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Chapter 1

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

May 2008 exam: A 62-year-old man is investigated for hypertension and proximal myopathy. On examination he is noted to have abdominal striae. Which one of the following is most associated with ectopic ACTH secretion?
 Small cell lung cancer

Disorder Investigation of choice Cushing Overnight Dexamethasone Test Cushing- vs. Pseudo-cushing Insulin Stress Test Addison Short Synacthen Test Pheochromocytoma 24H Urinary metanephrines Acromegaly Oral Glucose Tolerance Test

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Diabetology

Pancreatic Hormones
• Islet A cells produce glucagon • Islet beta cells produce:

1. insulin
2. C peptide
3. pro-insulin
4. amylin
5. GABA • Islet D cells produce somatostatin • F cells produce pancreatic polypeptide

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Glucose transporters Glucose entrance to the cells • To intestinal epithelial cells and proximal renal tubular cells → via Sodium/Glucose cotransporter (SGLT) • To all other cells of the body → Glucose Transporters (GLUTs).

Sodium/glucose cotransporter (SGLT) • Glucose uptake into the enterocyte from the lumen of the GI tract occurs primarily via the sodium-dependent SGLT-1 secondary active transport mechanism. SGLT-1 is a transporter found predominantly in the gut, and is responsible for glucose absorption. The Na+-glucose cotransporter also transports galactose. Thus, when the cotransporter is congenitally defective, the resulting glucose and galactose malabsorption causes

severe diarrhea that can be fatal if glucose and galactose are not removed from the diet. • Function transport glucose actively across lumen against concentration gradient energy provided by transport of sodium down its concentration gradient

• location small intestine (SGLT1) 2:1 Na+:Glu proximal tubule of nephron (SGLT2) 1:1 Na+:Glu • Glucose exit from the enterocyte into the extracellular fluid occurs by facilitated diffusion and is mediated by the membrane transporter, Glut-2.

Glucose Transporters (GLUTs). GLUT-1 • function basal glucose uptake (GLUT1 and GLUT3 continually transport glucose into cells at an essentially constant rate.) high affinity transporters saturated at normal blood glucose levels ensures glucose entry to cells • location wide distribution in tissues in the body (brain, erythrocytes, endothelial cells, cornea etc.) especially expressed in cells with barrier functions, such as Blood- Brain barrier, blood-retinal barrier, blood placental barrier, blood testes barrier most importantly it is expressed in erythrocytes. GLUT-2 • GLuT 2 is a glucose transporter expressed in pancreatic beta cells. • It is a fundamental part of the glucose sensing apparatus in the pancreatic beta cells and helps trigger insulin release in response to increasing glucose concentrations in the extracellular fluid. • GluT 2 is also expressed in hepatocytes and may act as a glucose sensor in the portal vein system. • It may have a role in regulating glucagon secretion and feeding behaviour. • function low affinity glucose uptake (high-capacity but a low affinity transporter) in the fasting state glucose does not enter cells mediates glucose surplus storage in liver when blood glucose levels rise facilitates insulin release in β-cells • location hepatocytes pancreatic β-cells kidney small intestines In healthy individuals, which glucose transporter is required for triggering insulin secretion in response to elevated blood glucose concentration? GluT 2

GLUT-3 • function high affinity glucose uptake glucose preferentially accessed by neurons in low-glucose states • location brain neurons

GLUT-4 • GLUT-4 is the only glucose transporter that is responsive to circulating insulin levels. ↑plasma glucose concentration ↑circulating insulin ↑expression of GLUT-4 ↑glucose transport into the cell. The other types of glucose receptors (GLUT-1,2,3,&5) are not responsive to circulating insulin levels exogenous insulin in the treatment of diabetes mellitus results in increased glucose uptake via the GLUT-4 transporter. This high-affinity glucose transporter plays a crucial role in avoiding postprandial hyperglycemia, since insulin secreted by the pancreatic beta cells promotes glucose uptake into myocytes. • function insulin-controlled uptake of glucose basal level of glucose intake without insulin presence of insulin ↑ translocation of transporters to the cell membrane ↑↑↑ glucose uptake also stimulated by exercise • location adipocytes myocytes cardiomyocytes

Which glucose transporter is responsible for assisting glucose across the plasma membrane in myocytes? □ GLUT 4

Glut-5
• located on the apical portion of the enterocyte
• function: entry of fructose into the cell.

