

Nutritional Interventions and Primary Prevention of Type 2 Diabetes

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Abstract: Type 2 diabetes mellitus (DM) is one of the most important public health challenges in the world. Its increasing prevalence in many countries and the difficult metabolic control of patients with type 2 DM justify the study of strategies for primary prevention. The present review describes evidence from epidemiologic studies and clinical trials regarding recommendations for dietary prevention of type 2 DM. Prospective epidemiologic studies have provided support for a role of individual dietary components in determining the development of DM independent of obesity and other lifestyle factors. Several prevention trials have demonstrated that intensive diet and lifestyle interventions substantially reduced risk of type 2 DM in high risk populations. Recent evidence suggests that less-intensive nutritional counseling and lifestyle programs are also effective in reducing diabetes risk factors at the primary health care settings.

Keywords: Type 2 diabetes prevention, nutritional counseling, lifestyle intervention.

INTRODUCTION

The increasing prevalence of type 2 diabetes mellitus (DM) and disturbances in glucose tolerance have become major public-health challenges worldwide. The highest prevalence rates have been reported among populations that have undergone rapid changes in lifestyle, such as Pima Indians and Japanese-Brazilians [1,2]. This could reflect the strong genetic susceptibility associated with the adoption of unfavorable environmental conditions in these ethnic groups.

The prevalence of type 2 DM in the general population for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030, with considerably higher proportion in developed countries. The total number of people with type 2 DM is projected to increase from 171 million in 2000 to 366 million in 2030, with the conservative assumption that levels of other risk factors such as obesity and decreased physical activity remain constant (in developed countries) or are accounted for by urbanization (in less-developed countries) [3]. The excess global mortality attributable to type 2 DM in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths. Excess mortality attributable to type 2 DM accounted for 2-3% of deaths in the poorest countries and for more than 8% in the United States, Canada, and the Middle East [4].

Genetic susceptibility appears to play a powerful role in the occurrence of type 2 DM in certain populations. Since the genetic background is unlikely to have changed during short time period, compelling evidence from epidemiologic studies indicates that the current worldwide diabetes epidemic is due largely to changes in diet and lifestyle [5-8]. Lifestyle changes characterized by decreased physical activity and increased energy consumption have together

promoted obesity, which is a remarkably strong risk factor for type 2 DM, which itself is influenced by both genes and behaviors [9]. However, intervention studies have provided evidence confirming earlier suggestions of a role for dietary factors in determining the development of type 2 DM independent of obesity and other lifestyle factors. The purpose of this article is to summarize epidemiologic and clinical evidence concerning the primary prevention of type 2 DM through dietary interventions.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Recent review articles have provided a more detailed discussion of the mechanisms involved in the maintenance of normal glucose homeostasis [10-12]. The increase in plasma glucose concentration after ingestion of glucose stimulates insulin release, and the combination of hyperinsulinemia and hyperglycemia stimulates glucose uptake by splanchnic (liver and gut) and peripheral (primarily muscle) tissues and suppresses endogenous (primarily hepatic) glucose production. Insulin stimulates the disposal of ingested glucose into skeletal muscle and adipose tissue and decreases the production of glucose by the liver by reducing glycogenolysis and gluconeogenesis. Insulin and glucagon play central roles in the regulation of glucose homeostasis. After a glucose-containing meal, glucagon secretion is inhibited by hyperinsulinemia, and the resultant hypoglucagonemia contributes to the suppression of hepatic glucose production and to the maintenance of normal postprandial glucose tolerance (Fig. 1).

Early in the natural history of type 2 DM, insulin resistance is well established but glucose tolerance remains normal because of a compensatory increase in insulin secretion. The progression from normal to impaired glucose tolerance (IGT) is associated with marked increases in both fasting and glucose-stimulated plasma insulin levels and a decrease in tissue sensitivity to insulin. The earliest detectable abnormality (preceding the onset of DM) is a decrease in tissue sensitivity to insulin, with a compensatory

