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UPDATE ON TYPE 2 DIABETES MELLITUS (DM)

- ☞ Type 2 DM is triggered by age, obesity and lack of exercise in genetically predisposed persons
- ☞ Hyperglycaemia should be managed by lifestyle interventions and step-by-step pharmacotherapy
- ☞ Metformin remains the most effective monotherapy, especially in obese patients
- ☞ DM-related vascular complications should be proactively managed from diagnosis

INTRODUCTION

The World Health Organisation (WHO) defines diabetes mellitus (DM) as a metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia, with disturbances of carbohydrates, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.¹ It is estimated that 85-90% of diabetic individuals have type 2 DM,² which results from insulin resistance; most of the remainder have type 1 DM, usually due to immune-mediated destruction of the pancreatic islet β -cells, resulting in insulin deficiency.³ The prevalence of type 2 DM has greatly increased in recent years with some countries recording a population prevalence of up to 6%.⁴ Diabetes-related complications are a major cause of disability and suffering; DM is reported to be a major cause of renal failure, limb amputations, new-onset blindness and a major risk factor for heart disease and stroke.² DM also causes a huge financial burden to health services, using up to 10% of national health budgets.² In recent years, many new anti-diabetic agents have been developed. In addition, the National Diabetes Working Group in Ireland has recommended a model of patient care that places greater emphasis on managing the diabetes patient, with the aim of reducing and/or preventing the complications of the disease.⁵

This bulletin will focus on the contemporary management of patients with type 2 diabetes mellitus.

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

The current internationally accepted WHO diagnostic criteria for DM are: fasting plasma glucose concentration > 7.0 mmol/l and 2-hour post-glucose load concentration > 11.1 mmol/l.⁵ Although anyone can develop type 2 DM, a positive family history confers a 2.4 fold increased risk, and monozygotic twins show higher concordance rates compared with dizygotic twins (35-58% vs. 17-20%) confirming the importance of genetic inheritance.⁴ However, overweight / obesity, lack of physical exercise and increasing age are thought to be the triggering pathogenic factors for most type 2 DM cases and these appear to be contributing to the increasing prevalence of the disease globally.

Insulin is the key hormone for regulation of blood glucose. Normoglycaemia is maintained by adaptation of the pancreatic islet β -cells; when insulin action reduces there is an up-regulation of insulin secretion, and vice versa. Obesity results in insulin resistance which interferes with insulin's action on glucose uptake, and also its effects on fatty acids and protein metabolism.² The reason for this is not fully understood but it is thought to be related to release of inflammatory cytokines, free fatty acids and other unknown genetically-determined factors. Initially, the body compensates by increasing insulin secretion from the β -cells.⁴ However, as part of insulin resistance there is usually a mild increase in blood glucose and fatty acids, which, over time, leads to glucotoxicity- and lipotoxicity-related β -cell dysfunction and apoptosis (cell death).² **Therefore, sustained insulin resistance may lead to type 2 DM, which in turn may lead to progressive pancreatic β -cell failure.**

In summary: Insulin resistance plays a fundamental role in the pathogenesis of type 2 DM, therefore it is vital that management includes interventions to improve tissue insulin sensitivity.

MANAGEMENT GOALS IN TYPE 2 DIABETES MELLITUS

The goals of management are to normalise blood glucose levels, improve tissue insulin sensitivity and prevent / delay the development of DM-related vascular complications. Glycosylated haemoglobin (HbA1c) is used as a principal measure for the effectiveness of glycaemic control because studies such as the UK prospective diabetes study (UKPDS)⁶ have shown that HbA1c levels can predict the risk of development of DM-related complications. In the UKPDS each 1% reduction in mean HbA1c was associated with a 21% risk reduction for any diabetes-related endpoint: 21% reduction for DM-related death; 14% reduction for myocardial infarction and 37% reduction for microvascular complications.^{6,7}

1. MANAGEMENT OF HYPERGLYCAEMIA

The main modalities of hyperglycaemia management are lifestyle interventions and pharmacotherapy.

