus diet group in Da-Qing, China (14), using a cluster-randomized trial design. Participants were assigned to clinics for dietary intervention and were encouraged to reduce weight if BMI was ≥25 kg/m^2 (61% of all participants) aiming at 23 kg/m^2; otherwise high-carbohydrate (55–65% of energy) and moderate-fat (25–30% of energy) diet was recommended. The participants were encouraged to increase their level of leisure-time physical activity by at least 1–2 "units" per day in clinics assigned to exercise intervention. One unit would correspond for instance to 30 min slow walking, 10 min slow running, or 5 min swimming. The cumulative 6-year incidence of type 2 diabetes was lower in each of the three intervention groups (41–46%) compared with 68% in the control group.

The results of the Finnish Diabetes Prevention Study (DPS) provided the first convincing evidence from a proper randomized controlled trial that type 2 diabetes can be prevented by lifestyle modification (21). A total of 522 individuals with IGT were randomized to either an intensive lifestyle or a control intervention: during an average of 3.2 years of follow-up, type 2 diabetes incidence was reduced by 58% in the lifestyle group. The lifestyle intervention goals were *1*) reduction in weight of ≥5%, *2*) total fat intake <30% of energy, *3*) saturated fat intake <10% of energy, *4*) fiber intake ≥15 g/1,000 kcal, and *5*) moderate exercise for ≥30 min/day. During the first year of the study, body weight decreased on average 4.5 kg in the intervention group and 1.0 kg in the control group subjects ($P < 0.0001$). Indicators of central adiposity and fasting glucose and insulin, 2-h postchallenge glucose and insulin, and A1C were all reduced significantly in the intervention group compared with the control group at 1-year examination (Fig. 1).

The U.S. Diabetes Prevention Program (DPP) (22) recruited 3,234 individuals with IGT (and fasting plasma glucose ≥95 mg/dl) who were randomized to receive intensive dietary and exercise counseling, metformin, or placebo. The main aims of the intervention were ≥7% weight reduction and ≥150 min/week moderate physical activity. The relative risk reduction after 2.8 years was 58% in the lifestyle intervention group compared with the placebo group. The effect of lifestyle was higher than the effect of metformin, which showed 35% relative risk reduction. During the first year of the intervention, weight reduction was 5.6 kg (~6%), with slight, gradual regain to the end of the study at year 4 (23).

The Indian Diabetes Prevention Program (14) recruited 531 people with IGT who were randomized into four groups (control, lifestyle modification, metformin, and combined lifestyle mod-

ification and metformin). Lifestyle modification included advice on physical activity (30 min of brisk walking per day) and reduction in total calories, refined carbohydrates and fats, avoidance of sugar, and increase in fiber-rich foods. The intensity of the intervention was lower than in the DPP and DPS. After median follow-up of 30 months, the relative risk reduction in type 2 diabetes incidence was with lifestyle modification, 26.4% with metformin, and 28.2% with lifestyle modification and metformin, as compared with the control group. Thus, there was no added benefit from combining the pharmacologic and lifestyle interventions.

The Japanese trial (24) included 458 IGT men randomized to receive either intensive lifestyle intervention ($n = 102$) or standard intervention ($n = 356$). The aims of the intensive intervention were body weight reduction if BMI was ≥22 kg/m^2 (otherwise, to maintain present weight), to consume large amounts of vegetables while reducing the amount of other foods by 10%, reduction of fat (<50 g/day) and alcohol intake (<50 g/day), and physical activity >30–40 min/day. The cumulative 4-year incidence of type 2 diabetes in the intervention group was 67% lower than in the control group. Body weight decreased by 2.2 and 0.4 kg in the intervention and control groups, respectively.

