

ABSTRACT

Data from the 2004 National Health Survey highlight important aspects of the burden of diabetes in Singapore. The need for preventing diabetes and its complications remains a topmost priority in the care of our patients. With the ever increasing armamentarium of anti-diabetic agents at our disposal, a succinct knowledge of the newer agents and their role to complement existing older therapies is needed.

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EPIDEMIOLOGY AND PREVALENCE

The recent Singapore National Health Survey in 2004 showed a significant fall in diabetes prevalence from a high of 9% in 1998 to 8.2%. However, with the reference resident population growing from 2.16 million in 1998 to 3.48 million in 2004, actual numbers of persons with diabetes may actually have increased. The difference amongst ethnic groups remained as it was in 1998 with more Indians (15.3%) than Malays (11%) than Chinese (7.1%) having diabetes. In clinical practice, this would mean that we should approach patients of different races in our practice differently, with respect to their risk of developing diabetes and would counsel, say, an Indian or Malay person more rigorously in lifestyle modification, exercise, and ideal weight attainment in prevention of diabetes. Across gender and race, the prevalence fell except for Malay men who showed an increase from 8.2% to 11.7% over the 6-year interval.

We could suppose that part of the explanation might be in the increase in the number of people who exercise regularly. 16.8% of adults aged 18 to 69 in 1998 did so and this rose to almost a quarter of adults in 2004. This applied to both men and women and in all racial groups. What would be the case with Malay men then? Though overall obesity rates have not changed significantly over the 6 year period, in this group, the rise in obesity has almost doubled from 8.8% in 1998 to 16.9% in 2004!

Three other findings need to be highlighted, as they also impact on clinical practice – about half (49.4%) of diabetes remains undiagnosed suggesting the need for intensified opportunistic screening; 12% of the adult population have impaired glucose tolerance highlighting a larger number of individuals, than having diabetes itself, who are at risk for developing diabetes and coronary artery disease; and less than

half (44.8%) with diabetes have good control over their condition ($HbA_{1c} < 7\%$), reflecting the continued effort needed on the part of both doctors and patients.

PREVENTING DIABETES

Diabetes Mellitus is a complex, heterogeneous, multifaceted entity. Though encompassing many categories, we tend to regard diabetes as falling into 2 broad etiopathogenetic forms – Type 1 and Type 2 diabetes mellitus. In Type 1 diabetes, the cause is an absolute deficiency of insulin resulting from a cellular-mediated autoimmune destruction of the beta-cells of the pancreas. This accounts for less than 5% of all cases of diabetes in Singapore. It is more common in Western populations and, for example, in the Nordic countries, where it may account for 10-20% of cases of diabetes. The 'Asian' variety of Type 1 diabetes may lack the auto-antibody markers commonly associated with it, e.g. insulin autoantibodies, islet cell autoantibodies, and autoantibodies against GAD-65.

Type 2 diabetes is more complex and has a stronger genetic pre-disposition than Type 1 diabetes, meaning that most patients would have other family members similarly affected. It is generally thought about as an interplay of insulin resistance and insulin deficiency. The former is brought about by aging, obesity and a sedentary lifestyle coupled, and therefore can be regarded as the acquired component. The latter is a genetically programmed inability of the pancreatic beta-cell to overcome this insulin resistance, what we term *relative* insulin deficiency, as opposed to *absolute* deficiency in Type 1 diabetes. As the imbalances between the 2 components progress, an individual moves down the path from normal glucose tolerance to pre-diabetes (encompassing both impaired fasting glycaemia, IFG, and impaired glucose tolerance, IGT) to diabetes. Insulin is by no means the only player in Type 2 diabetes; recently, the concepts of hyper-glucagonemia and reduced incretin (glucagon-like peptide, GLP-1, and glucose-inhibitory polypeptide, GIP) have been re-explained with the advent of a new class of therapeutic agents addressing these defects.

All efforts to prevent Type 1 diabetes (using low dose insulin injections and nicotinamide) have so far, been unsuccessful. Current research to cure Type 1 diabetes is focused on islet cell transplantation and stem-cell therapy.