Lifestyle Interventions

Exercise is considered an important part of treatment for patients with type 2 DM. A recent Cochrane review showed that **exercise significantly improved glycaemic control and reduced plasma triglycerides and visceral adipose tissue even without weight loss.**⁷ In order to improve compliance, the exercise intervention should start at low intensity (e.g. walking), gradually increasing in intensity so that the regimen can be incorporated into the person's daily routine on a longterm basis.

Dietary Advice. **There is strong evidence that progression from hyperglycaemia to type 2 DM can be prevented or at least delayed by dietary effort;** a US diabetes prevention programme showed a 58% reduction in the incidence of DM when participants were treated with lifestyle intervention, including diet, compared with a 31% reduction in persons treated with metformin.⁸ However, there are relatively few data evaluating the effect of dietary intervention in patients with type 2 DM; most

of the published studies have used varying types of dietary regimens, making interpretation of the data difficult. However, a recent review has reported that the addition of exercise to dietary advice improves metabolic control, as estimated by HbA1c, at 6 and 12 months in people with type 2 DM.⁸ An ongoing longterm study of US overweight type 2 DM patients (aged 45 – 75 years) should provide definitive data in this regard.⁸

Pharmacotherapeutic Interventions: Oral Therapies

Studies have shown that the development of microvascular disease in type 2 DM is reduced when glycaemic control is improved; therefore the goal of treatment is to keep glycaemic control as tight as possible (ideally a maximum level of HbA1c of 6%, the upper limit of normal in most laboratories)⁹ without running the risk of hypoglycaemia.¹⁰ A recently issued consensus guideline from the American Diabetes Association and European Association for the Study of Diabetes (EASD) has stated that **a HbA1c of > 7% should signal the need to initiate / intensify therapy in order to restore glucose control as near as possible to the non-diabetic state.**⁹ An individual's treatment regimen needs to be frequently monitored because of the progressive decline in β -cell function; the National Institute for Health and Clinical Excellence (NICE) has recommended testing treatment effectiveness in type 2 DM at 2 – 6 monthly intervals.¹¹

Table 1 outlines currently available antidiabetic agents used to manage hyperglycaemia in type 2 DM.

Table 1: Pharmacotherapeutic options for management of Type 2 Diabetes Mellitus⁹⁻¹³

Drug / Class	Mode of Action	% Drop in HbA1c	Average Monthly* Cost (€) / patient
Metformin	Reduces liver glucose production	1.5 +	3.65
Sulfonylureas	Insulin secretagogue	1.5 +	7.70 – 12.76
Acarbose	Impedes absorption of sugars	0.4 – 0.8	17.67
Thiazolidinediones	Insulin sensitiser	0.5 – 1.5	60.99 – 61.73
Meglitinides	Insulin secretagogue	0.6 – 1.5	32.67 – 48.89
DPP-IV inhibitors	Enhance incretin action	0.68**	not available
Exenatide (s/c)	Incretin mimetic	0.6 – 0.9**	103.96***
Inhaled insulin	Insulin replacement	-	79.74***
[Insulin +/- analogues	Insulin replacement]	-	-

*based on range of class costs from GMS database, January 2007; ** limited data from clinical trials which may have included combination therapy:

*** pack costs from GMS database, May 2007

Biguanides. There is widespread experience with the use of the biguanide **metformin** and it **is still regarded as the drug of first choice in type 2 DM patients, especially those who are overweight.**^{10,11} In the UKPDS, metformin reduced diabetes-related deaths by 43% over a 10-year follow-up.⁶ As it acts at the liver to lower production of glucose and reduce glycogenolysis, it has no effect on insulin release, therefore, it is not associated with hypoglycaemia. It also delays glucose absorption and stimulates intracellular glycogen synthesis.¹⁴ It does not cause weight gain, and therefore is suitable for patients with BMI >25.¹¹ Doses of up to 3g daily are authorised for use.¹⁴ **A recent Cochrane review concluded that no other antidiabetic agent showed more benefit in terms of glycaemia control, body weight or lipids than metformin in type 2 DM.**¹⁵

Adverse Effects. Gastrointestinal (GI) upset has been reported in up to 50% of patients¹³ and may be a cause for discontinuing use, especially if the patient is not forewarned. Metformin should be taken with or after food. **Reducing the dose at which GI upset was reported frequently reduces the GI toxicity and the drug may be slowly titrated upwards again without recurrence.**¹⁴ Lactic acidosis is extremely rare (estimated to occur in 1–5: 100,000 patients): predisposing factors include hypoxic states, (acute MI, serious infection or uncontrolled heart failure) or renal or hepatic insufficiency.¹⁴ Patients with any of these complaints are not suitable for treatment with metformin.

