Review

Primary prevention of type 2 diabetes: A review of the current state

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Introduction

The prevalence of Type 2 diabetes is increasing globally.[1] It is the cause of significant mortality and morbidity due to the development of micro- and macrovascular complications. It can cause blindness, end-stage renal disease, and lower extremity amputations and is also a major risk factor for myocardial infarction and stroke. Macrovascular disease and its risk factors are often already present in patients with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), suggesting that an additional benefit of an intervention before the diagnosis of diabetes, may be to prevent the progression of the macrovascular disease.[2]

In principle, disease prevention can be considered in three broad areas, i.e. primary, secondary and tertiary prevention. Primary prevention is at hand when the disease is prevented from occurring. This can be implemented for diabetes through a population based strategy, i.e. changing the life style and environmental determinants that are known to be risk factors, or through a high risk strategy, i.e. targeting preventive measures only at those specific individuals or groups that are at high risk for the future development of Type 2 diabetes.

Although the pathogenesis of Type 2 diabetes is not fully understood, there are at least three defects: 1) individual or ethnic genetic factors leading to susceptibility; 2) defects in pancreatic beta-cell function; and 3) decreased action of insulin in insulin-sensitive tissues including liver and extra pancreatic tissues such as skeletal muscle and adipose tissue [3-5] (Fig. 1). In normal man, when insulin sensitivity is decreased, e.g. by obesity, normal glucose tolerance may be preserved by increased secretion of insulin. On the other hand, in individuals predisposed to develop diabetes, impaired beta cell function

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fails to compensate for insulin resistance, and IGT or IFG evolves. Eventually, Type 2 diabetes develops in up to 40% of patients with IGT, with a rate of progression between 1% and 5% per year.[6] Whether the impaired beta cell function is a consequence of a preprogrammed genetic defect or an acquired abnormality remains to be determined. In the proposed aetiologic sequence leading to type 2 diabetes, hyperglycaemia and hyperlipidaemia may further impair insulin secretion and action by glucotoxicity and lipotoxicity, respectively (Fig. 1). To disrupt this sequence and prevent development of diabetes, efforts need to be directed at ameliorating insulin resistance, improving beta-cell function or achieving some combination of these effects through life-style changes or by pharmaco-