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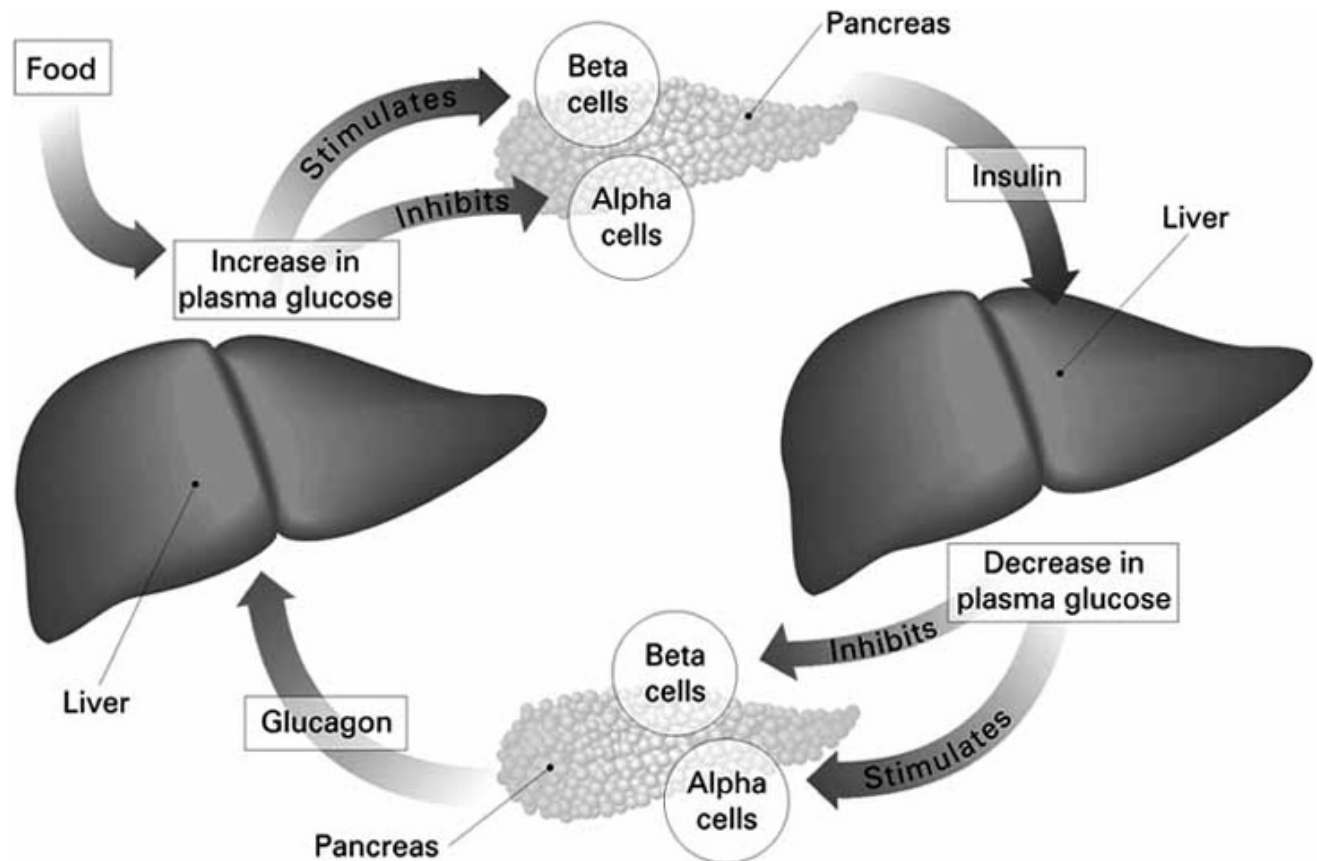


Fig. (1). Regulation of plasma glucose levels. Normoglycemic state is maintained by the combined action of the pancreatic hormones insulin and glucagon. After a glucose-containing meal, glucagon secretion is inhibited by hyperinsulinemia, and the resultant hypoglucagonemia contributes to the suppression of hepatic glucose production and to the maintenance of normal postprandial glucose tolerance.

increase in fasting glucose concentration (impaired fasting glucose [IFG]). The definition of IGT was first introduced in 1979 to replace the term 'borderline' diabetes and other categories of hyperglycemia, considered as a clinical class of glucose intolerance in 1985 World Health Organization (WHO) classification [13]. IFG was defined as a category of nondiabetic fasting hyperglycemia only in the latest reports from WHO [14] and the American Diabetes Association [15].

