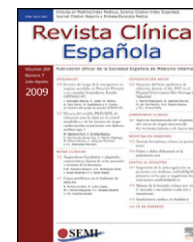


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EDITORIAL

Primary prevention of type 2 diabetes by lifestyle intervention in primary care setting

Prevención de diabetes mellitus tipo 2 por intervenciones de estilo de vida en un ámbito de asistencia primaria

The prevalence of diabetes around the world is alarmingly high and it is only growing. The World Health Organization estimates that 347 million people worldwide have diabetes and by 2030, that number is expected to rise to 552 million.¹ Many more people have prediabetes, a high-risk state for diabetes developing defined by blood glucose concentrations higher than normal, but lower than established diabetes thresholds.² Data from the population-based US National Health and Nutrition Examination Survey (NHANES) indicates that 35% of US adults older than 20 years and 50% of those older than 65 years had prediabetes, with an estimated 79 million adults with prediabetes.³ Worldwide, the number of people with prediabetes is expected to reach 472 million by 2030.⁴ About 5–10% of people with prediabetes will reach the clinical criteria for diabetes every year, and as many as 70% of individuals with prediabetes will progress to diabetes during their lifespan.⁵

Prediabetes is characterized by fasting and/or postprandial blood glucose concentrations higher than normal, but lower than established thresholds for diabetes. As per World Health Organization, people with prediabetes have impaired fasting glucose (IFG) if their fasting plasma glucose (FPG) concentration is between 6.1 and 7.0 mmol/L (110 and 126 mg/dL); and impaired glucose tolerance (IGT), if the FPG concentration is <7.0 mmol/L (126 mg/dL) and a 2 h post-load plasma glucose concentration ≥ 7.8 and <11.1 mmol/L (140 and 200 mg/dL), during a 75 g oral glucose tolerance test.⁶ The American Diabetes Association (ADA) applies the same thresholds for IGT, but uses a lower cutoff value for IFG of 5.6–6.9 mmol/L (100–125 mg/dL). In addition, the ADA recently recommended the use of glycated hemoglobin A1c (HbA1c) with a value of 5.7–6.4% to identify this category for high diabetes risk.⁷

Several lifestyle intervention studies based on diet and exercise have unequivocally shown that progression to diabetes is possible in high-risk individuals with prediabetes (Table 1). These trials have shown to be effective in all

ethnic groups and various social and cultural settings worldwide.

The Swedish Malmö feasibility study⁸ determined the effect of increased physical exercise and weight control as major intervention strategies to prevent or delay type 2 diabetes in 181 men with impaired glucose tolerance (IGT) and 79 non-randomized subjects with IGT, who received no specific diabetes prevention treatment. At the 5-year treatment follow-up, mean weight reduction was 2.0–3.3 kg in the intervention group, whereas there was an increase of 0.2–2 kg in control group. In the intervention group, glucose tolerance improved in 75.8% of cases and 10.6% developed diabetes during follow-up. In the non-intervention group, glucose tolerance worsened in 67.1%, and diabetes was found in 28.6%. The relative risk of diabetes development in intervention compared to control group was 0.37 (95% confidence interval of 0.20–0.68, $p < 0.003$).⁸

The Chinese Da Qing Study,⁹ randomized people with IGT into one of four groups: exercise only, diet only, diet plus exercise, and no intervention (control group). The cumulative incidence of diabetes during 6 years was lower in the intervention groups compared with the control group (41% in the exercise group, 44% in the diet group, 46% in the diet plus exercise group, and 68% in the control group). A 20-year follow-up report of this trial reported that subjects in the diet and exercise groups continue to benefit having a similar risk reduction during the post intervention period.¹⁰

The Finnish Diabetes Prevention Study (DPS)¹¹ randomized middle-aged overweight subjects with IGT to an intervention group of diet and exercise or to a control group. The goals of the lifestyle interventions were to achieve a >5% reduction in body weight, reduce all fat intake to <30% of energy consumption, and a program of moderate physical activity for >30 min/day. They reported that an intensive diet and exercise program was associated with a 58% reduction in the risk of developing type 2 diabetes. An extended follow-up observation of the DPS trial revealed that subjects

Table 1 Summary of randomized clinical trials of primary prevention of type 2 diabetes.

