MANAGEMENT OF NON-INSULIN-DEPENDENT DIABETES

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SUMMARY

Understanding the management of non-insulin-dependent (type 2) diabetes (NIDDM) requires the grasp of three concepts. Firstly, the condition is steadily progressive and demands appropriate changes of therapy over time. Secondly, therapeutic aims must be set for three parameters: plasma lipids, plasma glucose and blood pressure. Thirdly, the condition is dangerous and regular screening for early complications is mandatory. In this brief review the nature of NIDDM is discussed and an approach to clinical management outlined.

PATHOGENESIS OF NIDDM

The clinical course of non-insulin-dependent (type 2) diabetes (NIDDM) has only recently been appreciated. Two major factors are important: loss of insulin secretory capacity and insulin resistance. It is now clear that hyperglycaemia never develops before substantial loss of beta cell function, and that relative insulin insensitivity helps to determine the time of presentation. Thus, an obese individual will develop symptoms at an earlier stage in the inexorable dive of beta cell function than would an insulin-sensitive slim person. Although the degree of insulin sensitivity does not necessarily change with time, it certainly may be modified (see below). The slowly progressive islet cell dysfunction does not stop at the time of clinical presentation, and this natural history is illustrated in Fig. 1.[1,2] The major unanswered question is why some people exhibit relatively rapid progression over a few years, whereas others remain more or less stable at one stage for many years before appearing to progress. The phrase 'well controlled' is often used to imply that the patient is very compliant with therapy. While this is likely to be true to a degree, a more accurate phrase would be 'adequate degree of beta cell function in the face of a certain degree of insulin resistance'. This has been discussed elsewhere.[3]

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AIMS OF TREATMENT

Unlike most other diseases, the goal(s) for therapy of NIDDM cannot be generalised but rather have to be set for each individual. Separate goals for plasma glucose, serum lipids and blood pressure are necessary and will be considered in turn.

Plasma Glucose

Doctors may differ as regards the precise criteria for blood glucose control in an individaul patient, but few would dispute that the younger the patient the tighter the glycaemic control should be. In a 40-year-old, near-normoglycaemia must be the aim. A European consensus has been published.[4] In the elderly, numerical targets are less important and symptomatic relief is paramount. However, before the possibility of long-term complications in a 70-year-old is dismissed, it must be considered that the disease may have been present for many years before diagnosis and also that average life expectancy at this age is 14 years for a woman and 10 years for a man. Several factors

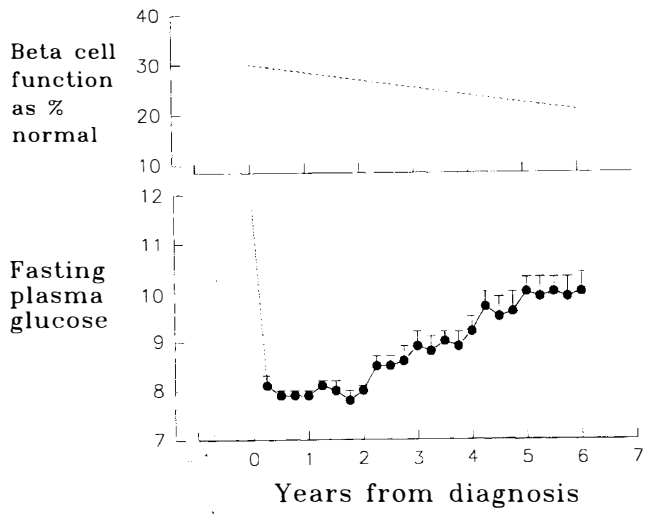

Fig. 1. *Changes in beta cell function and fasting plasma glucose levels with time from diagnosis of non-insulin-dependent diabetes mellitus. (From Taylor[3] with permission.)*

other than age are likely to be taken into account, including maximum possible motivation and ability to comply. However, the reasons for striving for tight, tighter or tightest possible plasma glucose control require some examination.

The original evidence that good control prevented microvascular complications was based upon the observation that complications were rare if random blood glucose levels never strayed above 11 mmol/l.[5] Since then it has been widely accepted that the lower the mean blood glucose the lower the risk of microvascular complications. So much attention has been devoted to this topic that macrovascular disease, the major cause of loss of life and limb in NIDDM, has been relatively neglected. Epidemiological studies have demonstrated the linear increase in rate of coronary heart disease with small increments of fasting blood glucose. It is conceivable that this linear increase in risk reaches a plateau at a level so low that all diabetic people exhibit the increased risk irrespective of whether fasting blood glucose is usually 6 or 10 mmol/l. New data suggest that this is not the case and that near-normoglycaemia may be associated with a lower risk of coronary heart disease than modest hyperglycaemia.[6] It can no longer be said that there is no clear reason to maximise control in NIDDM. Further evidence on the use of insulin in NIDDM will become available on completion of the United Kingdom Prospective Study of Non-insulin Dependent Diabetes.[7]

Often obscured by discussion of long-term complications of diabetes is the question of daily quality of life. Hyperglycaemic malaise, causing excessive tiredness and lack of energy, is not widely acknowledged in the literature. It is always easier to recognise in retrospect, such as after initial treatment of NIDDM or after initiation of insulin therapy. It occurs at different levels of average blood glucose in different individuals, but is likely to be present once fasting blood glucose exceeds 9 mmol/l.