LONG-TERM EFFECTIVENESS OF LIFESTYLE PREVENTION OF TYPE 2 DIABETES IN PEOPLE WITH IGT

— The trials listed above have demonstrated the benefits of healthy lifestyle on delaying the deterioration of glucose tolerance to manifest type 2 diabetes, at least as long as the intervention continued. Data on possible long-term effects of such active lifestyle counseling are scarce. The 12-year follow-up of the Malmö study (25) revealed that mortality among men in the former IGT intervention group was lower than in the control group (6.5 vs. 14.0/1,000 person-years, $P = 0.009$).

In a median 7-year follow-up of the DPS, the marked reduction in type 2 diabetes incidence was sustained (13). More importantly, after a median postintervention follow-up of 3 years, type 2 diabetes incidence was 4.6 and 7.2 per 100 person-years in the intervention and control groups, respectively (log-rank test, $P = 0.0401$), i.e., a 36% additional risk reduction. The absolute risk difference between groups increased during the postintervention period: intensive lifestyle intervention for a limited time can yield long-term benefits on type 2 diabetes risk in individuals with IGT.

The 20-year follow-up of the original Da Qing cohort showed that a lower type 2 diabetes incidence persisted in the lifestyle intervention groups (combined) compared with control participants. The risk reduction remained essentially the same also during the postintervention period (26). Li et al. (26) observed no statistically significant differences in CVD events, CVD, or total mortality between the control group and the combined intervention groups, but CVD mortality tended to be lower (17%) among individuals who had received lifestyle intervention.

CLINICAL TRIAL EVIDENCE OF THE EFFECT OF LIFESTYLE FACTORS ON TYPE 2 DIABETES RISK

— In most of the published prevention trials, the main aim was to see if comprehensive lifestyle intervention reduces type 2 diabetes risk. In the Chinese prevention study (14), an attempt to determine whether diet or exercise intervention is more effective by randomizing the participating clinics to diet only, physical activity only, or diet plus physical activity intervention 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 (21). Success in achieving the intervention goals in the DPS was estimated from the food records and exercise questionnaires. The success score (from 0 to 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 (13). The hazard ratios were 1.00, 0.87, 0.67, 0.70, and 0.23, for success scores from 0 to 4–5, respectively (P for trend <0.001).

The effects of various components of intervention are interesting, and therefore some post hoc analyses related to this issue were completed. The independent effects of achieving the success score components at 3-year examination were assessed by including each of the five lifestyle goal variables individually in a Cox model (Table 1). 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 (27).

Correspondingly, the reduction in body weight was reported to be the main determinant of risk reduction in the U.S. DPP (23). 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 percent 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/week reduced diabetes risk, especially among those participants who did not achieve the weight reduction goal of 7%, with risk reduction of 44% compared with those who achieved neither the weight reduction nor the physical activity goal.

These findings suggest that dietary composition and physical activity are important in diabetes prevention, but their effect on diabetes risk is primarily mediated through resulting weight reduction. Nevertheless, because of multicolinearity, the interpretation of the results should be done cautiously. It should also be noted that in the Indian Diabetes Prevention Program (15) and Chinese prevention study (14), 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, components of the intervention other than

Table 1—*Multivariate logistic regression model to predict diabetes during a 10-year follow-up*

	Odds ratio (95% CI)	Coefficient β	Score*
Intercept	—	−5.658	
Age (years)			
<45	1	0	0
45–54	1.92 (1.13–3.25)	0.650	2
55–64	2.56 (1.53–4.28)	0.940	3
BMI (kg/m^2)			
≤25	1	0	0
>25–30	1.02 (0.48–2.15)	0.015	1
>30	2.55 (1.10–5.92)	0.938	3
Waist circumference (cm)			
Men <94, women <80	1	0	0
Men 94 to <102, women 80 to <88	2.78 (1.43–5.40)	1.021	3
Men ≥102, women ≥88	4.16 (2.00–8.63)	1.424	4
Blood pressure medication			
No	1	0	0
Yes	2.04 (1.45–2.88)	0.714	2
History of high blood glucose			
No	1	0	0
Yes	9.61 (6.31–14.63)	2.263	5
Physical activity			
≥4 h per week	1	0	0
<4 h per week	1.31 (0.88–1.95)	0.268	2
Consumption of vegetables, fruits, or berries			
Every day	1	0	0
Less often than once a day	1.18 (0.85–1.64)	0.165	1
Area under the receiver-operating characteristic curve		0.860	0.852

weight control were responsible for the beneficial effects on diabetes risk.