Preventing Type 2 diabetes can be more rewarding. There is definite evidence for both lifestyle modification as well as oral medication. Lifestyle modification, involving weight loss (of the order of 7%) and regular exercise (150 minutes/week), can reduce the risk of developing diabetes by half. How we translate this to practical advice to our patients is to ask them, at whatever weight they are at, to try to aim for a gradual but sustained weight loss of about 10% of their initial weight over 6 months. This translates to roughly 0.5 kg/week or 2 kg/

month. They should aim for at least 30 minutes of exercise 5 days a week, at a sport or activity that they enjoy doing.

Medication alone, using metformin or acarbose, is also effective, though less so than an intensified lifestyle program – reducing the risk by a third. Combining the two though – medication with intensive lifestyle modification – can reduce the risk by over 75%. This same level of risk reduction is almost achievable with another class of medication, the thiazolidenediones. However, the recent controversy as well as known side effects associated with these agents may resist their use in prevention.

In Singapore, with 12% of the adult population having IGT, it would make sense to risk-stratify within this group and identify those at higher risk for progression to diabetes. These individuals can then, perhaps be offered a strategy of combining lifestyle modification with medication. Some identifiable parameters might be those with the metabolic syndrome, in high risk ethnic groups, with combined IGT and IFG, and with a family history of diabetes. Everyone else should adopt an intensively modified lifestyle plan.

Medication other than the anti-hyperglycaemic agents have also been shown to reduce the numbers of new-onset diabetes. These include ACE-inhibitors, Angiotensin-receptor blockers and the weight-reducing agent, Orlistat.

PREVENTING DIABETES COMPLICATIONS

Preventing diabetes-related end-organ damage remains a key element in diabetes management. Central to this is blood glucose control. Intensive glycaemic control has been convincingly shown to reduce the development and progression of microvascular complications (retinopathy, nephropathy, and neuropathy) in both Type 1 and Type 2 diabetes as seen in the landmark DCCT and UKPDS respectively. After the DCCT ended, the patients from the two treatment arms (conventional and intensive control) entered into a follow-up study called EDIC (Epidemiology of Diabetes Interventions and Complications). During the next 8 years, glycaemic levels no longer differed substantially between the two original treatment groups. Despite this, there was a persistence in benefit on blood pressure, albumin excretion, and retinopathy in the earlier intensive glycaemic control cohort; suggesting a form of metabolic ‘imprinting’ or ‘memory’ on target organs. What are the implications of these results? It encourages EARLY and SUSTAINED achievement of glycaemic targets in diabetes management.

The relationship between macrovascular disease (cardiovascular events) and glycaemia is more tenuous. There is epidemiological evidence of a relationship between cardiovascular risk and blood glucose levels, and it suggests that this continues down to blood glucose levels even below current diabetes cut-offs (i.e. 7 mmol/l fasting and 11.1 mmol/l post-prandial), into the pre-diabetes range (fasting 6 – 7 mmol/l and post-prandial 7.8 – 11 mmol/l). However, intervention trials have

not borne this out convincingly. In both the DCCT and UKPDS, a trend towards a significant reduction in macrovascular disease was noted. In individuals who are overweight in the UKPDS, the reduction was significant on metformin therapy only. Interestingly, in the EDIC study, again, benefit is seen – of early intensive glycaemic control on long-term cardiovascular outcomes including cardiovascular mortality, 13 years after the conclusion of DCCT.

This makes the preliminary conclusions of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study all the more surprising. ACCORD was a study looking at 10,000 patients with Type 2 diabetes who had heart disease or at least two cardiovascular risk factors. All patients were enrolled in the glycaemic arm which was testing an intensive strategy targeting an HbA1c of below 6 % with a standard strategy of 7 – 7.9%, on the rate of cardiovascular events. The glycaemic part of the study was stopped prematurely because of an increase in mortality in patients in the intensive arm. However, a similar study – ADVANCE (Action in Diabetes and Vascular Disease – Preterex and Diamicron MR Controlled Evaluation), also looking at intensive glycaemic targets using a diamicon (gliclazide)-based regimen did not show the same results.

