

Management of Non-Insulin Dependent Diabetes Mellitus (NIDDM)

- ☐ Early diagnosis, good glycaemic control and screening for complications are essential.
- ☐ Therapeutics should be aimed at reducing insulin resistance and augmenting insulin deficiency.
- ☐ Diet is the cornerstone of treatment and should be used first-line before drug treatment.
- ☐ Metformin is the drug of choice in obese NIDDM patients; sulphonylureas in non-obese patients.
- ☐ Many NIDDM patients (>30%) will eventually require insulin therapy.

INTRODUCTION

Non-insulin dependent diabetes mellitus (NIDDM), also classified as **Type 2 diabetes** or mature-onset diabetes, is a chronic metabolic disorder associated with significant morbidity and mortality. The condition constitutes 85% of diabetes and affects approximately 2% of the Irish population.^{1,2} For every patient diagnosed with NIDDM another remains undetected.^{3,4} Prevalence is particularly high in the elderly (10%)

Diabetes is the leading cause of adult blindness, end-stage renal disease and non-traumatic amputations.^{7,8,9} In addition it is associated with a two to four fold increase in the risk of cardiovascular disease and stroke, the major causes of premature death in the diabetic population.⁸ The common misconception that NIDDM is a "mild disease" is therefore inappropriate.^{5,10} The potential reduction in life expectancy for a 40-50 year old newly diagnosed patient is 6-10 years.¹¹ **Hyperglycaemia** is the hallmark of NIDDM. The rise in blood sugar is an insidious event which often precedes clinical onset of the disease by many years. Early diagnosis, good glycaemic control and screening for complications of the disease are essential for effective management.¹⁰⁻¹³ Current treatment strategies are aimed at controlling glycaemia by both non-pharmacological and pharmacological interventions.

AETIOLOGY

The pathogenesis of NIDDM is multifactorial involving both genetic (**impaired insulin secretion**) and environmental (**insulin resistance**) factors resulting in overproduction of glucose and inefficient glucose utilisation.^{4,6,8,13-15} Genetic factors include defective pancreatic beta-cell function and abnormal insulin action in target cells. Hyperglycaemia also impairs beta-cell function and insulin action ("**glucotoxicity**").¹³ Environmental influences include obesity, age, lack of physical activity and a high fat diet. Age-related changes in glucose homeostasis start in the third decade.¹⁶ Prenatal nutrition is also thought to determine predisposition to the disease.^{1,6} NIDDM can also occur secondary to other diseases and drugs.¹⁷ **Risk factors** for development of NIDDM are listed in **Table 1**.

DIAGNOSIS

Classical symptoms of NIDDM include **polyuria**, **polydipsia**, **lethargy**, unexplained **weight loss** and **blurred vision**.^{1,4,17,18} Symptoms are often absent and do not manifest until significant disease progression has occurred. At diagnosis, 20-25% of patients have evidence of one or more microvascular complications of the disease (i.e: **retinopathy**, **nephropathy**, **neuropathy**).^{13,18,19} Screening of high-risk groups is therefore essential for early diagnosis. Diagnostic plasma glucose levels for NIDDM are > 7.8mmol/L (**fasting**) and > 11.1 mmol/L (**random**). If classical symptoms are present, only one diagnostic blood glucose is needed. In the absence of clinical features, two diagnostic glucose levels are needed to confirm diagnosis.^{1,10,18} A glucose tolerance test should only be performed if uncertainty exists.^{1,10} Glycosuria is not a sensitive test and should not be used for screening. Glycosylated haemoglobin (HbA_{1c}, HbA_{1c}) levels should be reserved for monitoring of glycaemic control.

TREATMENT

Treatment goals for the management of NIDDM are given in **Table 2**. The aims of treatment are to relieve acute symptoms, improve quality of life and prevent long-term complications without precipitating hypoglycaemia. **Good glycaemic control** is essential to reduce the risk of microvascular disease.^{20,21} Current treatments are aimed at reducing insulin resistance (**diet, weight loss, metformin**), augmentation of endogenous insulin (**sulphonylureas, insulin**) and reduction of post-prandial hyperglycaemia (**acarbose**). Atherogenic risk factors (eg: **smoking, hypertension, hyperlipidaemia**) must also be addressed. **Patient education** and motivation is vital for achieving treatment goals.¹⁸ Personal targets must be agreed with each patient and reviewed at each visit.⁵ Good self-management and monitoring of urine and blood glucose is recommended.