The concept for the prevention of type 2 DM has been developed on the basis of a better understanding of the pathophysiology of glucose intolerance. Overt type 2 DM develops only when the beta cells are unable to appropriately augment their secretion of insulin to compensate for the defect in insulin action. However, there are well-described populations with type 2 DM whose insulin sensitivity is normal at the onset of DM but whose insulin secretion is severely impaired (more common in African American, elderly, and lean white individuals) [11].

The progressive impairment in insulin secretion results from the interaction between pathogenic genetic and acquired factors. It has been suggested that, if the insulin resistance occurs in the presence of a genetically determined propensity to beta cell dysfunction, glucose intolerance can develop [16]. However, since people with impaired glucose

tolerance are already hyperglycemic, it has recently been suggested that high-risk people who have not yet experienced hyperglycemia are better targets for primary prevention of type 2 DM than are those who are already hyperglycemic [17].

DIETARY EXPOSURES: LESSONS FROM OBSERVATIONAL STUDIES

During the last decade, many observational studies on diet and risk factors for type 2 DM have been published, providing evidence to support dietary interventions in clinical trials. To date, the most convincing evidence for dietary factors related to DM, impaired glucose tolerance, and insulin sensitivity are the amount and types of fats and carbohydrates in the diet [18,19].

In early prospective studies, higher intakes of total and saturated fat were associated with the risk of impaired glucose tolerance and higher fasting levels of glucose and insulin [20,21]. In cross-sectional studies, total fat intake was higher in glucose-intolerant and type 2 DM subjects [22,23] and among those with metabolic syndrome [24,25] than in normoglycemic individuals. Nevertheless, these findings were not confirmed in larger cohort studies, which, in turn, found that higher intake of vegetable fat (unsaturated fat) was associated with a lower risk for type 2 DM. Results from the Nurses' Health Study reported by Salmeron *et al.* [26]

showed an inverse association between diabetes risk and intake of vegetable fat and polyunsaturated fatty acids (PUFA), after adjustments for diabetes risk factors. In a similarly designed study, Meyer *et al.* [27] found in the Iowa Women's Health Study that PUFA intake was inversely associated with risk of type 2 DM, with a 16% reduction in the highest quintile (median intake 16.6 g/day). Similar findings in these cohort studies were the absence of a clear association with intake of saturated fat and monounsaturated fatty acids (MUFA) but a positive association with dietary cholesterol. In contrast, *trans*-fatty acid intake was associated with increased type 2 DM risk in the Nurses' Health Study but not in the Iowa Women's Health Study. Among male participants of the Health Professionals Follow-up Study, total fat and saturated fat intake were associated with a higher risk of type 2 DM, but these associations were not independent of body mass index (BMI) [28]. With respect to MUFA, the epidemiologic data have been considered inconsistent, most likely related to the dietary sources of typical 'Western' diet, which are not derived from vegetable oils and coexist with saturated fat in sources such as meat and milk products [9,29].

The available epidemiologic data on the relation of dietary carbohydrates and type 2 DM, like that for dietary fat, are controversial. Most dietary guidelines have recommended the use of complex carbohydrates and the avoidance of simple carbohydrates or sugars. However, the biological mechanisms to explain distinct roles of carbohydrate-containing foods on markers of glucose homeostasis might be related to the amount and type of dietary fiber [30]. The earliest suggestion that the replacement of whole foods by refined products could be implicated in the etiology of type 2 DM was reported in ecologic analyses by Trowell [31,32]. After that, cross-sectional studies suggested that low consumption of dietary fiber [33-35] and large intake of refined grains [36] may be risk factors for type 2 DM and disturbances in glucose metabolism. Large cohort studies, the Health Professionals Follow-up Study [37], the Nurses Study [38], the Nurses Study II [39], the ARIC Study [40], and the Iowa Women's Health Study [41], found that lower intake of dietary fiber was significantly associated with increased risk of type 2 DM. The association was found to be stronger for cereal fiber, a rich source of insoluble fiber, but much weaker for sources of soluble fiber.

