Leading Article

Primary, secondary and tertiary prevention of non-insulin-dependent diabetes

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Diabetic mortality and morbidity

Non-insulin-dependent diabetes (NIDDM) is an important contributor to premature vascular disease¹, blindness², renal failure³ and lower limb amputation.⁴ Morbidity and mortality from NIDDM is under-reported as NIDDM is frequently undiagnosed, the diagnosis often being excluded from death certificates⁵ and hospital discharge summaries.⁶ Despite the cumulative incidence of diabetic microvascular disease being greater in insulin-dependent diabetes (IDDM), the much higher prevalence of NIDDM results in more morbidity occurring in NIDDM.¹

The cost of non-insulin-dependent diabetes

The cost of NIDDM can be considered in both human and monetary terms. The human cost of NIDDM is the excess mortality rate due to an increase in vascular deaths, between the ages of 45 to 75.^{7,8} The impact of diabetes on mortality risk is greater in women than men, due to a 3–4 fold increase in ischaemic heart disease deaths in women compared to a 2–3 fold increase in men. The impact of NIDDM on mortality risk lessens with increasing age, while it reduces life expectancy by 5–10 years in younger subjects, little influence on mortality occurs beyond the seventh decade.⁹

Diabetic health care has been estimated to consume 4–5% of the total National Health Service budget.¹⁰ Much of this expenditure goes towards the treatment of diabetic complications. The important question to be addressed is whether more money spent on primary and secondary prevention would lessen the costs incurred from treating diabetic complications, such as coronary

artery disease, sight-threatening retinopathy, end-stage renal disease and lower limb amputations.

Epidemiology of non-insulin-dependent diabetes

Prevalence rates for NIDDM are influenced by ethnicity, demography and lifestyles. The prevalence rate of NIDDM is higher in non-White populations. Subjects from the Indian sub-continent, Caribbean, Central American and African states have a particularly high incidence of NIDDM.¹¹ Non-insulin-dependent diabetes increases with age, and is estimated to rise from approximately 7% in the US middle-aged population to nearly 20% in the population above 70 years old.^{12,13} The prevalence of NIDDM rises in populations adopting an urbanized lifestyle characterized by obesity, decreased physical activity and greater fat consumption,¹⁴ a ten-fold increase in NIDDM has occurred in the Pima Indians and South Pacific Islanders over the last three decades with greater urbanization.¹¹

The prevalence of NIDDM in the United Kingdom, as in other countries, will rise over the next few decades as the population ages and the proportion of non-White ethnic groups increases.¹⁵ In the US the prevalence of NIDDM is predicted to double over the next 40 years¹³ whilst a ten-fold increase has been predicted for other populations, including China, as they adopt a more affluent and westernized lifestyle.¹⁶

Delay in diagnosis

Non-insulin-dependent diabetes is frequently asymptomatic and remains undiagnosed for many years. Epidemiological studies suggest that the average time from development of NIDDM to clinical presentation is 7 years.¹⁷ Public awareness of diabetic symptoms are poor, especially amongst

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those ethnic minority groups most at risk of developing NIDDM.¹⁸ Delay in diagnosis of NIDDM translates to a delay in initiating treatment both for the hyperglycaemia and other coexisting risk factors. Diabetic complications are frequently present at the time of initial diagnosis, with 20% of patients reported to have retinopathy and 18% electrocardiographic changes.¹⁹

Scope of prevention

In the context of this review, primary prevention is the delay or prevention of NIDDM whilst secondary prevention is the prevention of diabetic complications with tertiary prevention being the treatment of specific diabetic complications. The objectives of prevention are to lessen diabetes-related morbidity and mortality. If these goals are to be realized, then a combination of all three preventative strategies is needed. It has been calculated that a combination of delaying the onset of NIDDM by 6 years (through primary prevention) and the early diagnosis and treatment of NIDDM (through secondary prevention) would reduce proliferative diabetic retinopathy by up to 65%.²⁰ Successful primary and secondary prevention would reduce the rate of progression of diabetic complications, permitting earlier treatment of complications (tertiary prevention) at a time when morbidity and mortality can be reduced. The spirit of these ideas is embodied in the St Vincent Declaration.²¹