Table 1: Risk factors for NIDDM

Family history of NIDDM
Family history of cardiovascular disease
Obesity (especially central obesity)
Age (> 65 years)
Sedentary lifestyle
High fat diet
Hypertension
Ethnic minority
Gestational diabetes
Impaired glucose tolerance (IGT)
Intrauterine nutrition
Women who have babies >4.1kg
Diseases eg: recurrent infections
Drugs eg: steroids, phenothiazines
Dyslipidaemia

Table 2: Treatment goals for NIDDM

Target	Good	Acceptable	Poor
Blood glucose (mmol/L)			
-fasting	<6.7	<8.0	>8.0
-random	<9.0	<10.0	>10.0
Glycosylated Hb*			
-HbA ₁	<7.5	7.5 - 8.8	>8.8
-HbA _{1c}	<6.0	6.0 - 7.0	>7.0
Body mass index (kg/m ²)			
(BMI)	<25	<25-27	>27
Serum cholesterol (mmol/L)			
-total	<5.2	<6.5	>6.5
-HDL	>1.1	>0.9	<0.9
BP (mm Hg)			
	<140/90	<160/95	>160/95

*Ranges for HbA will vary between labs (Table from Ref. 10).

Non-pharmacological treatment

Diet modification and **weight loss** (in obese) are the key components of diabetes care and should be used as **first-line therapy**.^{10,11,17} The

most common therapeutic error in NIDDM management is prescribing drugs too soon.^{10,11} Over 75% of NIDDM patients are obese and must be encouraged to lose weight.^{5,7} A BMI in the range 20-25kg/m² is ideal.²² Where possible, patients should be referred to a dietitian.^{22,23} Dietary guidelines for NIDDM recommend a high intake of complex carbohydrates (50-60%).²³⁻²⁵ Refined sugars should be restricted. Protein should contribute to 10-20% of energy intake, providing there is no renal disease (<10% if albuminuria).²⁴ Fat should account for less than 30% of calories with no more than 10% coming from saturated fat.²⁴ Artificial sweeteners may be used but there is no rationale for special diabetic foods and beers as they are often high in fat and are expensive.^{11,23} Normal weekly alcohol allowances (male: 21 units, female:14 units) are permitted.²³ Regular **physical exercise** reduces insulin resistance and should be encouraged; exercise should be tailored to the patients medical condition.^{5,7,13} Patients should be advised to **stop smoking**. Adoption of these lifestyle changes will improve insulin sensitivity and lower glycaemia with favourable effects on blood pressure and lipid profile. These recommendations should be re-inforced regularly.

Pharmacological Treatment

If treatment goals are not achieved after a trial of dietary and lifestyle changes, an oral hypoglycaemic should be prescribed. In the UK Prospective Diabetes Study (UKPDS) only 23% of patients allocated to diet alone attained fasting plasma glucose (FPG) levels below 7.8mmol/L.²⁶ Oral hypoglycaemics currently available include the **sulphonylureas, metformin** and **acarbose**. Choice of drug will depend on body weight and clinical status. Metformin is the drug of choice in obese patients, otherwise a

sulphonylurea should be prescribed first-line.¹⁰

SULPHONYLUREAS

The sulphonylureas were first introduced in the 1950s. There are currently six available on the market: **chlorpropamide** and **tolbutamide** (first generation) and **glibenclamide**, **glipizide**, **gliclazide** and **glimepiride** (second generation). They act by stimulating insulin release from pancreatic beta-cells.¹⁰⁻¹⁵ Treatment should start with the lowest dose, increased gradually as needed ("**start low and go slow**"). A mean fasting glucose of 3.3mmol/L and a reduction in HbA_{1c} levels of 1-2% can be expected.^{5,13-15} In terms of efficacy they are all comparable although they differ in their pharmacokinetics²⁹ (**Table 3**). Generic preparations should be prescribed where available to reduce prescribing costs.³⁰ Many patients do not respond (primary failure) and a further 5-10% per year who do respond later become resistant (secondary failure).¹⁰⁻¹⁴