• GLUT-1 = BBB (Blood- Brain barrier) • GLUT-3 = "Brain"

Glycaemic index (GI) Definition • The glycaemic index (GI) describes the capacity of a food to raise blood glucose compared with glucose in normal glucose-tolerant individuals.
Classification • Carbohydrates can be scored from 0 to 100 where glucose has a GI of 100. • High GI index foods have a value of 70 or above, medium 56-69 and low <55. • Apples, peaches oranges and even chocolate are considered low GI (less than 55).
• through different preparation, the GI can alter – mashed potatoes (70) and baked potatoes (85) have a high GI (above 70) whilst boiled potatoes have a moderate GI of 58.
• Foods only appear if they contain carbohydrate hence meats, eggs and fish do not appear in the GI index.
• Generally, the lower the GI index the 'better' the carbohydrate.

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Classification Examples High GI White rice (87), baked potato (85), white bread (70) Medium GI Couscous (65), boiled new potato (62), digestive biscuit (59), brown rice (58) Low GI Fruit and vegetables, peanuts

The risk of foods with a high GI
• may be associated with an increased risk of obesity
• the post-prandial hyperglycaemia associated with such foods may also increase the risk of type 2 diabetes mellitus.

Metabolic syndrome

Features of the metabolic syndrome are: • Diabetes or pre-diabetes. • Hypertension • Central adiposity • High triglycerides or low HDL cholesterol

Definition
• the co-occurrence of metabolic risk factors for both type 2 diabetes and cardiovascular disease (CVD) (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension).

Pathophysiology • the key pathophysiological factor is insulin resistance.

Diagnostic criteria • WHO criteria (1999): Presence of insulin resistance (type 2 diabetes mellitus , impaired glucose tolerance, or impaired fasting glucose), Plus two of the following:

1. blood pressure: > 140/90 mmHg
2. dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
3. central obesity: waist: hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
4. microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin: creatinine ratio > 30 mg/g • International Diabetes Federation criteria (2005): presence of central obesity (defined as waist circumference > 94cm for Europid men and > 80cm for Europid women, but can be assumed if BMI >30 kg/m^2) Plus two of the following:
5. Triglycerides: > 1.7 mmol/L, or specific treatment for this lipid abnormality
6. HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality.
7. BP: > 130/85 mm Hg, or active treatment of hypertension
8. Fasting glucose > 5.6 mmol/L, or previously diagnosed type 2 DM. Management • Aggressive lifestyle modification focused on weight reduction and increased physical activity • Long-term exercise upregulates expression of GLUT4, which may reduce hyperglycemia in patients with type 2 DM or metabolic syndrome. • Orlistat (an inhibitor of gastrointestinal lipases) with diet, reduces the risk of diabetes in an obese patients by 38% more than diet alone.

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Alström syndrome (AS)
• rare autosomal recessive disease
• caused by mutations in the ALMS1 gene.
• characterized by multiorgan dysfunction.
• Key features are: • childhood obesity, hyperinsulinemia, early-onset type 2 diabetes, and hypertriglyceridemia. Thus, AS shares several features with the common metabolic syndrome, namely obesity, • blindness due to congenital retinal dystrophy,
• sensorineural hearing loss.
• dilated cardiomyopathy in over 60% of cases,
• developmental delays in 50 % of cases.

Pre-diabetes or impaired glucose regulation (IGR)

Definition:
• impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. Includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).
• Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation (IGR) when talking to other healthcare professionals

Incidence • Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes.

Impaired fasting glucose (IFG) • Definition → fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l Mechanism due to hepatic insulin resistance people with IFG should then be offered an oral glucose tolerance test (OGTT) to rule out a diagnosis of diabetes. Impaired glucose tolerance (IGT) • Definition fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l • Mechanism due to muscle insulin resistance • Patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Identification of patients with prediabetes: Who should be assessed for the risk of type 2 diabetes?
• all adults aged 40 and over,
• people of South Asian and Chinese descent aged 25-39,
• adults with conditions that increase the risk of type 2 diabetes: cardiovascular disease, stroke, hypertension,
 obesity,
 polycystic ovary syndrome,
 history of gestational diabetes mental health problems.