For carbohydrate-contributing foods other than cereal fiber, a decreased risk for cardiovascular disease and type 2 DM have been reported among women with higher intakes of fruits and vegetables (10 servings/day) as compared with women with the lowest consumption (2.5 servings/day) [42,43]. Eating large amounts of fruits and vegetables has been recommended for the prevention of type-2 DM [18]. Previous cross-sectional studies found a protective effect of frequent consumption of vegetables on the risk of type 2 DM and impaired glucose metabolism [44,45]. Although substantial evidence indicates beneficial effects of fruits and vegetables for coronary heart disease [46], the protective effect of higher consumption of this food group is supported by some [47,48] but not all cohort studies [41,43].

Other dietary factors have been related to the development of type 2 DM. Consumption of vitamin E [49-51],

magnesium [52-54], and dairy products [55,56] may affect glucose and insulin metabolism, but the available data are inconsistent. Data on long-term effects of sugar intake on risk of type 2 DM have also been controversial [57-59], though higher consumption of sugar-sweetened beverages is associated with weight gain and an increased risk for development of type 2 DM in women [60]. More recently, consumption of coffee has been examined in relation to risk of type 2 DM, and a systematic review of observational studies concluded that habitual coffee intake is associated with a substantially lower risk of type 2 DM [61].

The role of overall dietary pattern in predicting long-term risk of type 2 DM have also been reported in recent articles [62-64]. In these studies, a "prudent" pattern characterized by higher intakes of fruits, vegetables, legumes, whole grains, poultry, and fish was associated with lower risk of type 2 DM, whereas a "Western" pattern characterized by higher intakes of red and processed meats, sweets and desserts, potatoes, French fries, and refined grains was associated with higher risk, independent of other lifestyle factors.

However, at this time, nutritional intervention studies have focused on moderate energy intake (dependent on the level of physical activity), increased intake of dietary fiber (soluble as well as nonsoluble), and reduced intake of saturated fat, partly replaced by starch and vegetable fats (PUFA as well as MUFA). We have considered those recommendations that best describe the most recent findings, which are in agreement with the dietary guidelines for the prevention of other chronic diseases [18,46].

NUTRITIONAL AND LIFESTYLE INTERVENTIONS: EVIDENCE FROM CLINICAL TRIALS

As the gold standard of clinical research, randomized controlled trials (RCTs) provide the strongest evidence necessary to make recommendations. Lifestyle interventions shown to reduce type 2 DM among individuals at high risk include those of the Da Qing IGT and Diabetes Study, the Finnish Diabetes Prevention Study (DPS), and the Diabetes Prevention Program (DPP). Table 1 summarizes the major lifestyle modification strategies used in these large RCTs.

In the Da Qing Study, 110,000 persons from 33 health clinics were screened, with 577 classified as having IGT and randomized by clinic into diet, diet and exercise, exercise, or control. The activity goal for walking was 140 min/week. The dietary intervention was associated with a 31% reduction, exercise intervention with a 46% reduction, and combined diet and exercise with a 42% reduction in risk of developing type 2 DM over 6 years [65]. Before this trial, there had been only a few nonrandomized intervention studies. Although the randomization by clinic was an important limitation of this study, the results suggested that exercise was the major contributing factor. However, two subsequent larger RCTs (DPP and DPS) have confirmed the combined effect of changes in diet and physical activity on diabetes prevention.

The Finnish Diabetes Prevention Study (DPS) randomly assigned 522 middle-aged, overweight subjects (172 men and 350 women; mean age 55 years; mean BMI 31) with impaired glucose tolerance to either the intervention group or

Table 1. Summary of Lifestyle Modification Strategies Used in Large Randomized Controlled Trials for Prevention of Type 2 Diabetes