Primary prevention

For primary prevention of NIDDM to be successful, we need to address the causative factor or factors in its aetiology. NIDDM is a heterogeneous disorder, with only a minority of cases caused by single gene mutation. Most NIDDM is caused by a combination of polygenetic and environmental factors, including intrauterine influences^{22–24} with decreased insulin secretory capacity and decreased sensitivity to insulin being universal features.²⁵ The contribution that these abnormalities play in the development of NIDDM is likely to be dependent on both genetic and environment factors.²⁶

The primary prevention of NIDDM could theoretically be achieved by genetic or environmental manipulation. Realistically, gene therapy is unlikely to be successful in such a polygenic disorder. A much more likely approach to the primary prevention of NIDDM is through lifestyle changes that favourably influence insulin sensitivity and insulin secretory capacity. These changes would include the avoidance of obesity, increased physical activity, dietary modification and optimization of the intrauterine environment.

Avoidance of obesity

The avoidance of obesity is an important primary preventive measure for reducing the prevalence and delaying the onset of NIDDM within the general population. Obesity is associated with an earlier presentation of NIDDM.²⁷ Avoiding obesity halves the future risk of diabetes in those subjects at increased risk such as women with a history of previous gestational diabetes.²⁸ Population studies have shown that the prevalence of IGT (impaired glucose tolerance) and diabetes rises steeply when the body mass index (BMI) exceeds 27 kg/m²,²⁹ a level of obesity at which insulin sensitivity falls rapidly.³⁰ Obesity is associated with decreased insulin sensitivity characterized by decreased insulin-stimulated glucose uptake in muscle and reduced insulin suppression of hepatic glucose production.^{31,32} Obese individuals do not demonstrate the normal increase in muscle blood flow following oral glucose load. This is likely to contribute to decreased insulin sensitivity³³ in these individuals. Overfeeding decreases insulin sensitivity causing IGT in some individuals.³⁴ The anatomical distribution of fat as well as the degree of obesity influences insulin sensitivity. Abdominal rather than gluteal fat is associated with greater insulin insensitivity and an increased prevalence of IGT and NIDDM.³⁵ The adverse metabolic effects of abdominal obesity are attributed to an increased release of non-esterified fatty acids into the portal circulation.^{36,37}

Potential for increased physical activity

Increasing physical activity in both men and women reduces the incidence of IGT and NIDDM in both individuals at low and high risk of NIDDM.^{38–40} An 8-year prospective study involving 80,000 middle-aged non-diabetic American women showed that regular exercise reduced the risk of developing NIDDM by a third even in the presence of a positive family history.⁴¹ Similar benefits from exercise were observed in a male prospective study of 6,000 alumni students, with the greatest protection seen in those individuals with a positive family history of NIDDM or obesity.⁴²

Dietary modification

The prevalence of NIDDM is influenced by both the energy content and the composition of the diet. In the 1930s it was recognized that countries with a high fat intake had a high prevalence of NIDDM while those with a high carbohydrate diet were protected.⁴³ Recent studies have confirmed an increased risk of NIDDM when >40% of total calories is from fat.⁴⁴ The protection from NIDDM

of low fat/high complex carbohydrate diets is likely to result from increased insulin sensitivity.^{45,46} The dietary inclusion of anti-oxidants such as vitamin E may also improve insulin sensitivity and provide extra cardioprotection in NIDDM by reducing free radical activity.⁴⁷

Optimizing the intrauterine environment

The intrauterine environment influences the incidence of future NIDDM in the foetus.^{24,48,49} Low birthweight is associated with an increased risk of future diabetes.^{50,51} Furthermore, animal studies show that protein deficiency in early pregnancy results in low birthweight with a decrease in both β -cell mass and insulin sensitivity.^{52–55} Maternal hyperglycaemia during pregnancy also predisposes to an earlier presentation of NIDDM in the child.^{24,48} More individuals with NIDDM/IGT have a maternal rather than a paternal history of diabetes.^{56,57} Experimentally induced maternal hyperglycaemia in the rat results in offspring developing diabetes in adulthood which is transmissible to the next generation.⁵² These studies suggest that adequate maternal nutrition and avoiding maternal hyperglycaemia have a primary preventative role in NIDDM.