Diagnosis

normal Prediabetes Diabetes mellitus Fasting glucose
≤ 6 mmol/l ≥ 6.1 – 6.9 mmol/l impaired fasting glucose (IFG) 2h glucose during an OGTT < 7.8 mmol/l 7.8 -n 11 mmol/l Impaired glucose tolerance (IGT) HA1c < 42 mmol/mol < 6% 42 – 47 mmol/mol (6.0 – 6.4%)

Complication
• progression to type 2 diabetes mellitus (T2DM) • The risk of developing type 2 diabetes in patient with (IGT) → 60% over 6 years
• ↑ risk of macrovascular disease (e.g. coronary artery disease). No risk of microvascular complications of diabetes such as retinopathy and nephropathy.

Management

The best way to reduce the incidence of type 2 diabetes in individuals with IGT is → Intensive lifestyle change

• Lifestyle modification: weight loss, increased exercise, change in diet intensive diet and lifestyle change (that results in loss of approximately 5% of initial body weight) can reduce progression from impaired fasting glucose (or impaired glucose tolerance) to frank type 2 diabetes by approximately 50%. • NICE recommend metformin for adults at high risk 'whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme'

Which drug classes is most well known as a cause of impaired glucose tolerance? Atypical antipsychotics

Both typical antipsychotics and antihypertensives (thiazides and beta blockers), have been shown in meta-analyses to be associated with impaired glucose tolerance and increased risk of type 2

diabetes. The risk is relatively larger for risperidone than thiazides & β.blocker

MRCPUK- part- 1-September 2009 exam: The fasting glucose of asymptomatic patient comes back as 6.5 mmol/l. The test is repeated and reported as 6.7 mmol/l. How should these results be interpreted? Impaired fasting glycaemia Notes & Notes for MRCP
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≥ 7 mmol/l ≥ 11.1 mmol/l ≥ 6.5%

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Diabetes mellitus: Type 1 overview

Definition • Type 1 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia due to absolute insulin deficiency.

Epidemiology • 5% to 10% of all patients with diabetes. • more common in Europeans and less common in Asians.

Pathophysiology
• Genetic susceptibility and environmental triggers (often associated with previous viral infection) → autoimmune response (CD4 +T-cell mediated) with production of autoantibodies, e.g., anti-glutamic acid decarboxylase antibody (anti-GAD), anti-islet cell cytoplasmic antibody (anti-ICA) → progressive destruction of β cells in the pancreatic islets → absolute insulin deficiency → decreased glucose uptake in the tissues. • Type 1 diabetes becomes clinically evident upon destruction of approximately 70-80 % of beta cell mass.

Risk factors • Genetic risks HLA association (HLA DR4 > HLA DR3) The familial risk of Type 1 diabetes:
 Only 10% of patients have a positive family history If both parents have type 1 DM → ≈ 40% (in offspring) If the father has type 1 DM → 3–6% If the mother has type 1 DM → 2-3% If one identical twin has type 1 DM, the risk in the unaffected twin → 3050%. If a sibling (brother or sister) has type 1 diabetes → 5–6% • Viral infections Only congenital rubella infection has been definitively linked to an increased risk for type 1 diabetes.
 Studies attempting to link other viruses to type 1 diabetes, including enterovirus and rotavirus, have had mixed results. Enteroviruses may play a role in both protection from and susceptibility to type 1 diabetes.
• Presence of autoantibodies → 50% risk of DM over five years.
• Loss of first phase insulin response (postprandial insulin secretion in response to a meal, begins within 2 minutes of nutrient ingestion and continues for 10 to 15 minutes) → indicator of significant impending beta cell destruction → 100% risk of DM over two years. • Association with other autoimmune conditions Hashimoto thyroiditis Type A gastritis Celiac disease Primary adrenal insufficiency

Features • Age of onset below 50 years • Diabetic ketoacidosis (DKA) is the first manifestation in one-third of cases • BMI below 25 kg/m2 • Rapid weight loss (the cardinal feature of absolute insulin deficiency.) • Classic symptoms of hyperglycemia (Polyuria, Polydipsia, Polyphagia) • Increased susceptibility to infections

Weight loss is an indicator of type 1DM even if the patient is obese → insulin is the best treatment (SCE. Questions sample. Mrcpuk.org)

Diagnosis of DM: any one of the following • Fasting plasma glucose ≥126 mg/dL (7 mmol/L) on at least two occasions • Symptoms of hyperglycemia and a plasma glucose ≥200 mg/dL (11.1 mmol/L) • Plasma glucose ≥200 mg/dL (11.1 mmol/L) measured two hours after a standard glucose load in an oral glucose tolerance test • Glycated hemoglobin (A1C) ≥6.5%.