Sulfonylureas. These act to stimulate insulin secretion; therefore they are most effective in newly or recently diagnosed patients who still have reasonable β -cell function. In the UKPDS, they were shown to reduce diabetes-related deaths by 36%.⁶ **It is estimated that monotherapy is effective in 75-80% of type 2 DM patients, with treatment “failure” occurring in 5-10% of patients / year.**¹⁶

Adverse Effects. There is a risk of hypoglycaemia, especially in older patients, due to their mode of action.¹¹ Therefore the shorter acting agents (e.g. gliclazide, glipizide) are preferred to the older long-acting agents, no longer in use. **Patients should be instructed on how to diagnose and manage hypoglycaemic episodes.**¹¹ They usually also cause weight gain, therefore **sulfonylureas are not suitable for overweight patients as monotherapy.**

α -Glucosidase inhibitors. Acarbose delays the digestion and absorption of starch and sucrose by competitively inhibiting the intestinal enzymes (α -glucosidases) involved in the degradation of disaccharides, oligosaccharides and polysaccharides. Although the reduction in HbA1c is modest, it does not cause weight gain.¹⁰ Use over 3 years was reported to improve glycaemic control but the study size was insufficient to provide outcome data.¹¹ It usually is administered 3 times daily to sustain the effect.

Adverse Effects. **GI toxicity is the main dose-limiting side effect (>10% users)** including flatulence, abdominal bloating and pain,¹⁷ due to intra-colonic fermentation of the unabsorbed sugars.¹⁶ These effects frequently result in discontinuation although they tend to decrease with time.¹⁸

Meglitinides. These agents (repaglinide and nateglinide) act as postprandial glucose regulators. They bind to specific sites within the β -cells in the pancreas to increase insulin secretion. They have a rapid onset of effect, therefore they need to be administered shortly (1 – 30 minutes) before a meal.^{19,20} They have a short duration of action, requiring multiple daily dosing.²¹ Some experts suggest that **meglitinides may play a useful role in patients with irregular meal times (e.g. shift workers).**¹¹ Longterm outcome data are not available.¹¹

Adverse Effects. These drugs may cause abdominal pain and nausea, although the GI upset is less than that reported with metformin.²¹ A recent Cochrane review noted that weight gain was generally greater in those treated with meglitinides compared with metformin (up to 3 kg in 3 months).²¹ In addition, because of their mode of action, **they may induce hypoglycaemia and patients should be made aware of how to diagnose and treat such episodes.**¹¹ These drugs are metabolised by the cytochrome P450 system and therefore there is a risk of drug interactions with concomitant drugs that are also cleared by the cytochrome P450 system. Full details of potentially interacting drugs are listed in the relevant Summaries of Product Characteristics (SPCs).^{19,20}

Thiazolidinediones. These agents are agonists of the peroxisome proliferator activated receptor gamma (PPAR γ); they produce their effect by reducing insulin resistance in adipose tissue, muscle and liver.¹⁶ **Studies have shown it may take up to 12 weeks to get the full effect.** A recently published study reported that rosiglitazone showed a greater durability of treatment (15% cumulative risk of monotherapy failure at 5 years) compared with metformin (21%) and the sulfonylurea glyburide (34%).²² However, rosiglitazone was associated with more weight gain and oedema, and higher levels of LDL compared with metformin and glyburide; an unexpected finding of a higher rate of upper limb fractures in female participants was also reported in the rosiglitazone group compared with the other treatment groups.