Secondary prevention

In addition to the lifestyle changes essential for primary prevention, secondary prevention is the prevention of diabetic complications through the optimization of glycaemic control, and the avoidance and treatment of coexisting risk factors. For optimal impact secondary prevention needs to begin at the biochemical presentation as opposed to the clinical presentation. The treatment and avoidance of hypertension, microalbuminuria, dyslipidaemia and cigarette smoking are theoretically important secondary preventative strategies for lessening diabetic complications.^{58–61}

Glycaemic control

Achieving optimal glycaemic control has proven benefits in reducing the development and progression of microvascular complications of diabetes in patients with insulin-dependent diabetes (IDDM) by approximately 50–60%.⁶² The magnitude of the long-term benefits of glycaemic control in the secondary prevention in NIDDM complication awaits the findings of the United Kingdom Prospective Diabetic Study which is due to report in 1994.¹⁹ Preliminary studies do, however, suggest that there is a positive correlation between level of glycaemia and retinopathy.⁶³ The effects of improved glycaemic control on macrovascular disease are less clear.

Hypertension

Hypertension is a recognized risk factor for cardiovascular disease as well as the progression of diabetic retinopathy and nephropathy.⁶⁴ Hypertension is common in NIDDM, the prevalence being 2–3 times more than that of the non-diabetic population⁶⁵ with an even higher incidence in some ethnic groups. The prevalence of hypertension in NIDDM, particularly systolic hypertension, increases with age and is a risk factor for the development of atherosclerotic vascular disease.^{66,67} Early diagnosis and treatment of hypertension is therefore, theoretically, an important factor in the secondary prevention of diabetes. Hypertension in NIDDM is associated with obesity and reduced insulin sensitivity. Lifestyle alterations that are aimed at weight reduction will help lower blood pressure and increase insulin sensitivity. If pharmacological therapy is required, agents such as calcium antagonists, angiotensin converting enzyme (ACE) inhibitors and alpha blockers that do not adversely affect glucose tolerance, insulin sensitivity and concentrations of serum lipids should be used initially in preference to thiazide diuretics and β -blockers which may have adverse effects on these parameters.⁶⁸ Guidelines for the treatment of hypertension in diabetes are published elsewhere.^{69,70}

Microalbuminuria

Microalbuminuria is defined as an albumin excretion rate between 20 and 200 $\mu\text{g}/\text{minute}$, that is, below the threshold for detection of proteinuria on routine dip-stick (for example, MultistixTM) examination of the urine. Microalbuminuria is a predictor of persistent proteinuria in both IDDM and NIDDM.^{59,71} Microalbuminuria is also a predictor of premature cardiovascular morbidity in NIDDM.⁵⁹ Microalbuminuria is a stronger predictor of end-stage renal disease in IDDM than NIDDM. This is probably due to the greater likelihood of subjects with NIDDM succumbing to vascular disease before the development of end-stage renal failure.⁵⁹ In microalbuminuric subjects with IDDM, reduction of albumin excretion rates and slowing of progression of renal disease is achieved with both improvement in glycaemic control⁶² and treatment of coexisting hypertension.⁷² It remains to be seen whether similar benefits will be observed in microalbuminuric subjects with NIDDM. The potential benefits of angiotensin inhibitors on reducing albumin excretion rates through a specific renal action in IDDM have been reported in both those with and those without 'hypertension'.^{73–75} However, the benefits in NIDDM remain as yet unproven and ACE inhibitors should be used with caution in elderly

subjects with NIDDM for fear of unmasking undiagnosed atherosclerotic renal artery stenosis and provoking renal insufficiency.

Hyperlipidemia

Non-insulin-dependent diabetes is associated with both quantitative and qualitative abnormalities in concentrations of serum lipid and lipoproteins.^{76,77} These changes include an increase in circulating very low-density lipoprotein (VLDL) either as total triglyceride or VLDL-triglyceride and a reduction in high-density lipoprotein (HDL)-cholesterol concentrations. In addition oxidative changes in the low-density lipoprotein (LDL) moiety render it potentially more atherogenic. Elevated LDL-cholesterol, LDL, VLDL, and total triglyceride and lowered HDL-cholesterol concentrations are all associated with coronary heart and peripheral vascular disease.^{78,79} Secondary prevention should include the screening for lipid abnormalities in NIDDM. Dietary and lifestyle advice are the first-line treatments but specific lipid-lowering therapy should be given when these alone prove ineffective. There is little direct evidence that lipid-lowering therapy reduces macrovascular complications in NIDDM. However, in the diabetic subgroup of the Helsinki Heart Study, those subjects receiving active therapy (gemfibrozil) had a lower incidence of coronary heart disease than those treated with placebo.⁸⁰ Unfortunately, this did not quite reach statistical significance.