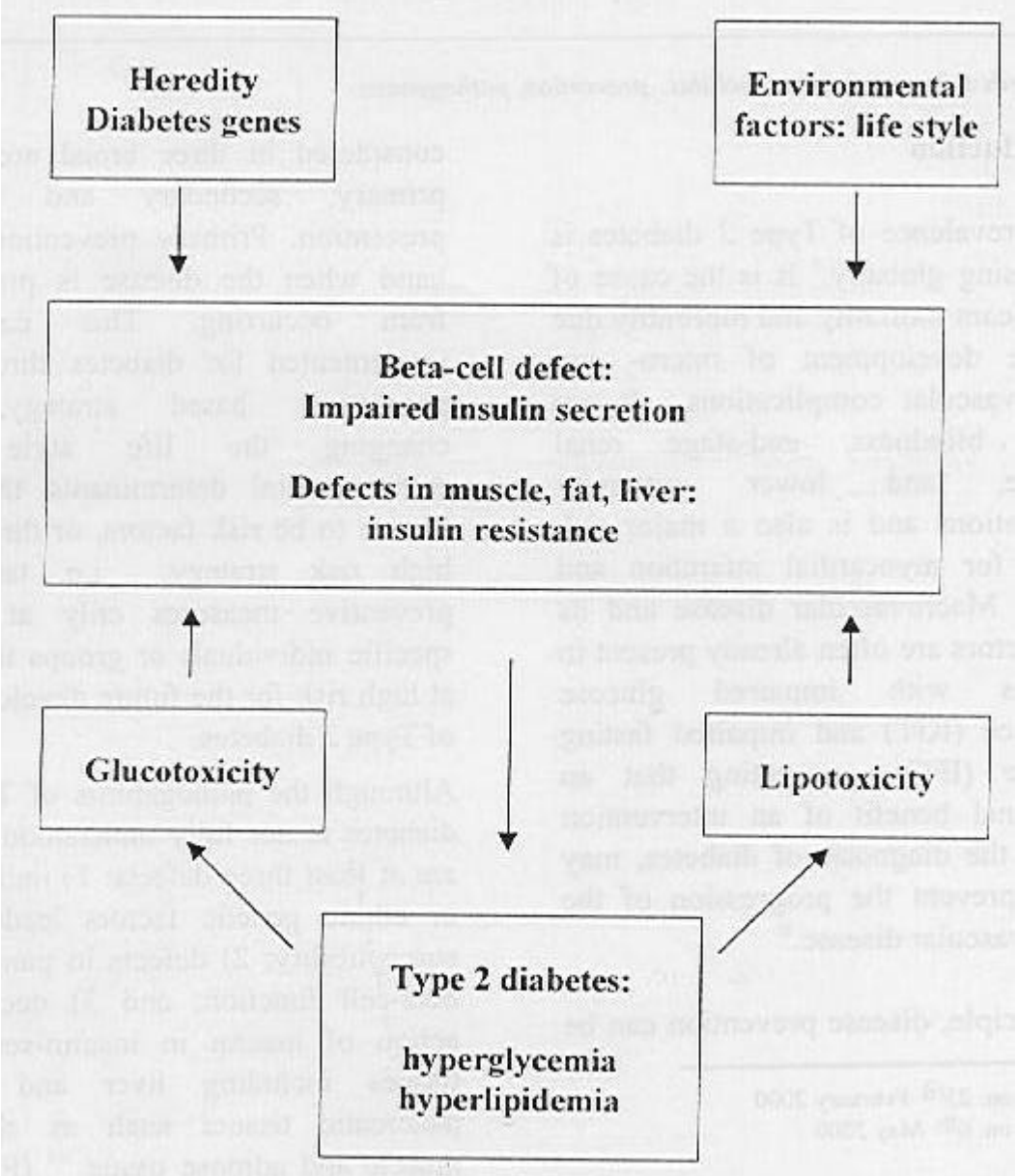

Fig. 1: Proposed aetiologic sequence in the pathogenesis of Type 2 diabetes

logical means.[7]

Life style interventions

Both genetic and environmental factors contribute to the development of IGT and Type 2 diabetes. Obesity, physical inactivity and high fat diet have been found to be risk factors for IGT and Type 2 diabetes. Thus, body mass index is positively associated with increased risk of Type 2 diabetes in both sexes in many ethnic groups.[8-10] Therefore a diet and exercise intervention programme can be started in IGT subjects to prevent obesity, to increase physical activity and support taking a healthy diet. The results of the following studies indicate that interventional strategies may be beneficial in the primary prevention of Type 2 diabetes. These strategies can be divided into those aiming at a change in life-style i.e. weight control, diet and exercise, and those using a pharmacological intervention.

Temporary reversion to traditional life style has been shown to greatly improve or to completely normalise the metabolic abnormalities of Type 2 diabetes in a group of Australian aborigines.[11] The most important observation in this study was that a marked improvement occurred in glucose tolerance in 10 diabetic subjects 7 weeks after they had returned to their hunter-gatherer life style. At least three factors known to improve insulin sensitivity were operating in this study - weight loss, low fat diet and increased physical activity.

In the Swedish Malmöhus study it was found that the conversion rate to diabetes over 10 years was reduced from 29% to 13% in a group of IGT subjects advised to limit their intake of carbohydrates and lipids and to reduce the weight when overweight.[12]

So far one of the most extensive and promising report came from another Swedish study over 6 years.[13] Following an initial community screening survey, 181 individuals with IGT were enrolled in an intervention programme; the control group consisted of 79 untreated IGT subjects. During the first year the participants were given dietary advice and the choice to train either in a group for 1h twice a week or to follow their own exercise protocol. The training programme consisted of walking and jogging. After the first year, supervised training was discontinued but the participants were encouraged to continue alone or in their groups or at a local sport club. Check-ups were performed annually, with a compliance rate of 90%. After 6 years, maximal aerobic power in the intervention group had increased by 10% over baseline values, but decreased by 5% in the control group. In addition, only 7% of the intervention group used antihypertensive drugs as compared with 24% in the sedentary group. Diabetes developed in 21% of the control group but only in 11% of the intervention group, a difference that was highly significant. Although non-randomised, this study strongly suggests that life-style modifications are feasible in many IGT subjects and can prevent or postpone the development of Type 2 diabetes.

In India, 262 non-diabetic offspring of Type 2 diabetes patients were studied for four years to evaluate the role of diet, exercise and weight loss.[14] Weight loss occurred in persons who adhered to diet and exercise programmes and conversion to diabetes was lower

compared to those who gained weight. This study highlights the fact that measures to control weight help to delay the onset of diabetes, despite a strong family history of the disorder.