The main **adverse effects** are weight gain and hypoglycaemia. Mean weight gain is 3.5-4.0 kg. Hypoglycaemia is common and can be severe and occasionally fatal. Hypoglycaemia is more likely with the longer-acting drugs **chlorpropamide** and **glibenclamide**. In the UKPDS hypoglycaemia was more common with glibenclamide than chlorpropamide, due to its active metabolites.²⁷ Both drugs should be **avoided** in the elderly and in renal impairment.³⁰⁻³⁵ **Glipizide** and **gliclazide** are preferable in these patient groups. **Tolbutamide** is seldom used as the frequency of dosing and large tablet size compromise compliance.³⁴ All patients must be counselled as to the warning signs of hypoglycaemia and its management.²³ Sensitivity reactions eg: rashes, jaundice have also been reported; other side effects are rare. Chlorpropamide can cause disulfiram-like reactions and hyponatraemia. Although it is the cheapest agent, chlorpropamide does **not** tend to be used in clinical practice.

Contra-indications include pregnancy, breast-feeding, post-surgery and porphyria.^{5,36} Dosage reduction may be required in liver impairment.³⁶ Important **drug-interactions** include warfarin and NSAIDs which can displace sulphonylureas from protein binding sites thereby enhancing hypoglycaemia. Other significant interactions include antibiotics and antifungals. Alcohol may potentiate drug-induced hypoglycaemia.³⁶

Table 3: Properties of Oral Antidiabetics in Current Use

Drug	Duration of action (hrs)	Starting dose (mg)	Frequency of dosing	Maximum total daily dose (mg)	Elimination route	Cost ** (£-Irish)
Chlorpropamide	36 - 72	100	1	500	Renal	0.62 - 2.74
Tolbutamide	6 - 8	500	2 - 3	2000	Hepatic	1.03 - 4.12
Glibenclamide	16 - 24*	2.5	1 - 2	15	Hepatic*	1.75 - 8.70
Glipizide	12 - 18	2.5	1 - 2	40	Hepatic	1.01 - 16.12
Gliclazide	12 - 18	40	1 - 2	320	Hepatic	1.68 - 13.44
Glimepiride	18 - 24	1	1 - 2	8	Hepatic	3.64 - 20.50
Metformin	12	500	2 - 3	2550	Renal	1.51 - 3.76
Acarbose	n/a	25	3	600	Faeces	6.95 - 33.04

* but active metabolites ** Cost for 28 days treatment Mims Dec '97

METFORMIN

Metformin acts primarily by reducing hepatic glucose production and increasing peripheral glucose uptake. Insulin production is not affected and so hypoglycaemia as a side effect does not occur.^{5,37-9} Metformin does not cause weight gain and so is the treatment of choice in obese patients; modest weight loss has been reported in some patients.^{13,40} Metformin is equally effective in the non-obese. It induces comparable effects on FPG and HbA_{1c} levels to the sulphonylureas.^{15,27,34,38} Metformin has a favourable effect on plasma lipids and the haemostatic mechanism.^{5,7,40}

Adverse effects are mainly gastrointestinal and include nausea, vomiting, abdominal cramps, bloating, diarrhoea and metallic taste. Diarrhoea occurs in up to 20% of cases.^{5,7,19,34} Effects can be limited by

taking doses with food and starting with low doses, gradually increasing over several weeks.^{18,37} The maximum daily dose is 2550mg/day. Malabsorption of vitamin B₁₂ has been described.^{37,41} Lactic acidosis is a rare (8 per 100,000 treatment years) but serious side effect with a 30% mortality rate.^{5,13,17} Metformin is **contra-indicated** in renal impairment and liver failure and should be used with caution in cardiac disease.¹⁰ It is therefore often unsuitable in the elderly.³⁷ Regular renal and hepatic monitoring is essential. **Drug interactions** involve drugs also excreted by the renal tubular pathway (e.g: amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, vancomycin, trimethoprim)³⁷ Cimetidine may increase metformin levels by up to 50%⁴¹.