COMMENT — With compelling evidence that type 2 diabetes can be prevented or delayed, strategies to implement the primary prevention of type 2 diabetes both in high-risk subjects as well as at the population level are urgently needed. While type 2 diabetes prevention trials rigorously defined populations by explicitly characterizing their glycemic status, these studies did not include all groups at risk for developing type 2 diabetes. Methods that can also define other groups at high risk for developing type 2 diabetes have been recently developed and are increasingly used in several countries (28). The recent analysis of the DPS has also shown that such people will significantly benefit from lifestyle interventions (27).

A prospective study based on the data from the U.K. estimated the association between the achievement of the five lifestyle goals used in the DPS and the type 2 diabetes risk developing diabetes during a 4.6-year follow-up (29). The incidence of type 2 diabetes was inversely related to the number of goals achieved ($P < 0.001$). None of the participants who met all five of the goals (0.8% of the total population) developed diabetes, whereas the risk of diabetes was highest in those who did not meet any of these goals. If the entire population were able to meet one more goal, the total incidence of diabetes is predicted to decrease by 20%. This finding suggests that health promotion interventions that result in an increase in healthy lifestyle in the general population might significantly reduce the growing burden of type 2 diabetes.

Groups that will be the targets for prevention efforts can be identified through several reasonably effective strategies. However, there is no universal well-tested method that will identify all at high risk for developing type 2 diabetes, and there may be some variation in the optimal strategies for different populations and regions around the world. It is also important to realize that the identification of people having a high risk of type 2 diabetes or asymptomatic type 2 diabetes is not identical with the diagnosis of type 2 diabetes. In practice, we can identify people at high risk with simple and cost-efficient tools. The main question, however, is how to implement an efficient preventive strategy in individuals identified to be at high risk, i.e., how to translate the results of the recent successful type 2 diabetes prevention trials to a real-life setting (30). Much attention has been put on the biochemical methods for the assessment of glycemia in the early diagnosis of type 2 diabetes, but much less on the coverage of the detection of asymptomatic type 2 diabetes. The evidence is compelling that without applying an oral glucose tolerance test or an assessment of postprandial glucose, a large proportion of early cases of type 2 diabetes will remain unrecognized (31).

The International Diabetes Federation Consensus Group recently prepared a document on the prevention of type 2 diabetes (32). This shows that the international diabetes community is now ready to accept the principle that the primary prevention of type 2 diabetes must be considered as an essential part of public health policy for diabetes.

The American Diabetes Association consensus development conference in 2006 outlined principles regarding impaired fasting glucose (IFG) and IGT and interventions to be applied among such individuals (26). The American Diabetes Association consensus group also recommended lifestyle intervention initially for people with IFG or IGT (weight control and physical activity) but does not mention diet at all. If both IFG and IGT are present as well as additional risk factors (and most of such people have additional risk factors), then a combination of lifestyle intervention and metformin is recommended. However, the evidence is not there to show that the combination of lifestyle and metformin is effective; on the contrary, the results from the Indian Diabetes Prevention Program suggest that there is no additional benefit from metformin over and above lifestyle intervention (15). It is not clear how much antidiabetic drugs can help in preventing progression from IFG or IGT to overt diabetes and what is their overall costs and risk/benefit ratio in the long term. It is evident that long-term effects of lifestyle interventions are highly beneficial and that long-term costs are very low (13,26). Colaqiuri et al. (33) in their analysis stress that the real answer to reductions in incidence and prevalence of diabetes is in social policy, not in medical care. This is likely to be the reality.

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