Cessation of smoking

As in the general population, cigarette smoking is associated with an increased incidence of vascular disease in NIDDM. It has been estimated that as much as 65% of cardiovascular deaths can be attributed to the interaction of cigarette smoking and diabetes.⁸¹ However, data from the Framingham⁸² and Whitehall studies⁸³ showed no greater impact of smoking on arterial disease in hyperglycaemic as opposed to normal individuals. These data suggest that cessation of smoking should have similar (if not greater) beneficial effects in subjects with NIDDM as compared to the non-diabetic population.

Tertiary prevention

Tertiary prevention is the early detection and treatment of diabetic complication. This includes the screening for diabetic retinopathy, nephropathy, cardiovascular and peripheral vascular disease.

Retinopathy

The most important preventative strategy for delaying the progression of background retinopathy to sight-threatening retinopathy is regular screening and early referral to an ophthalmologist.^{84,85} Earlier detection and treatment of diabetic maculopathy or proliferative retinopathy, with laser photocoagulation and/or vitreo-retinal surgery prevents blindness. Despite this, diabetic retinopathy remains the commonest cause of blindness between the ages of 30–64 years.⁸⁶ The majority of diabetic blindness results from patients being inadequately screened and being referred too late for effective ophthalmological treatment.⁸⁴

All diabetic subjects are at risk of retinopathy, the prevalence increasing with increasing duration of the disease, such that approximately 80% of diabetic subjects will have detectable background retinopathy by 15 years, with a smaller percentage having maculopathy or proliferative retinopathy.² Maculopathy is more frequently associated with NIDDM than IDDM and, due to the greater number of NIDDM subjects, represents the commonest cause of diabetic blindness.

Guidelines on screening for diabetic retinopathy in Europe have been drawn up and include a minimum of bi-annual screening from puberty until the time of first appearance of retinopathy and then yearly, with increased frequency in pregnancy and inter-current illnesses.⁸⁷ As diabetic care is dissolved more into the community it will become increasingly important to ensure adequately trained personnel are available to carry out this screening, using either local optometrist or retinal cameras.⁸⁵

Nephropathy

It is likely that the most important preventative strategy for delaying the progression of nephropathy is the detection and treatment of microalbuminuria. Once nephropathy is established, then the management of coexisting hypertension is of paramount importance. Diet may also have an important role in reducing the rate of decline in renal function.⁸⁸ In NIDDM systolic blood pressure is correlated with the rate of decline in renal function.⁶⁴ Treatment of hypertension has proven benefits on inhibiting this decline in IDDM.⁷² More specifically the use of ACE inhibitors in normotensive and hypertensive IDDM patients with microalbuminuria slows the decline of renal function^{73,74,89} and the progression to end-stage renal failure.⁷⁵ The place for these agents in NIDDM subjects with established nephropathy is not yet clear.

Lower limb amputations

Lower limb amputations are about 15 times more likely in diabetic subjects; it has been estimated that up to 85% of these amputations are potentially preventable with adequate foot care.⁴ Peripheral vascular disease and neuropathy are important factors predisposing to lower limb amputation. Despite the proven benefits of regular chiropody, patient education, cessation of smoking and early treatment of infection, the early management of diabetic foot problems remain critically sub-optimal.⁹⁰ Annual screening of the feet is the minimum standard of care that the patient with NIDDM should expect. Identification of those feet at risk, early and appropriate surgical referral, and the treatment of associated risk factors should lessen the social and financial burden that lower limb amputations and their sequelae place on the community.

The importance of education

For preventative strategies to be effective, long-term co-operation and compliance from individ-

uals is required. The degree of compliance required will only be achieved if the individual understands and takes some share in the responsibility of their disease. Primary prevention of NIDDM will require public health initiatives to lessen obesity and increase physical activity within the population as a whole. Secondary prevention will require screening initiatives for individuals at greatest risk of diabetes, including those with a family history or previous gestational diabetes.⁹¹ Education initiatives to heighten public awareness of the early symptoms of diabetes are needed to allow for earlier diagnosis. Successful secondary prevention will depend on identifying and treating cardiovascular risk factors early. Tertiary prevention should be helped with the acceptance of The St Vincent Declaration minimum standards for the delivery of diabetic care across Europe. Patient knowledge of these ideals should augment tertiary prevention.²¹ Health care providers need to be aware of these standards and to ensure that adequate provisions are available to screen and treat early diabetic complications at a time when diabetic mortality and morbidity can be reduced.

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