ACARBOSE

Acarbose may be used in patients who do not respond to diet alone or cannot tolerate conventional hypoglycaemics. It may also be used as an adjunct to other drugs.⁴² Acarbose inhibits alpha-glucosidase enzymes responsible for polysaccharide digestion in the small intestine thereby reducing glucose absorption.⁴²⁻³ Taken at the beginning of a meal it reduces post-prandial hyperglycaemia by up to 3 mmol/L. It is less potent than other antidiabetic agents, lowering HbA levels by 1% and FPG levels by 1mmol/L.^{5,14} Acarbose does not cause weight gain or hypoglycaemia.

The major **adverse effect** of acarbose is GI intolerance which can occur in up to 60% of cases.⁴²⁻⁷ Flatulence, bloating, abdominal pain and diarrhoea are common and are due to undigested carbohydrate in the bowel. Starting with a low dose (50mg bd) and increasing gradually to the maximum dose (200mg tds) will minimise GI side effects.^{11,42} Only 1% of acarbose is absorbed systemically and so other adverse effects are rare. Elevated liver transaminases have been reported.⁴⁵ Acarbose is **contra-indicated** in malabsorption syndromes, IBD, intestinal obstruction and hepatic impairment. It should also be avoided in pregnancy, lactation and severe renal impairment.^{42,47}

COMBINATION THERAPY

When patients become refractory to monotherapy, combination therapy is indicated.¹⁰⁻¹⁸ The most common combination used is metformin and a sulphonylurea; up to 50% of patients uncontrolled with high dose sulphonylureas will achieve good glycaemic control with the addition of metformin.^{5,13,14,48} Combined use of two sulphonylureas is inappropriate. Metformin and acarbose are seldom used together due to the likelihood of GI intolerance. Regimens of three or more drugs are not recommended. When both dietary and oral combination therapy fails insulin is indicated.

INSULIN

It has been estimated that 30% of NIDDM patients will eventually require insulin.⁷ Introduction of insulin as an intermediate formulation (isophane, lente) in the evening with a daytime sulphonylurea or metformin is often effective.¹¹ This combination allows glycaemic control at lower insulin doses than insulin alone. If post-prandial hyperglycaemia occurs a pre-meal short-acting insulin may be needed.^{5,13} Insulin is anabolic and causes significant weight gain (4.2-13kg).^{12,49} Insulin is used **first-line** in severe insulin deficiency and when oral antidiabetics are contra-indicated e.g: pregnancy. Patients requiring insulin should be referred to a specialised unit.

GUAR GUAM

Guar is a dietary fibre extract from cluster bean, licensed for use in NIDDM. On mixing with water it forms a viscous gel which when taken orally impedes glucose absorption and can reduce appetite. Patient acceptability is a problem. Adverse effects include GI discomfort, flatulence, nausea and diarrhoea.^{5,11} The use of this product is not recommended.³⁴

PREGNANCY

Oral hypoglycaemics are contra-indicated in pregnancy; NIDDM in pregnancy should be managed with insulin under specialist care.⁵⁰⁻⁵²

COMPLICATONS

Poor glycaemic control is associated with development of **microvascular** (retinopathy, nephropathy, neuropathy) and **macrovascular** (cardiovascular disease) complications. Regular screening is essential. Retinal and foot examinations should be performed on an annual basis; patients should be referred to ophthalmologists and chiropodists if possible. Urine should be checked routinely for protein. Dietitians should be readily accessible. Other atherogenic risk factors should be managed effectively with lifestyle changes and drug therapy as appropriate. Caution is required when prescribing antihypertensives. Thiazides and beta-blockers are diabetogenic although should not be a problem at low doses. ACE inhibitors are nephroprotective and so are the agent of choice in patients with hypertension and/or nephropathy. Hyperlipidaemia may require lipid lowering treatment. Shared care initiatives should be developed between GPs and local consultants to provide high quality care for diabetic patients.

The Irish Diabetic Association (IDA) provides an information pack for diabetics and ongoing patient education and support. Details available from the IDA at: 76 Lower Gardiner St, Dublin 1: Tel (01) - 8363022

References

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Additional references (21-52) available on request.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet for specific information on drug use.