Investigations for type 1 • C-peptide
 ↓ C-peptide levels indicate an absolute insulin deficiency → type 1 diabetes ↑ C-peptide levels may indicate insulin resistance and hyperinsulinemia → type 2diabetes • Antibodies detected in patients who later go on to develop type 1 DM:
 Glutamic Acid Decarboxylase (GAD) antibody found in 70-90% of type1 diabetics. 10 fold increases the risk of developing IDDM. 10% of adults who have been classified as having type 2 diabetes may have (ICA) or (GAD) antibodies, indicating autoimmune destruction of beta cells. Islet Cell Antibodies (ICA): found in up to 60 - 80% of patients with type 1 diabetes

Complications • Microvascular complications include retinopathy, nephropathy, and neuropathy. • Macrovascular complications include cerebrovascular, coronary artery, and peripheral vascular disease. Which feature is most closely associated with the imminent development of type 1 diabetes? → Loss of first phase insulin response

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Diabetes mellitus: management of type 1

Diet • Do not advise adults with type 1 diabetes to follow a low glycaemic index diet for blood glucose control.
Insulin
• Insulin injection regimen: offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice. • For basal insulin:
 twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine is an alternative.
 once-daily ultra-long-acting insulin such as degludec, if there is a concern about nocturnal hypoglycaemia or for people who need help from a carer. • For mealtime insulin: offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins. • Insulin dose: normal insulin requirements are around 0.5–0.6 units/kg/day, split equally between

background (basal) and mealtime (bolus) requirements • Insulin dose adjustments During periods of illness: the TREND UK guidance advises that: If blood glucose is less than 13 mmol/L and no ketones are present then insulin should be taken as normal. If blood glucose is more than 13 mmol/L and ketones are present then insulin adjustment is needed. add 10% of the daily insulin dose as rapid acting insulin every four hours, and then four hourly glucose and ketone monitoring to guide ongoing dosage/management.
 After alcohol or exercise → reduce evening basal insulin by 25–50%. Metformin • NICE recommend considering adding metformin if the BMI ≥ 25 kg/m² Referral indication for islet or pancreas transplantation • type 1 diabetes with recurrent severe hypoglycaemia that has not responded to other treatments
• type 1 diabetes with suboptimal diabetes control who have had a renal transplant and are currently on immunosuppressive therapy. Monitoring
• Frequency of self-monitoring of blood glucose recommend testing at least 4 times a day, including before each meal and before bed. more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding.
 during periods of illness, blood glucose and ketones should be checked at least every 4 hours. In newly diagnosed adults with type 1 diabetes, the first-line insulin regime should be a basal–bolus using twice-daily insulin detemir.

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Targets Test
Targets HbA1c ≤ 48 mmol/mol (6.5%) fasting plasma glucose 5–7 mmol/litre on waking
4–7 mmol/litre before meals Post-prandial
5–9 mmol/litre (< 10) during surgery or acute illness 5–8 mmol/litre blood pressure 135/85 mmHg

Impaired fasting glucose and impaired glucose tolerance • Impaired fasting glucose (IFG) is defined as fasting glucose ≥ 6.1 but < 7.0 mmol/l • Impaired glucose tolerance (IGT) is defined as fasting glucose < 7.0 mmol/l and OGTT 2-hour ≥ 7.8 mmol/l but < 11.1 mmol/l

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Diabetes mellitus: Type 2 overview

Definition • Type 2 diabetes mellitus is a progressive disorder defined by deficits in insulin secretion and increased insulin resistance

Epidemiology • greater incidence among those of black and South Asian origin. • Most are over 40yrs, but teenagers are now getting type 2 DM

Genetics • Polygenic
• No HLA associations. • Strong familial predisposition. Familial risks for developing diabetes Concordance between identical twins is higher in type 2 diabetes mellitus than type 1 if one identical twin has type 2 diabetes, the risk in the unaffected twin → 60 – 100 %.
 The incident diabetes risk in siblings and offspring of patients with type 2 diabetes is approximately 10%.

