Is Prevention the Solution to the Worldwide Epidemic Explosion of Type 2 Diabetes Mellitus?

a report by
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In the last two decades, the worldwide explosion in the prevalence of type 2 diabetes mellitus has become a major societal challenge of the 21st century.[1] Diabetes still remains the first cause of blindness below the age of 65 in industrialised countries, the first cause of end-stage renal disease and non-traumatic amputation, and a major cause of cardiovascular disease (CVD). For these reasons, it has a strong impact on healthcare costs.[2,3] Type 2 diabetes generally develops in genetically susceptible individuals with superimposed environmental and behavioural factors – mainly sedentary lifestyle and obesity. These two conditions will lead to development of insulin resistance, one of the major metabolic impairments involved in the pathophysiology of type 2 diabetes. But it is only when the pancreatic beta cells fail to fully compensate for this insulin resistance that glucose intolerance will appear as impaired glucose tolerance (IGT) (postprandial hyperglycemia) and/or impaired fasting glucose (IFG) (mild fasting hyperglycemia).[4] These two entities are now recognised as pre-diabetic states as both are associated with a very high risk of progressing to overt diabetes. It has to be remembered that glucose intolerance is usually part of a cluster of risk factors for CVD – including hypertension, dyslipidemia and central obesity – called the metabolic syndrome, with insulin resistance as the common denominator.[5] But IGT and diabetes *per se* are an independent risk factor for CVD.[6] The concept of prevention of type 2 diabetes has now been confirmed by a number of studies showing that both non-pharmacological and pharmacological interventions in a high risk population with IGT could prevent, or at least delay, the progression to diabetes.[7]

Non-pharmacological Interventions and the Prevention of Type 2 Diabetes as a Primary Outcome

Prospective or longitudinal observational studies have shown that decreased physical activity is an independent predictor of type 2 diabetes in men and women. A number of studies have also confirmed the relationship between the risk of developing type 2 diabetes to the presence and duration of overweight and obesity.[8] It was therefore postulated that, in high risk subjects with IGT, a lifestyle modification program – including a weight-reducing diet and exercise programme – should decrease the risk of progressing to diabetes. Six intervention studies have now confirmed that lifestyle modification reduces the risk of diabetes by over 50% in subjects with IGT[7] (see *Table 1*). Though some of the studies have methodological problems, the overall data are overwhelmingly convincing that lifestyle modification is highly effective in preventing or delaying the progression of IGT to type 2 diabetes.

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Pharmacological Interventions and the Prevention of Type 2 Diabetes as a Primary Outcome

It is believed that the stress on the beta cells in a genetically susceptible individual due to insulin resistance, secondary to obesity and decreased physical activity, will eventually lead to reduce capacity in insulin secretion and the development of IGT, a pre-diabetic state characterised by postprandial hyperglycemia. This moderate postprandial hyperglycemia is sufficient to induce glucose toxicity and further contribute to the progression of IGT to type 2 diabetes.[9] It was therefore postulated that any pharmacological intervention that could decrease insulin resistance and/or the stress on the beta cells could potentially prevent the progression of IGT to type 2 diabetes. Five randomised control trials have now examined this issue as a primary outcome and have shown significant risk reduction of the incidence of type 2 diabetes (ranging from 31–88%), using acarbose, metformin, troglitazone or orlistat (see *Table 1*). Again, the data are fairly strong and convincing that pharmacological intervention in IGT subjects can reduce the risk of diabetes.[10]

The results of the DREAM (Diabetes REduction Approaches with ramipril and rosiglitazone Medications) study and Navigator study (nateglinide/valsartan) in an IGT population are expected for 2006.

Table 1: Non-pharmacological and Pharmacological Interventions and the Prevention of Type 2 Diabetes as a Primary Outcome

Studies	No. of subjects	Interventions	Duration of intervention (yr)	Incidence of diabetes in control group (%/yr)	Risk reduction (%)
Non-Pharmacological					
The Malmo study[12]	217	Lifestyle programme	5	5.6	64
The Da Qing study[13]	577	Lifestyle programme	6	15.7	41
The DPS study[14]	522	Lifestyle programme	3.2	7.8	58
The DPP study[15]	2,161	Lifestyle programme	2.8	11.0	58
The Chinese study[10]	145	Lifestyle programme	3.0	11.6	33
The Japanese study[16]	458	Lifestyle programme	3.0	9.3	67
Pharmacological					
The Chinese study[10]	261	Acarbose	3.0	11.6	88
		Metformin	3.0		77
The DPP study[15]	2,155	Metformin	2.8	11.0	31
The STOP-NIDDM trial[17]	1,368	Acarbose	3.2	12.1	36
The TRIPOD study[18]	236	Troglitazone	2.5	12.1	55
The XENDOS study[19]	3305	Orlistat	4.0	2.25	37