How should we respond?

Any conclusion should best wait for further details and analysis of the results and publication of the two studies. The preliminary feel is that the patients in ACCORD are a subset of our daily diabetes patients. They were of average age 62 years and had Type 2 diabetes with either coronary heart disease or two or more coronary risk factors, for 10 years. They may have been on a combination of multiple oral agents and/or multiple insulin injections in order to achieve the target HbA1c levels.

On the other hand, data from the Steno 2 study from Copenhagen reinforce a multiple risk-factor targeted approach on lipids, blood pressure, smoking, and using aspirin and ACE-inhibitors, together with a balanced diet and lifestyle with regular exercise, and also the benefits of adopting a less ‘glucose-centric’ view. With this kind of approach, microvascular events, cardiovascular events, and total mortality all fell by as much as 50%.

What should we tell our patients in the light of this evidence?

Blood glucose control is important. At whatever level patients are at, they should strive for improvement. Every 1% improvement in HbA1c level reduces microvascular complications by 30-35% and macrovascular complications by 14%. They should aim for an HbA1c of 7% and less, and try to reach it early on in their diabetes history and maintain good control for as long as they can. Besides blood glucose control, achieving recommended target levels for lipid parameters, blood pressure and the use of aspirin and ACE-inhibitors as indicated is as important.

NEW THERAPEUTIC AGENTS

There are currently 6 categories of Therapeutic Agents:

- a. Insulin secretagogues including Sulphonylureas and Meglitinides (repaglinide or Novonorm and nateglinide or Starlix)
- b. Biguanides including Metformin
- c. Thiazolidinediones including Pioglitazone (Actos) and Rosiglitazone (Avandia)
- d. Alpha-glucosidase inhibitors including Acarbose (Glucobay)
- e. Incretin mimetics and DPP-4 inhibitors
- f. Insulin

Insulin secretagogues, especially the **sulphonylureas**, have been in use for decades. They are indeed the workhorses in diabetes due to the widespread availability of generic compounds. Weight gain and hypoglycaemia remain important considerations. The relatively newer **meglitinides** are more costly, but have the advantages of 'one-meal, one-dosing' and to be used 5-10 minutes prior to eating. They therefore allow flexibility in use and titration.

Metformin is the other compound long in use in diabetes management. It is weight neutral and complements insulin secretagogues. Its main limitation is the gastrointestinal (GI) effects and contraindication in renal impairment. The former can be reduced with a new XR formulation.

Thiazolidinediones (TZDs) is represented by rosiglitazone in Singapore. It holds the promise of beta-cell preservation and forestalling the progression of Type 2 diabetes. Issues with rosiglitazone are fluid retention and weight gain, fractures in post-menopausal women, and controversy over increasing cardiovascular mortality.

Acarbose has the advantage of safety. It remains in the small intestine (<2% is absorbed systemically) inhibiting the action of alpha-glucosidase in the breakdown of oligosaccharide sugars. The clinical effect is a blunting or smoothing out of post-prandial glucose peaks. Limiting its use are GI effects which can be reduced through slow upward titration of dose.

The newest class of medication act through enhancing the action of incretin hormones. The major incretins are glucagon-like peptide (GLP-1) and glucose inhibitory polypeptide (GIP), produced at different sites in the small intestine. GLP-1 is deficient in Type 2 diabetes, while GIP action is diminished. Incretin effects include insulin release, reducing glucagon, slowing gastric emptying and promoting satiety. The current methods of enhancing incretin action are either through **GLP-1 analogues** like exenatide or liraglutide which are more resistant to enzymatic degradation than the natural compound itself,

or through inhibiting the enzyme (DPP-4) that inactivates incretins, i.e. **DPP-4 inhibitors**. Exenatide, which is given by fixed dose subcutaneous injection, is awaiting approval in Singapore. Two DPP-4 inhibitors have been launched over the last year – sitagliptin and vildagliptin, and both are orally active. Both can be used as monotherapy in Type 2 diabetes, or in combination with sulphonylureas (vildagliptin), metformin (both), TZDs (both), and insulin (vildagliptin).