Pathophysiology • Peripheral insulin resistance Obesity→ ↓Adiponectin (secreted by adipocytes and involved in lipid catabolism) → insulin resistance (inversely correlated with the risk for diabetes). Central obesity → ↑free fatty acids → impaired insulin-dependent glucose uptake into hepatocytes, myocytes, and adipocytes ↑Plasminogen activator inhibitor 1 (↑in obesity & ↓ in weight loss → insulin resistance → type 2 diabetes mellitus.

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• Beta cell dysfunction: accumulation of pro-amylin (islet amyloid polypeptide) in the pancreas → decreased endogenous insulin production Amyloid deposition → ↓islet cell number and function. The presence of amyloid polypeptide on pancreatic histology is highly suggestive of type 2 DM. Beta cell function is reduced by up to 70% at the point of type 2 diabetes diagnosis. The earliest manifestation of beta cell dysfunction occurs in the form of reduced and delayed postprandial early phase insulin secretion. • Alpha cell dysfunction →↑ plasma glucagon
• Secondary diabetes (e.g. Haemochromatosis)

Risk factors • Age, ethnicity and positive family history
• Conditions associated with insulin resistance: e.g., severe obesity, dyslipidemia
• Polycystic ovary syndrome • Physical inactivity • Hypertension
• History of gestational diabetes

Features
• The majority of patients are asymptomatic. • Elderly patients may present in a hyperosmolar hyperglycemic state. • Symptoms of hyperglycemia (Polyuria, Polydipsia Polyphagia) • Prone to recurrent infections DM → Impaired neutrophil chemotaxis and phagocytosis →immunosuppression → recurrent infections • 30% of patients presenting with acute coronary syndrome will have undiagnosed type 2 DM • Increased concentrations of C peptide are a marker of increased colorectal cancer risk

Diagnosis: WHO criteria • Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL), or • Plasma glucose ≥11.1 mmol/L (≥200 mg/dL) 2 hours after 75 g oral glucose, or • Glycosylated haemoglobin (HbA1c) ≥48 mmol/mol (≥6.5%), or • In a symptomatic patient, random plasma glucose of ≥11.1 mmol/L (≥200 mg/dL). • Repeat confirmatory test is required in asymptomatic patients.

Beta cell mass
• Compared with subjects with normoglycaemia,
 beta cell mass is reduced by 50% in subjects with Impaired Fasting Glucose,
 by 70% in subjects with Type 2 diabetes, and
 over 90% in subjects with type 1 diabetes.

Diabetes UK suggests :'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes? →Small dense LDL molecules

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Glycosylated haemoglobin (HbA1c)

Indications • Diagnosis of diabetes mellitus and prediabetes state.
 Normal level → < 42 mmol/mol (< 6%) An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes.
 Prediabetes → 42 – 47 mmol/mol (6.0 – 6.4%) Diabetes mellitus → ≥ 6.5% • Measure of long-term glycaemic control in diabetes mellitus.
 Reflects average blood glucose over the previous 2 - 3 months.
Follow up intervals
• NICE recommend 'HbA1c should be checked every 3-6 months until stable, then 6 monthly'.
Methods of reporting :
• Percentage vs mmol/mol A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached. HBA1c (%) IFCC-HbA1c (mmol/mol)

• Estimated average glucose

HBA1c (%) Average plasma glucose (mmol/l)

5.5

7.5

9.5

11.5

13.5

15.5

17.5

19.5

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• Equations
 New mmol/mol = [Old % – 2.15] x 10.929
 Old % = [New mmol/mol divided by 10.929] + 2.15 Average plasma glucose = (2 * HbA1c) - 4.5

HbA1c targets • For diabetic patient on lifestyle + metformin → 48 mmol/mol (6.5%) • For diabetic patient on drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea) → 53 mmol/mol (7.0%)

Unexpected or discordant HA1C values • When there is a disparity between the A1C values and blood glucose values, we rely on the glucose values. • Use frequent glucose monitoring . Fructosamine or glycated albumin may be useful alternatives.