In a Finnish diabetes prevention study, a total of 523 overweight subjects with IGT confirmed by OGTT were randomised to either control or intervention groups.[15]The control group received general information at the start of the trial about life-style changes necessary to prevent diabetes and were also offered annual follow up visits. The intervention subjects had seven sessions with a nutritionist during the first year and a visit every three months thereafter, aimed at reducing weight, reduced intake of saturated fat and increased intake of dietary fibre and increasing their physical activity. During the first year weight loss was significant and plasma glucose concentrations were significantly lower in the intervention group. Favourable changes were also found in blood pressure, serum lipids and anthropometric indices in the intervention group (interim results).

In the Chinese Da Qing IGT and diabetes study, 577 subjects with IGT were randomised into a clinical trial, either to a control group or to one of the active treatment groups: diet only, exercise only or diet plus exercise.[16] Follow-up examinations were conducted at 2-year intervals over a 6-year period to identify subjects who developed Type 2 diabetes. The cumulative incidence of diabetes at 6 years was 67.7% in the controls but only 43.8% in the diet group, 41.1% in the exercise group and 46.0% in the diet plus exercise group. Thus, diet and exercise interventions led to a significant decrease in the incidence of diabetes over the 6 year period among those with IGT.

Experimental and epidemiological studies suggest that adoption of the Westernised diet (low carbohydrate, low fibre, high fat) leads to deterioration in glucose tolerance.[3] The relationship between intake of carbohydrate that provides a high glycaemic index and the risk of development of Type 2 diabetes was studied in a cohort of 42,759 men without diabetes.[17] Their diet was assessed at baseline and followed for 6 years to establish whether they developed diabetes or not. It was concluded in this study that diet with a high glycaemic index and low fibre content increased the risk of Type 2 diabetes.

In the San Luis Valley Diabetes Study, dietary fat intake measured at a baseline examination in subjects with IGT predicted the subsequent development of Type 2 diabetes.[18] The mean energy percentage eaten as fat was 43.4% in subjects subsequently developing Type 2 diabetes compared with 40.6% in 43 subjects remaining as IGT and 38.9% in 60 subjects who subsequently reverted to normal glucose tolerance. In comparing the 20 subjects who developed Type 2 diabetes with the 103 individuals who remained as IGT or normal, an increase in fat intake of 40 g/day was associated with a 3.4 fold increase in risk of Type 2 diabetes. It was concluded that fat consumption significantly predicts risk of Type 2 diabetes in subjects with IGT.

Metabolic studies have demonstrated that the major effect of physical activity is increasing insulin sensitivity. It has been suggested that physical activity could decrease the

occurrence of Type 2 diabetes either directly (by increasing insulin sensitivity) or indirectly by preventing obesity and/or beneficially altering the distribution of fat. The relationship between the level of habitual physical activity and glucose intolerance was examined cross-sectionally and during a 2-year follow up among a sample of 388 subjects in Malta.[19] Those with low physical activity had a 2.7 times higher risk of glucose intolerance during follow-up than those with regular physical activity.

In another prospective study in USA the association between regular vigorous exercise and the subsequent incidence of Type 2 diabetes was assessed prospectively over 8 years in a cohort of 87,253 female nurses, aged 35-49 years, and free of diagnosed diabetes.[20] Women engaged in vigorous exercise at least once a week had an age-adjusted relative risk of Type 2 diabetes of 0.67 compared with women who did not exercise weekly. In a large prospective study on 21,271 US male physicians the age-adjusted relative risk of developing diabetes over 5 years decreased with increasing frequency of exercise.[21] Recent prospective studies have also shown significant reduction of risk of diabetes by physical exercise of moderate intensity and duration.[22-24]

In the University of Pennsylvania alumni health study, 5990 men were surveyed to determine the relationship between physical activity and the development of Type 2 diabetes. The incidence rates declined as energy expenditure increased.[25] For each 2000 kcals increment in energy expenditure, the risk of Type 2 diabetes was reduced by 24%. The protective effect of physical activity was strongest in individuals at highest risk of Type 2 diabetes.