Plasma Lipids

The old uncertainties over how to advise on plasma lipids can now be set aside. It is clear that both total cholesterol and triglycerides are risk factors for the major killer in NIDDM: coronary heart disease. Important new data suggest that good control of serum triglycerides has a clear impact upon the 5-year incidence of ischaemic heart disease in NIDDM.[6]

Furthermore, persistent elevation of plasma triglycerides exacerbates insulin resistance and worsens plasma glucose control. The above considerations regarding age and plasma glucose targets apply even more so to the setting of individual targets for plasma cholesterol and triglycerides. Ideally, for young people, near normal levels are appropriate (<5.2 mmol/l cholesterol, <2.1 mmol/l triglycerides). With advancing age of the patient, one may well be progressively less willing to use lipid-lowering drugs, and for most people over 70 years the reasons for major modification of serum lipids are rare.

Blood Pressure

In diabetes the usual reason for wishing to decrease blood pressure – preventing stroke – is joined by the need to delay the rate of progression of microvascular disease in eye and kidney. The incidence of retinopathy after an 8-year follow-up has been found to be higher in those patients who initially had a systolic pressure above 140 mmHg.[8] In another study, the level of diastolic blood pressure was related to proliferative retinopathy in all patients diagnosed after the age of 30 years.[9] The risk of nephropathy is raised in the presence of hypertension, but even more importantly, adequate lowering of blood pressure results in a dramatic slowing of progression towards renal failure.[10]

The decision on when to treat raised blood pressure levels must be based on age-corrected norms,[11] as blood pressure increases with advancing age in Western societies. For people with diabetes, blood pressure levels (either systolic or diastolic) over the 75th centile for age require intervention. However, over the age of 50 years, use of age-corrected norms loses validity as the unhealthy general population becomes an inadequate example to follow. Adoption of the WHO definition of hypertension as being a blood pressure over 150/90 mmHg is the favoured approach for this age group.

THE APPROACH TO TREATMENT

Plasma Glucose

The overall plan for any patient with NIDDM is shown in Fig. 2. If the individual aims of management are met on any given treatment, then all that is required is regular observation to determine when a change is needed. If not, then knowledge and compliance must be reviewed and should aims not be achieved the indicated change is made without delay.

Dietary therapy for diabetes causes enormous confusion, but is straightforward. The person should eat normally, although fatty and sweet foods should be avoided. Calorie restriction may be necessary. Details of specific foods to avoid are widely available.[12]

The plethora of sulphonylurea drugs should not obscure two facts: tolbutamide is cheap and as efficacious as any; glibenclamide causes an undue number of severe hypoglycaemic reactions due to its long half-life. If the large tablet size of tolbutamide is a problem, or if a degree of renal impairment is present, then gliclazide is my preferred choice. Changing from one sulphonylurea to another in the hope of achieving better plasma glucose control is futile.

Metformin is a potent oral hypoglycaemic agent and is particularly useful in obese subjects as it is not associated with the 1–2 kg weight gain seen during sulphonylurea usage. It must be started at a low dose and increased gradually, as otherwise gastrointestinal side effects are troublesome.

Despite the advent of ultra-fine needles and pen injectors, many doctors (and nurses) regard insulin as something to be avoided at all costs. This view is shared by patients until they experience insulin therapy for themselves. Many people have a deep-seated fear of self-injec-