Study	Counseling characteristics	Dietary Interventions	Physical activity intervention
Diabetes Prevention Program [69]	A total of 16 individual lessons in first 24 weeks. A follow-up group session (usually monthly) was designed to reinforce the behavioral changes. Facilitator: usually a dietitian	The intensive lifestyle intervention aimed to reduce patient's weight by at least 7% through a healthy low-calorie, low-fat diet.	Moderate-intensity exercise (such as brisk walking) for at least 150 minutes per week. Supervised sessions were provided twice a week.
Finish Diabetes Prevention Study [66]	Seven individual sessions during the first year, then every 3 months. Facilitator: dietitian	Low-fat, high fiber diet: total fat <30% and saturated fat <10% of total energy; at least 15 g/1000kcal; dietary cholesterol: <300 mg/day.	Moderate exercise for at least 30 minutes per day; supervised strength training; frequency varied among study centers.
Da Qing Study [65]	Both individual and group sessions weekly for the first month, then every 3 months. Facilitator: Physician	Participants with BMI < 25kg/m ² : diet with 25-30% energy from fat, reduce intake of simple sugar, control alcohol intake, and eat more vegetables. Participants with BMI >25kg/m ² were encouraged to lose weight gradually but details of the diet were not specified.	Increase physical activity by one unit, and preferably two units, per day (1 unit was 30 minutes of slow walking or five minutes of swimming).

BMI, body mass index.

the control group [66]. The intervention group received individualized counseling aimed at reducing weight, total intake of fat, and intake of saturated fat and increasing intake of fiber and physical activity. The intervention was most intensive during the first year, followed by a maintenance period. The subjects in the control group were given general oral and written information about diet and exercise at baseline and at subsequent annual visits. After an average follow-up of 3.2 years, there was a 58% reduction in the progression to type 2 DM in the intervention group compared with the control group. Long-term beneficial changes in diet, physical activity, and clinical and biochemical parameters have also been reported [67,68].

The Diabetes Prevention Program (DPP) randomly assigned 3234 nondiabetic persons (1043 men and 2191 women; mean age 51 years; mean BMI 34) with elevated fasting and post-loading plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of a weight loss of at least 7% and at least 150 minutes of physical activity per week (mean duration of follow-up 2.8 years). The lifestyle intervention was significantly more effective than metformin (which reduced the incidence of diabetes by 31% as compared with that in the placebo group) [69]. The DPP, like the DPS, showed a 58% decrease in the development of type 2 DM with lifestyle intervention. This study was the first to test lifestyle intervention versus pharmacologic prevention for type 2 DM and also the first to include the elderly, women, and non-white people, confirming the findings of the DPS.

A recent systematic review searched in MEDLINE for RCTs of nutritional counseling (including body weight control and dietary interventions) in diabetes prevention during the last decade [70]. Searching for studies among free-living adults, the authors identified 162 studies

published from January 1995 to January 2005. Of the nine studies with random allocation and assessment of glucose tolerance status (including Da Qing IGT Diabetes Study, DPS, and DPP), only three included IFG and normal glucose tolerance at baseline, providing insights into the pathways through which consumption of food from different sources may affect the development of disturbances in glucose tolerance. Two more RCTs were recently published; Table 2 summarizes the major design features for all five RCTs.

All these studies were designed to assess the effects of lifestyle intervention (diet and/or exercise) on risk factors for type 2 DM, since their small sample size and duration did not allow the incidence of diabetes to be determined. Among the short-term interventions, individualized nutritional counseling seems to be effective in changing behavior, body weight, and physiological parameters. The physical activity interventions varied from counseling to encourage increased activity to supervised sessions. Only one study examined the effect of a low-fat vegan diet, avoiding animal products, avocados, olives, nuts and seeds [73]. Overall, successful short-term interventions included one-to-one dietary counseling, given on two or three occasions, based on current nutrition knowledge derived primarily from observational studies and focused on increased intake of vegetables and whole grains and reduced intake of total fat and saturated fat (up to 30% and 10% of total energy intake, respectively). From long-term interventions, only one study assessed the effect of lifestyle counseling over 2 years on changes in body weight and incidence of diabetes in overweight individuals with a parental history of diabetes [75]. Although initially successful, the interventions were not effective in producing long-term changes in behavior, body weight or physiological parameters. However, the authors concluded that even a modest weight loss in a 2-year interval significantly reduced risk of type 2 DM.