Study	Type of intervention	Participants, number	Duration of intervention, years ^a	Risk reduction, %	Total duration of follow-up, years*	Risk reduction during follow-up, %
Malmö, Sweden ⁸	LSI	181	6	37	–	–
	Control	79				
Da-Qing, China ^{9,10}	Diet	130	6	31	20	43
	Exercise	141		46		
	Diet & exercise	126		42		
	Control	133				
DPS, Finland ^{11,12}	LSI	265	3.2	58	7	43
	Control	257				
DPP, US ^{13,14}	LSI	1079	2.8	58	10	34
	Metformin	1073		31		
	Placebo	1082				
Japanese Lifestyle Intervention Trial, Japan ¹⁵	LSI	102	4	67.4	–	–
	Control	356				
IDPP, India ¹⁶	LSI	133	2.5	28.5	–	–
	Metformin	133		26.4		
	LSI & Metformin	129		28.2		
	Control	136				
DE-PLAN, Spain ¹⁷	LSI	333	4	36.5	–	–
	Control	219				

LSI: lifestyle intervention based on diet and exercise; DPS: Diabetes Prevention Study; DPP, US: Diabetes Prevention Study, United States; IDPP-1: Indian Diabetes Prevention Program; DE-PLAN: Diabetes in Europe – Prevention using Lifestyle, Physical Activity and Nutritional intervention.

^a Mean value.

in the intervention group continued to show a sustained reduction in the cumulative incidence of diabetes after a median of 7 years.¹² The relative risk reduction during the total follow-up was 43%.¹²

The U.S. Diabetes Prevention Program (DPP)¹³ randomized 3234 adults with prediabetes to a standard lifestyle recommendations plus placebo or 850 mg metformin twice daily or to an intensive lifestyle modification program. The goal of the program was to achieve and maintain >7% reduction in body weight through a low-calorie, low fat diet plus physical activity of moderate intensity for at least 150 min/week. The lifestyle modification reduced the incidence of type 2 diabetes by 58%. The cumulative incidence of diabetes during the follow-up period was lower in the lifestyle intervention and metformin groups than in the placebo group, with incidence rates of 4.8, 7.8, and 11.0 cases per 100 person-years, respectively. The reduction in incidence can be translated to one case of diabetes prevented for every 7 individuals with IGT treated for 3 years in the lifestyle intervention group. During an extension follow-up of 10 years after completion of the trial, the Diabetes Prevention Program outcomes Study¹⁴ reported continuous benefits with reduction in the cumulative incidence of type 2 diabetes incidence by 34% compared with the control group.

A Japanese lifestyle intervention study in Tokyo randomized a total of 458 men with IGT to an intensive lifestyle intervention ($n=102$) and standard intervention group ($n=356$). The subjects were seen in an ordinary outpatient clinic.¹⁵ The cumulative 4-year incidence of diabetes was 9.3% in the control group, versus 3.0% in the intervention

group, and the reduction in risk of diabetes was 67.4% ($p<0.001$).

The Indian Diabetes Prevention Program,¹⁶ randomized 531 individuals with IGT into four groups: metformin, lifestyle modification, both lifestyle modification and metformin, or a control group. The cumulative incidence of type 2 diabetes during the median follow-up period of 30 months was significantly lower in the lifestyle modification group (39%), the metformin group (41%), and the lifestyle modification plus metformin group (40%) compared with the control group (55%). The relative risk reduction was 28.5% with lifestyle modification (95% CI 20.5–37.3, $p=0.018$), 26.4% with metformin (95% CI 19.1–35.1, $p=0.029$) and 28.2% with lifestyle plus metformin (95% CI 20.3–37.0, $p=0.022$), as compared with the control group.