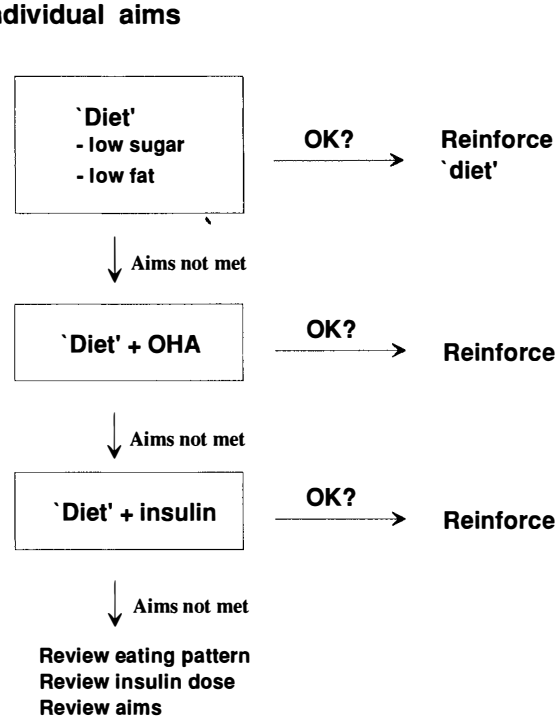

Fig. 2. *The overall treatment plan for a patient with non-insulin dependent diabetes mellitus. OHA, oral hypoglycaemic agents.*

tion, and this very understandable fear is most simply overcome by organising services so that instruction followed by the first self-injection can be given at the same visit that the definite need for insulin therapy is identified. This applies equally to older patients, and it is salutary to realise that doctors and nurses rather than patients tend to underestimate dexterity of the elderly. Similar sentiments have been expressed in relation to medical practice outside the United Kingdom.[13]

Today, insulin therapy is always commenced on an outpatient basis and this reflects the introduction of diabetes specialist nurses as well as better understanding of insulin regimes. Use of an appropriate regime is most important. The simplest regimen and the one least likely to cause hypoglycaemia is probably that of twice daily intermediate-acting insulin (Insulatard [Nordisk Wellcome], Monotard [Novo], other isophane insulin). This may be given via a pen device, simplifying administration. Home blood glucose monitoring does allow for easier adjustment of insulin dosage during initiation of therapy, but one must not be swept away with the popular tide of opinion suggesting that this is absolutely mandatory.

The situation is more difficult for public service vehicle and heavy goods vehicle drivers, when the patient stands to lose earning capacity if started on insulin treatment. Ulterior motives may operate in those about to take out life insurance policies. Other than in the face of weight loss and marked hyperglycaemia, full consideration of social and medical factors is always required before advising insulin therapy. In a few individuals, the initiation of insulin therapy is followed by a notable increase in weight and no marked improvement in control. These are usually the patients most markedly overweight before the insulin therapy. There is no reason why insulin should not be withdrawn if not beneficial.

The three principles governing insulin usage in NIDDM are clear: to relieve symptoms; to achieve appropriate individual aims; to be reviewed if necessary.

Plasma Lipids

Having identified an abnormal lipid profile, assessment of habitual food intake is required as a first step to providing specific advice. Changing one's pattern of eating is far from easy, and individuals vary in how much modification if possible. Naturally, recruiting the support of whoever shops and prepares the household's meals is vital. If after follow-up it is clear that a problem remains, then a decision as to whether or not to use lipid-lowering drugs is needed.

For the most common problem, a mixed elevation of both triglycerides and total cholesterol, either bezafibrate or gemfibrozil is indicated. For an isolated elevated total cholesterol, simvastatin is now the drug of choice. Continued encouragement is essential to maximise compliance with these drugs and with the advised pattern of eating.

Blood Pressure

If blood pressure is above the desirable range for an individual, three questions must be asked before drug therapy is contemplated. Is salt intake excessive? If obese, can the individual achieve weight loss? Is alcohol intake excessive? After these 'simple' therapeutic moves have been made, the choice of drug must be made.

The central point concerns the side effects of antihypertensive drugs. Some will exacerbate the hyperglycaemia, such as thiazides and beta blockers (particularly so in combination). Many agents may cause insidious side effects which may impair quality of life. No single drug is the first choice for all people, but angiotensin converting enzyme inhibitors (e.g. captopril, lisinopril, enalapril), calcium channel blockers (e.g. nifedipine, nicardipine, amlodipine) and alpha blockers (e.g. prazosin) are suitable agents. As with lipid-lowering agents, attention to continued compliance is required.

ORGANISATION OF CARE

In order for the complicated syndrome of NIDDM to be adequately managed, organisation within the hospital or practice diabetes clinic is essential. This allows regular screening for long-term complications to detect problems with feet, eyes or kidney at an early, treatable stage. It also ensures regular follow-up for monitoring of the therapeutic aims described above. It is critical that a knowledgeable doctor and two other key personnel, i.e. a skilled diabetes specialist nurse and a dietitian aware of the practical problems of modifying eating patterns, are involved.

CONCLUSIONS

The tools for the management of NIDDM are standard:

individual assessment; well-tried drugs; means of monitoring. However, optimum use of these tools requires experience. Organisation of the team approach requires skill. Too often NIDDM is regarded as a simple condition to treat. Violins look easy to play.

Key words: Hyperlipidaemia, Hypertension, Insulin, Non-insulin-dependent diabetes, Sulphonylurea.

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