Table 2. Summary of Selected Randomized Controlled Trials of Nutritional Interventions on Type 2 Diabetes Risk Factors

Study	Number of people	Age and BMI range	Characteristics	Study groups	Frequency/duration of intervention	Behavioral interventions	Effect of intervention
Sartorelli <i>et al.</i> [71]	104 (83 women, 21 men) attending a health care center in Brazil	30-65 years, 24-35 kg/m ²	Overweight/obese adults or first-degree relatives with type 2 diabetes	1. Diet (n=51) 2. Control (n=53)	Short-term (4 months): 3 individualized diet sessions	Increase intake of olive oil, fruits, vegetables, and skimmed dairy products; reduce intake of red meat without emphasis on total energy restriction. At least 30 min of walking per day	Significant decrease in fasting blood glucose, total and LDL cholesterol, body weight, waist circumference, and diastolic blood pressure
Brekke <i>et al.</i> [72]	77 (49 men, 28 women) outpatients in Sweden	25-55 years, <35 kg/m ² (unspecified range)	First-degree relatives with type 2 diabetes	Diet (n=25) Diet, exercise (n=30) Control (n=22)	Short-term (16 weeks): 2 group counseling sessions with follow-up through telephone interviews every 10 days	Dietary counseling based on current recommendations with increased intake of fatty fish and low-glycemic-index foods. The goal for exercise: at least 30 min of walking, 4-5 times per week	Diet group reduced total and LDL cholesterol. Diet/exercise group decreased body weight and waist circumference, with a 13% reduction in fasting insulin
Barnard <i>et al.</i> [73]	59 outpatients in Washington area (U.S.)	44-73 years, 26-44 kg/m ²	Postmenopausal women.	1. Low-fat vegan diet (n=29) 2. Control diet: NCEP* (n=30)	Short-term (14 weeks): 2 nutrition lectures and weekly 1-hour group meetings	Vegan diet: fat 10% and protein 15% of total energy. Animal products, added oils, avocados, olives, nuts, and seeds were proscribed	Significant mean weight loss: 5.8 kg in the intervention vs. 3.8 kg in the control group
McAuley <i>et al.</i> [74]	79 (53 women, 26 men), in New Zealand	30-68 years	Normoglycemic insulin-resistant determined by the euglycemic insulin clamp	1. Diet and exercise (modest level, n=31) 2. Diet and exercise (intensive level, n = 25) 3. Control (n = 23)	Short-term (4 months): 3 individualized lifestyle counseling	Group 1: Fat <32%, protein 18% of total energy. Cholesterol <200 mg/day, dietary fiber >25 g/day Group 2: Fat <26%, protein 18% of total energy. Cholesterol <140 mg/day, dietary fiber >25 g/day	Only the intensive group showed a significant improvement in insulin sensitivity (23% increase vs. 9% in the modest group)
Wing <i>et al.</i> [75]	154 (122 women, 32 men), in Pittsburgh (U.S.)	40-55 years, mean BMI 35.9 kg/m ²	Overweight individuals with parental history of diabetes	1. Diet (n=37) 2. Exercise (n=37) 3. Diet and exercise (n=40)	Long-term (2 years): weekly group meetings for the first 6 months, biweekly for the following 6 months, and two 6-week courses during the second year	1. Goals for Diet: decrease intakes of calories and fat (20% of total energy) 2. Goals for exercise: 1500 kcal/week of moderate activity	At 6 months, mean weight losses in the diet (9.1 kg) and diet plus exercise (10.3 kg) groups were significantly greater than in exercise (2.1 kg) and control groups (1.5 kg). At 2 years, no between-group differences

* Diet following National Cholesterol Education Program (NCEP) Step II guidelines: total fat 30%, saturated fat 7%, protein approximately 15%, carbohydrate > 55% of energy; cholesterol < 200 mg/day).

CONCLUSIONS

The most promising potential strategy for further research on primary prevention of type 2 DM to emerge from these trials is the implementation of long-term intensive programs with individualized dietary and exercise counseling to improve insulin sensitivity among normoglycemic individuals at high risk for type 2 DM. However, these studies cannot separate the effects of exercise from diet. Nor can they assess the effects of individual dietary components. On the other hand, prospective cohort studies have provided strong evidence regarding the associations of dietary fatty acids, carbohydrates, minerals, and individual foods with risk of type 2 DM. Thus, randomized clinical trials and long-term observational studies are complementary in defining optimal dietary and lifestyle strategies for the primary prevention of type 2 DM.

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