Adverse Effects. Both pioglitazone and rosiglitazone have been associated with weight gain and oedema, which may result in congestive heart failure. **Their use is contraindicated in heart failure.**^{23,24} The original agent in this class was withdrawn from the market due to hepatotoxicity, but this has not been reported as a significant problem with the currently available agents; however **they should be used with caution in hepatic dysfunction.**^{23,24} **Rosiglitazone has been reported to cause hypercholesterolaemia;**²³ a recently published meta-analysis suggested that rosiglitazone was associated with an increased risk of myocardial infarction and cardiovascular death.²⁵ This analysis has been controversial.²⁶ However, the results suggest that **longterm use of rosiglitazone may not have a beneficial effect in preventing cardiovascular disease (CVD);**²⁷ these results have been supported by a recent Cochrane review, which reported that outcomes including mortality, morbidity or quality of life were not positively influenced by rosiglitazone.²⁸ In trials of up to 2 years, pioglitazone reduced total plasma triglycerides and free fatty acids and increased HDL cholesterol compared with placebo, metformin or gliclazide.²⁴ However, in a 3-year follow-up study pioglitazone showed a non-significant reduction in the primary endpoint - all cause mortality, non-fatal MI, stroke, acute coronary syndrome, leg amputation, coronary or leg revascularisation compared with placebo, although some secondary CVD outcomes were significantly reduced.²⁹ There was an increase in heart failure in the pioglitazone group.³⁰ Further data are needed to evaluate the longterm efficacy and safety of thiazolidinediones.

Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors. DPP-IV inhibitors are a new class of oral antidiabetic agent that work by enhancing the levels of active incretin hormones.³¹ Endogenous incretins are released by the intestine throughout the day and levels are increased in response to a meal (i.e. hyperglycaemia);³² however, they have a very short half-life, which can be prolonged by inhibition of DPP-IV, the enzyme responsible for their degradation. **DPP-IV inhibitors are thought to act by enhancing insulin and reducing glucagon secretions thereby reducing blood glucose levels.** They are also reported to slow gastric emptying and increase satiety.³³ The first drug licensed in this class is sitagliptin, which was recently approved for combination therapy only (see table 2).

Adverse Effects. In clinical trials, lasting up to one year, reported adverse effects included GI upset, oedema, and hypoglycaemia (when used with sulfonylureas). It does not appear to cause weight gain.³¹ The combination of sitagliptin / metformin appeared to be better tolerated (14.5% incidence of adverse effects) compared with a sulfonylurea / metformin (30.3% incidence). As the drug has only recently come to the market further postmarketing safety and longterm outcome data are awaited.

Pharmacotherapeutic Interventions: Parenteral Therapies

In certain patients, with type 2 DM a combination of oral antidiabetic agents and insulin, or insulin monotherapy may be considered more appropriate to achieve optimum control.^{11,18} Insulin analogues were dealt with in a previous NMIC bulletin (2003; Vol 9:4).³⁴ There are two recently authorised parenteral preparations that may be used in type 2 DM.

Exenatide. This synthetic peptide drug is structurally and functionally similar to the incretin hormone glucagon-like peptide-1 (GLP-1). **Its actions are similar i.e. increasing the secretion of insulin and reducing secretion of glucagons, in response to hyperglycaemia.**³⁵ It also delays gastric emptying. As it is a peptide it must be administered parenterally; the licensed route is by subcutaneous injection twice daily.

Adverse Effects. Data come primarily from clinical trials. GI upset (including nausea, vomiting and diarrhoea) was recorded in up to 50% of subjects.³⁶ **Hypoglycaemia also occurred in >10% of subjects when combined with a sulfonylurea; therefore the dose of the sulfonylurea should be reduced if combined with this agent.** Anti-exenatide antibodies were noted in 38% during the clinical trials; this appeared to affect the glycaemic response in 3% of patients. As the drug has only recently come to the market further postmarketing safety and longterm outcome data are awaited.

Inhaled Insulin. This novel delivery of insulin produces a more rapid onset of glucose lowering activity (within 10-20 minutes) compared with subcutaneously administered soluble insulin, and a longer duration of action (6 hours) than the fast-acting insulin analogues.³⁷ It is licensed for use as monotherapy or in combination with oral antidiabetic agents in type 2 DM.