The level of HbA1c therefore is dependent on: • red blood cell lifespan • average blood glucose concentration

Falsely high A1C values • Low red cell turnover vitamin B12 folate deficiency anemia.
• Splenectomy : spleen removes old RBCs. Not having a spleen increases RBC life span. Falsely low A1C values • Rapid red cell turnover
 Chronic hemolysis (eg, thalassemia, glucose-6-phosphate dehydrogenase deficiency);
 patients treated for iron, vitamin B12, or folate deficiency; and patients treated with erythropoietin. • Blood transfusion (factitiously low A1C level) • Advanced chronic kidney disease , haemodialysis
• Alcohol consumption
• Sudden weight loss

If A1C is higher than expected based on the mean glucose results
• Do fingerstick blood glucose levels between meals or short-term use of continuous glucose monitoring (CGM) to evaluate glucose patterns. One explanation is that the postprandial glucose is higher than pre-prandial test results that patients typically obtain.
• Exclude factors, which can falsely elevate the A1C (eg, low red cell turnover).

If the A1C is lower than expected based on the mean glucose results
• Do fingerstick blood glucose monitoring or CGM to detect nocturnal hypoglycemia, hypoglycemic unawareness, and/or frequent episodes of hypoglycemia. it is possible that blood glucose levels are low during times when testing is not being performed (such as undetected nocturnal hypoglycemia). • Exclude factors, which can falsely decrease the A1C (eg, rapid red cell turnover).

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Diabetes mellitus: management of type 2

General aim of management
• Reduce the incidence of macrovascular (ischaemic heart disease, stroke) and microvascular (eye, nerve and kidney damage) complications.

Risk factor modification • Blood pressure target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present) ACE inhibitors are first-line • Antiplatelets should not be offered unless a patient has existing cardiovascular disease • Lipids only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin.
 The first-line statin of choice is atorvastatin 20mg on HbA1c targets • HbA1c should be checked every 3-6 months until stable, then 6 monthly • NICE encourage us to consider relaxing targets on 'a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes' • According to NICE guidelines, the HbA1c targets are now dependent on treatment: • Lifestyle or single drug treatment Management of T2DM HbA1c target Lifestyle alone or + metformin 48 mmol/mol (6.5%) Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea) 53 mmol/mol (7.0%)

Be aware that there are other possible reasons for a low HbA1c level, for example, deteriorating renal function or sudden weight loss.

Self-monitoring of blood glucose • Indications
 person is on insulin or oral medication that may increase their risk of hypoglycaemia while driving or operating machinery. evidence of hypoglycaemic episodes or to confirm suspected hypoglycaemia. pregnant, or planning to become pregnant. when starting treatment with oral or intravenous corticosteroids

Patient who is taking metformin for T2DM: • if the HbA1c < 58 mmol/mol (7.5%): titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%). • if the HbA1c rises to 58 mmol/mol (7.5%): add a second drug

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Lifestyle modification • Dietary advice Encourage high- fibre, low- glycaemic- index sources of carbohydrate, such as fruit, vegetables, wholegrains and pulses Include low- fat dairy products and oily fish Control the intake of foods containing saturated and trans fatty acids. limited substitution of sucrose- containing foods for other carbohydrate in the meal plan is allowable, but that they should take care to avoid excess energy intake. Discourage use of foods marketed specifically at people with diabetes • Losing weight
 Initial target weight loss in an overweight person is 5-10% • Physical activity

Drug treatment • First line offer standard release metformin
 titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%),
 If gastrointestinal side effects are not tolerated, then a trial of modified release metformin would be appropriate.
 If metformin is not tolerated at all then a dipeptidyl peptidase-4 inhibitor, sulfonylurea or pioglitazone would be indicated.
• Second line should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%) there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) -