More recently, Costa et al.¹⁷ reported the results of the DE-PLAN Project (Diabetes in Europe – Prevention using Lifestyle, Physical Activity and Nutritional intervention), a real-life primary care lifestyle intervention in preventing type 2 diabetes in a high-risk population in Catalonia. Patients were screened using the Finnish Diabetes Risk Score (FINDRISC) and a 2-hour oral glucose tolerance test (OGTT). The protocol consisted of two interventions standard care or intensive lifestyle intervention delivered individually or in groups. The intensive group intervention consisted of a 6 h educational program scheduled in two to four sessions with five to 15 participants, who also received specific training materials. Targets for lifestyle intervention included less than 30% of daily energy from fat, no more than 10% of energy from saturated fat, at least 3.6 g/1000 kJ

(15 g/1000 kcal) of fiber, and at least 30 min/day of moderate physical activity to achieve a 3% weight reduction. Among patients allocated to standard care ($n=219$) and intensive intervention ($n=333$) groups, diabetes was diagnosed in 124 individuals: 63 (28.8%) in the standard care group and 61 (18.3%) in the intensive intervention group. During a 4.2-year median follow-up, the incidences of diabetes were 7.2 and 4.6 cases per 100 person-years, respectively (36.5% relative risk reduction). The number of participants needed to treat with intensive intervention for 4 years to reduce one case of diabetes was 9.5. The success was slighted lower than other lifestyle intervention trials; however, DE-PLAN was a real-life intervention conducted in a primary care setting.

In this issue of the journal, Sagarra et al.¹⁸ reports an analysis cost-effectiveness of the DE-PLAN study. The median cost was 752€ in the group and 656€ in the individual intervention. After 4.2-year median follow-up, the 36.5% relative-risk-reduction with intensive intervention was associated with an incremental cost of 106€ per participant in the individual level and 10€ in the group-based compared to the standard intervention. The median cost per participant in the standard and lifestyle intensive intervention was 646€ and 686€, respectively. Thus, the cost of the intensive intervention was 40€ over the standard intervention (106€ for the group and 10€ for the individual intervention). The cost per case for each case of diabetes prevention was estimated to be 746€ and 108€ in the individual and group intervention, respectively, because the probability of developing diabetes was lower in the group intervention (28.9%) compared to individual intervention (34.4%).

The cost of the intervention of the Spanish Trial was significant lower than the DPP study in the United States. Over 3 years, including the cost of identifying persons with IGT, the direct medical cost of the US DPP lifestyle intervention was \$2919 per participant.¹⁹ The lifestyle intervention was more expensive in year 1 (\$1399) than in year 2 (\$679) or 3 (\$702). Similarly, the cost was lower than the direct medical cost of about 2614€ spent in the Finish Diabetes prevention study.¹⁰ These studies demonstrate that lifestyle intervention programs aimed to prevent type 2 diabetes in populations at risk are cost effective.

In summary, diabetes is projected to be one of the five leading causes of death in high-income countries by 2030 and one of the ten leading causes of death worldwide, which emphasizes the public health importance of reducing diabetes risk at the population level.² Lifestyle change is the cornerstone for diabetes prevention. The primary aim of lifestyle interventions is to prevent or delay development of type 2 diabetes by targeting obesity and physical inactivity, the two most important modifiable risk factors of diabetes development.^{11,13} The results of the American, Finish and Spanish preventive interventions indicate that intensive lifestyle interventions are successful in preventing the progression to diabetes in populations at risk, and such interventions are cost-effective.¹⁹

The fundamental question is how the results from these clinical trials can be translated to clinical settings in real life. Population strategies focusing on raising awareness of diabetes, screening high-risk individuals and implementing appropriate and cultural sensitive lifestyle interventions may reduce the risk of developing diabetes and

its complications. A large-scale nationwide diabetes prevention program to be conducted in primary care setting, the National Program for the Prevention of Type 2 Diabetes (FIN-D2D), was recently implemented in Finland, and will cover a population of 1.5 million.²⁰ The DE-PLAN Spanish trial clearly shows that safe and cost effective diabetes prevention programs can be successfully delivery by primary care professionals.

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