Adverse Effects. The most frequently reported toxicities from clinical trials were hypoglycaemia and cough (onset in seconds – minutes after use). Active smoking is known to increase the rate and extent of absorption and therefore increase the risk of hypoglycaemia. **Smoking is contraindicated during, and for at least 6 months before, initiating therapy; inhaled insulin must be discontinued immediately if smoking is resumed.**³⁷ In addition, a small decline in FEV₁ (30-40ml), which returns to baseline after cessation of therapy, has been reported with use of inhaled insulin over time.³⁸ **All patients must have pulmonary function tests undertaken prior to initiation of therapy and repeated at regular intervals to monitor possible decline in function. Inhaled insulin should not be used in patients with lung disease (COPD or asthma).**³⁷ As the drug has only recently come to the market further postmarketing safety and longterm outcome data are awaited.

Summary: Table 2 outlines the current approach to the management of type 2 DM.

Table 2: Stepwise management of hyperglycaemia in Type 2 Diabetes Mellitus.^{10,12,13}

HbA1c > 7% ↓	Lifestyle counselling and monotherapy with metformin (sulfonylurea if not overweight); repaglinide and acarbose are also authorised for monotherapy; thiazolidinediones may be used as monotherapy only in overweight patients unable to take metformin because of contraindications or intolerance
HbA1c remains > 7% ↓	Dual therapy (metformin and/or sulfonylurea and/or thiazolidinedione); meglitinides and acarbose are also authorised for combination therapy; sitagliptin and exenatide authorised for second-line therapy only in specific patients
HbA1c remains > 7% ↓	Triple therapy (metformin and/ or sulfonylurea and/or thiazolidinedione and/or meglitinides and / or acarbose) OR consider insulin with dual therapy**
HbA1c remains > 7%	Insulin +/- oral antidiabetic therapy regimen**

**Specialist input recommended if insulin therapy (including analogues / inhaled insulin) required

All drugs are authorised as adjuncts to lifestyle counselling including dietary advice and exercise. The prescriber should take the individual patient's condition into account, including weight, concomitant diseases and potential for drug interactions with concurrent drugs before deciding on a suitable treatment regimen. **Many of the newer agents are less effective at lowering glucose (see Table 1) compared with the older drugs, and data on longterm benefits and safety are not available.** Full information on each drug is found in the relevant SPCs.¹²

2. MANAGEMENT OF DIABETES-RELATED VASCULAR COMPLICATIONS

Cardiovascular disease (CVD) is the leading cause of mortality in type 2 DM, accounting for > 70% of deaths due mostly to acute MI, congestive heart failure and stroke.³⁰ CVD also produces significant morbidity in type 2 DM, due to the propensity to develop premature or diffuse atherosclerotic disease, structural and functional abnormalities of the microvasculature, autonomic dysfunction and intrinsic myocardial dysfunction.³⁹ As a result **it is calculated that the risk of CVD in diabetes patients without established disease is similar to the risk in non-diabetes patients with a history of MI.**⁴⁰

Hypertension

It is estimated that about 80% of patients with type 2 DM have hypertension (defined as blood pressure (BP) >140/90mmHg); in fact, hypertension may precede development of type 2 DM.⁴⁰ The UKPDS noted that tighter control of BP in diabetes reduced morbidity and mortality – a final mean difference of 10/5mmHg was associated with a 24% reduction in the risk of any DM-related endpoint.⁴⁰ In patients who do not have vascular disease, rigid control of hypertension has been reported to reduce both the macrovascular and microvascular complications of DM, especially stroke.³⁰ **Most guidelines now recommend a target BP of <130/80mmHg for diabetes patients in order to optimally preserve renal function and reduce CVD.**

Pharmacotherapy. Consensus regarding optimal first-line monotherapy is lacking but available evidence supports the use of several drugs. The **ACE inhibitors / Angiotensin Receptor Blockers (ARBs)** are generally the preferred first-line agents for hypertension in diabetes patients, especially in the presence of microalbuminuria, since both classes have been shown to delay deterioration in renal function.³⁹ Renal function must be carefully monitored early in treatment to rule out unrecognised bilateral renal artery stenosis.⁴⁰ The ASCOT study showed that the **calcium channel blocker**, amlodipine, used in combination with perindopril, was effective in reducing BP and CVD events in diabetes patients.⁴¹ **Diuretics** may worsen insulin resistance particularly at higher doses but may be used effectively at low dose, especially in combination with other agents such as ACE inhibitors or ARBs.^{39,40} **Some β-blockers** worsen glycaemia control. In type 2 DM, β-blockers should only be used for BP management after the above drug classes have been tried; combination with thiazides in particular should be avoided.⁴⁰