The benefit of these newer and costlier drugs is in minimising hypoglycaemia and weight gain. Patients on Exenatide actually lose weight, whilst the DPP-4 inhibitor drugs are weight-neutral. The drug class also holds the promise of pancreatic beta-cell preservation and regeneration, though so far only in in-vitro studies. Their blood glucose-lowering effect is comparable to existing therapies. This cautions against the temptation to switch medication in order to achieve lower blood glucose levels.

Insulin remains a logical choice in Type 2 diabetes if glycaemic targets cannot be met. Its potency lies in part with the fact that insulin doses are limitless. In Type 1 diabetes, insulin is the only option. In Type 2 diabetes, it has generally, since the advent of oral agents, been relegated to the final option. This has led to a proliferation of 3 and 4 drug combination regimens that have mainly served to rack up the cost of treating diabetes. In reality, insulin analogues and modern improved insulin delivery devices (pens and pumps) have made insulin use more acceptable to patients and doctors alike. Doctors are now more comfortable to introduce and institute insulin therapy earlier for their patients, and in the primary health care setting as well!

Insulin analogues are now available in the basal form as insulin glargine (lantus) and detemir (levemir), as well as bolus rapid-acting insulins – lispro (humalog), aspart (novorapid) and glulisine (apidra). The more physiological profile of the insulin analogues leads to reduced hypoglycaemia and weight gain – the Achilles heel of conventional insulins.

TREATMENT ALGORITHMS

With the expanding class of anti-hyperglycaemic agents, algorithms have been devised to guide prescriber choices in initiating and escalating therapy. Our own Clinical Practice Guidelines outline a suggested algorithm based on the initial categorisation of a Type 2 diabetic patient into overweight (insulin-resistance predominant) and non-overweight (insulin-deficiency predominant) phenotypes. Receiving a lot of attention in the last 1½ years has been the combined ADA (American Diabetes Association) – EASD (European Association for the Study of Diabetes) consensus algorithm published in August 2006. Without

going into much detail on its construct, three key elements should be highlighted indicating the recent move towards a more aggressive approach to managing Type 2 diabetes.

1. Initial therapy combining lifestyle modification (diet, meal planning and regular exercise) with metformin (as a proven, relatively safe and economical drug) to ensure a more robust initial reduction of hyperglycaemia towards target glycaemia.
2. Rapid addition of second-line agents, when target glycaemic goals are not achieved or sustained. The suggested second tier agents were sulphonylureas, insulin, or thiazolidinediones. With the subsequent controversy

over Rosiglitazone, the algorithm was updated in November 2007 to advise caution in using Rosiglitazone and including Sitagliptin as a possible choice as well.

3. Early institution of insulin therapy when target glycaemic goals are not met. This was suggested even as a second-line agent to metformin.

By no means should this algorithm be blindly adopted in its entirety into our practice; however, we should pay heed to the messages of early initiation of medication and combination therapy if target glycaemic goals are not met or sustained, and early initiation of insulin if needed.

LEARNING POINTS

- o Though the prevalence of diabetes seems to have stabilised in Singapore, there is still a significant burden of both diabetes and impaired glucose tolerance upon the population. The burden is different amongst the various races in Singapore, with Indians most at risk.
 - o Preventing Type 2 diabetes can be tackled on different fronts. A strategy for identifying those at greatest risk of developing diabetes may allow for an intensive approach of combining lifestyle modification with medication.
 - o New classes of medication allow us wider choices of therapy for our patients. Nevertheless, we should resist the urge of combining all existing categories of medication in a single patient in an effort to achieve glycaemic targets. The availability of insulin analogues allows a safe and convenient method for early initiation of insulin if the need arises.
 - o Attaining glycaemic targets or short of it and any improvement in glycaemia will reduce diabetic micro- and macro-vascular complications; as well as adopting a comprehensive risk factor reduction strategy in diabetes.
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