Table 2: Bariatric Surgery and the Prevention of Type 2 Diabetes

Studies	No. of subjects (surgery/control)	Duration of follow-up (yr)	Weight loss (%)	Incidence of diabetes (%/yr)
Pories et al.[20]	152 / –	7.6	33*	0.17
Long et al.[21]	109 / 27	5.8	52**	0.15
SOS study[22]	517 / 539	10.0	16*	0.10

* % body weight

** % excess body weight

Bariatric Surgery and the Prevention of Type 2 Diabetes

There are still few data on the effect of bariatric surgery in morbidly obese subjects on the prevention of diabetes. Three studies, however, have published data on subjects with or without IGT that are interesting (see *Table 2*). Though these were not randomized studies, bariatric surgery was associated with a risk reduction greater than 95% compared to historical or matched controls. It is suggested that in morbidly obese subjects with or without IGT, gastric bypass can be an alternative to reduce the incidence of diabetes.

Pharmacological Intervention and the Prevention of Type 2 Diabetes as a Secondary Outcome

At least 10 studies have examined the effect of the renin angiotensin aldosterone (RAA) system inhibitors as a secondary outcome in a high risk population;[7] five studies were with the angiotensin-converting enzyme inhibitors (ACEIs) and five studies with the angiotensin receptor antagonists (ARAs). Altogether, 85,000 subjects have been randomised to ACEIs or ARAs versus other antihypertensive medications. Eight of these studies were associated with a significant reduction in the incidence of new cases of type 2 diabetes on secondary analysis, except for the HOPE (Heart Outcomes Prevention Evaluation) study which was a *post hoc* analysis.[11] The relative risk reduction varied between 14% and 87%, with an overall mean adjusted for a population of 25.6%. The comparator medications were either placebo (four studies) or ß-blockers ± calcium channel blockers (four studies).

Although these studies are encouraging, a number of methodological limitations have to be considered. First, in all of these, the prevention of diabetes was a secondary analysis. The diagnosis of diabetes was based on fasting plasma glucose and not on the oral glucose fasting test (OGTT), and the prevalence of IGT in those study populations is not known.[7] In four studies where ACEIs or ARAs were compared to placebo, three of them showed a significant reduction in the risk of diabetes (mean 24.8%) and one did not reach statistical significance. These observations are encouraging, and prospective studies on the effect of those drugs on the prevention of diabetes in a high risk population is justified.

Besides the RAA inhibitors, there are two other pharmacological agents that have shown potential for the prevention of type 2 diabetes as a secondary

Table 3: Renin Angiotensin Aldosterone (RAA) System Inhibitors, Pravastatin and Estrogen/Progestin Interventions and the Prevention of Type 2 Diabetes as Secondary Outcome

Studies	Interventions	No. of subjects	Duration of follow-up (yr)	Comparators	Risk reduction (%)	p-value
CAPP[23]	Captonil	10,413	6.1	Diuretic and/or ß-blockers	14	0.039
STOP-HTN2[24]	Enalapril/ lisinopril	3,930	6.0	ß-blocker	15	NS
LIFE[25]	Losartan	7,598	4.8	ß-blocker	25	0.001
HOPE[11]	Ramipril	5,720	4.5	Placebo	34	< 0.001
ALLHAT[26]	Lisinopril	33,357	4.9	Diuretic Ca^{++} channel blocker	30	< 0.001
SOLVD[27]	Enalapril	391	2.9	Placebo	74	< 0.001
ALPINE[28]	Candesartan	393	1.0	Diuretic ± ß-blocker	87	0.03
SCOPE[29]	Candesartan	4,964	3.7	Placebo	19	0.09
CHARM[30]	Candesartan	7,601	2.0	Placebo	19	< 0.001
VALUE[31]	Valsartan	15,245	4.2	Diuretic/ ß-blocker	23	< 0.001
WOSCOPS[32]	Pravastatin	5,974	4.8	Placebo	30	0.042
HERS[33]	Estrogen/progestin	2,763	4.1	Placebo	35	0.006

outcome: pravastatin and estrogen/progestin replacement therapy[7] (see *Table 3*). These two studies have shown that pravastatin treatment and hormonal replacement therapy were associated with a risk reduction for diabetes of 30% and 35% respectively. These observations need to be confirmed in prospective studies sufficiently powered before they can be translated into recommendations.

Conclusions

It is now established that type 2 diabetes can be prevented or delayed through lifestyle modification or pharmacological interventions. Lifestyle change remains the most powerful tool, but the major challenge is to maintain those changes in the long term – in overweight or obese subjects submitted to a weight-reducing program the success is less than 10%. That is why pharmacological agents such as acarbose, metformin and orlistat can play an important role as an adjunct or as an alternative to lifestyle modification.

Though a number of studies have suggested that inhibitors of the RAA system, pravastatin and estrogen/progestin replacement therapy could potentially prevent or delay diabetes in a high risk population, these have to be confirmed in prospective studies. This new evidence-based data has to be translated into recommendations to screen and treat subjects with pre-diabetes. This is our only hope to alleviate the worldwide burden of diabetes in the near future. ■

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