Summary. Despite the critical importance of tight BP control in diabetes patients, under-treatment and sub-optimal control of hypertension continue to cause problems for patients. It should be remembered that **many patients require a combination of at least three antihypertensive drugs to achieve the recommended BP target of <130/80mmHg in diabetes.**⁴² Regular monitoring of BP is vital in type 2 DM patients; **referral to a specialist unit** should be considered if hypertension remains refractory despite the use of three or more drugs, where there are therapeutic problems (e.g. intolerance or contraindications to drugs) or in the presence of accelerated or severe hypertension.⁴⁰

Other Risk Factors for CVD

In addition to tight blood glucose control and intensive control of hypertension, the following issues also need to be addressed in type 2 diabetes patients:

Dyslipidaemia. Studies have shown a three times higher incidence of dyslipidaemia in type 2 DM compared with the non-diabetic population, (females > males).⁴³ Typically, there is moderate hypertriglyceridaemia, and low HDL. LDL levels may be within the normal range, but are composed of small dense particles, which are associated with increased atherogenicity. The greatest evidence for benefit is seen with statins. The European Society of Cardiology (ESC) and the EASD have recommended that **statin therapy should be considered in type 2 DM adults without CVD if total cholesterol is >3.5mmol/L, to achieve a target reduction of 30-40% in LDL.**⁴³ **In DM patients with CVD, statin therapy should be initiated regardless of baseline LDL cholesterol, with a treatment goal of LDL of <2.0mmol/L.**

Thrombosis. Because DM is associated with an increased risk of developing CVD, patients with type 2 DM should be considered for aspirin therapy, even in the absence of overt disease. Some studies have suggested that diabetes patients may have a slightly lower than expected anti-stroke benefit with aspirin compared with non-diabetes patients. Therefore experts have recommended that the **optimal effective aspirin dose is 75-150mg daily, titrated on an individual basis.**⁴⁴

Coronary Artery Disease (CAD). Patients with type 2 DM, over the age of 40 years should be considered for secondary prevention therapy of CVD, even in the absence of overt CAD.⁴³ Secondary prevention has been reviewed in a previous NMIC bulletin (2002; Vol 8:6).⁴⁵ It is important to note that **ACE inhibitors / ARBs are associated not only with increased survival in patients with CAD but have been shown to prevent or delay the occurrence of microalbuminuria in diabetes patients, especially those with hypertension.**⁴³

Lifestyle Factors. Smoking is one of the risk factors for macrovascular disease in diabetes.³⁰ Therefore type 2 DM patients who smoke should be counselled on **smoking cessation**; treatment with nicotine replacement therapy may be required and should be monitored. **Regular physical activity** is also recommended, as a high level of leisure-type physical activity has been associated with a 33% drop in fatal CVD while moderate activity showed a 17% drop compared with the most sedentary group.⁴³ As overweight and/or obesity is an independent risk factor for CVD **advice on a suitable dietary regimen and/or weight reduction** should also be included. The need for adjunctive pharmacotherapy for weight reduction should be made on an individual patient basis.⁴⁵ (The next NMIC bulletin will review the management of obesity)

SUMMARY

Type 2 DM is thought to occur from a combination of genetic predisposition, unhealthy diet, physical inactivity and increasing weight, with a central distribution, resulting in complex pathophysiological processes. It is associated with the development of specific longterm organ damage due to macrovascular complications (including cardiovascular, cerebrovascular and peripheral artery disease) and microvascular disease, resulting in renal, neurological and eye damage.⁴³ Studies have shown that **tight glycaemic control, active management of the risk factors for CVD and early treatment of vascular complications result in reduced mortality and morbidity.**³⁰ Management of type 2 DM should involve a multidisciplinary approach to include lifestyle interventions, appropriate glycaemic control (as measured by HbA1c) and proactive management to prevent / delay the onset or deterioration of CVD.

List of references available on request. Date of preparation: July 2007. 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 individual SPC for full information on a drug.

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