Cigarette smoking may be an independent, modifiable risk factor for Type 2 diabetes. The association between smoking and incidence of Type 2 diabetes was studied in the Stockholm Diabetes Prevention Programme. Subjects who smoked more than 25 cigarettes per day had a 2.6 times risk of developing diabetes over those who did not smoke.[26]

In another study during 230,769 person years of follow-up, 509 men were newly diagnosed with diabetes. After controlling for known risk factors, men who smoked 25 or more cigarettes daily had a relative risk of diabetes of 1.94 compared with non smokers.[27]

Pharmacological interventions

Sulfonylurea compounds decrease hyperglycaemia by stimulating insulin secretion. Despite the risk of causing hypoglycaemia tolbutamide was used in two interventional studies. The Bedford study was a 10 year follow-up study where 125 subjects with IGT on placebo were compared with 123 patients on tolbutamide.[28] The ratio of incidence of diabetes between drug and placebo treated group was 1.1. In the Malmöhus study, 98 IGT subjects on placebo were compared with 49 on tolbutamide over 10 years,[12] and the ratio of incidence of diabetes in the treatment group was 0.8. The Whitehall study included a 5-year follow-up where 89 IGT subjects on placebo were compared with 92 IGT subjects on phenformin.[29] The incidence ratio of diabetes was 0.9 between the drug and placebo-treated group. Altogether these studies were small and showed no significant effect of drugs on incidence of diabetes.

In a Chinese study seventy subjects with IGT were randomised double-blind to receive placebo or metformin at a dosage of 250 mg three times a day for a duration of 12 months.[30] At the end of 12 months the conversion rate to diabetes was 16.2% in the placebo group compared to 3.0% in the metformin group. Of subjects treated with metformin for 12 months, 84.9% became normoglycaemic compared to 51.4 % of those receiving the placebo. It was concluded that metformin could improve glucose metabolism in IGT subjects and may be a treatment option in the management of IGT subjects.

The effect of troglitazone, a thiazolidine-dione compound, was studied on insulin sensitivity and pancreatic beta cell function in women at high risk of Type 2 diabetes i.e. with IGT and a history of gestational diabetes mellitus.[31] The subjects were assigned to take placebo or 200 or 400 mg troglitazone daily for 12 weeks; OGTT and intravenous GTT were repeated during the 12th week of treatment. Findings indicated that troglitazone improved whole body insulin sensitivity and lowered circulating insulin concentrations.

Alpha glucosidase inhibitors were assessed in a Canadian study with acarbose. IGT subjects were randomly treated in a double-blind fashion with placebo or acarbose at 100 mg tid for 4 months.[32] All subjects were submitted before randomisation and at the end of the study to a standardised breakfast and a 12 h day-time plasma glucose and plasma insulin profile, and insulin sensitivity was measured at steady-state plasma glucose using insulin suppression test. It was concluded that in subjects with IGT, acarbose treatment decreased post-prandial plasma glucose and insulin and improved insulin sensitivity.

On-going studies

The Stockholm Diabetes Prevention Programme (SDPP) is directed to the entire population of three municipalities of Stockholm county.[33] The intervention during a 10-year period from 1995, is focused on increasing physical activity, improving diet, reducing obesity and quitting tobacco use among the inhabitants. In addition to achievements in the municipality as a whole, aiming at increasing opportunities as well as demands of healthier products and habits for all, the programme directs preventive measures towards specific groups within the society, such as professional drivers or overweight subjects with a family history of diabetes. These groups have been selected partly on the basis of the outcome of a cross-sectional base-line study of oral glucose tolerance, anthropometric data and life-style parameters in about 3,000 men and 5,000 women, aged 35-54 years.

The U.S. Diabetes Prevention Programme is a new, 150 million dollar NIH sponsored study designed to determine whether Type 2 diabetes can be prevented or delayed in persons with IGT.[34] Four thousand subjects have been randomly assigned to one of four study groups and will be followed for 4-5 years. The study groups include intensive lifestyle interventions with diet and exercise; metformin or troglitazone with standard diet and exercise; and a control group. Participants will be followed to a common closing date in 2002 .The treatment group, troglitazone combined with standard diet and exercise, was discontinued because of the liver

toxicity of this drug. This randomised clinical trial will test the possibility of preventing or delaying the onset of Type 2 diabetes individuals at high risk.

In the light of the above referred studies, and considering the proportions of the global epidemic of Type 2 diabetes, life style intervention appears at present to be a realistic and necessary procedure for primary prevention of the disease. It will involve action by all sectors of the community, government, media, education and health services as well as the general population. Prevention programmes will need to be integrated into the existing health services and into the existing prevention programmes, e.g. those already in place for prevention of coronary vascular disease and/ or hypertension.[35]

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