you now have a choice of 4 oral antidiabetic agents Second line for patient who tolerates metformin:
 add one of the: Sulfonylurea, Gliptin, pioglitazone or SGLT-2 inhibitor (dual therapy) If despite the dual therapy, the HbA1c remains above 58 mmol/mol (7.5%) or increased then triple therapy with one of the following combinations should be offered: metformin + gliptin + sulfonylurea metformin + pioglitazone + sulfonylurea metformin + sulfonylurea + SGLT-2 inhibitor metformin + pioglitazone + SGLT-2 inhibitor OR insulin therapy should be considered Second line if metformin is not tolerated or contraindicated: Consider one of the: Sulfonylurea, Gliptin or pioglitazone if the HbA1c has risen to 58 mmol/mol (7.5%) then add one of the following (Dual therapy): gliptin + pioglitazone gliptin + sulfonylurea pioglitazone + sulfonylurea if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy • Third line If triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if: BMI ≥ 35 kg/m² and specific psychological or other medical problems associated with obesity or

 BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity related comorbidities. Starting insulin • If HbA1c remains > 58 mmol/mol (DCCT = 7.5%) inspite of maximum tolerated oral therapy, then consider human insulin • Metformin should be continued. In terms of other drugs NICE advice: 'Review the continued need for other blood glucose lowering therapies' • NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need. • Consider using insulin detemir or insulin glargine as an alternative to NPH insulin, if: the person needs assistance to inject insulin, so as to reduce the frequency of injections from twice to once daily. recurrent symptomatic hypoglycaemic episodes the person need twice- daily NPH injections in combination with oral glucose- lowering drugs. • Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either: separately or as a pre-mixed (biphasic) human insulin preparation. • Consider pre-mixed (biphasic) preparations that include short- acting insulin analogues, rather than pre- mixed (biphasic) preparations that include short- acting human insulin preparations, if: a person prefers injecting insulin immediately before a meal or hypoglycaemia is a problem or blood glucose levels rise markedly after meals. • For patients who are on pre-mixed (biphasic) insulin and uncontrolled blood glucose, consider:
 further injection of short-acting insulin before meals OR change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine.

Special considerations

• If the patient is at risk from hypoglycaemia (or the consequences of) then a DPP-4 inhibitor or thiazolidinedione should be considered rather than a sulfonylurea • Meglitinides (insulin secretagogues) should be considered for patients with an erratic lifestyle • You can consider using sitagliptin or a thiazolidinedione instead of insulin if there would be employment (eg: truck driver), social, recreational, or personal issues.

• In patients with diabetes starting thyroxine, doses of antidiabetic drugs including insulin may need to be increased. Diabetes associated with pancreatitis is due to damage to the endocrine pancreas and associated lack of insulin. the patient’s presentation: thin, with symptoms of insulinopaenia. As such, exogenous insulin replacement is the only appropriate intervention

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Which laboratory test results would be most significantly associated with an increased incidence of cardiovascular disease in type 2 diabetics?
• Raised proinsulin levels

January 2013 exam: A taxi driver with type 2 DM , on metformin and the dose was titrated up. His HbA1c one year ago was 75 mmol/mol (9%) and is now 69 mmol/mol (8.5%). His BMI 33 kg/m². What is the most appropriate next step in management?
• Add sitagliptin (because DPP-4 inhibitors are weight neutral & no risk of hypoglycaemia)

September 2010 exam: H/O (T2DM) & bladder cancer on gliclazide and atorvastatin. A recent trial of metformin was unsuccessful due to gastrointestinal side-effects. He works as an accountant; is a non-smoker his BMI is 31 kg/m². HisHbA1c = 62 mmol/mol (7.8%) What is the most appropriate next step in management?
• Add sitagliptin (Pioglitazone is contraindicated in bladder cancer and may contribute to his obesity. he does not meet the NICE body mass index criteria of 35 kg/m².)

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Biguanides (metformin)

Mechanism of action • Inhibits mitochondrial glycerophosphate dehydrogenase (mGPD) → ↓ hepatic gluconeogenesis and intestinal glucose absorption
• Increases peripheral insulin sensitivity → ↑ peripheral glucose uptake and glycolysis

Indications • type 2 diabetes mellitus • polycystic ovarian syndrome • non-alcoholic fatty liver disease Action of metformin in polycystic ovary syndrome: • metformin →↓ Insulin resistance → ↑peripheral glucose uptake → ↓ hyperinsulinaemia which implicated in pathogenesis of PCOS.

Advantages • Glycemic efficacy: lowers HbA1c by 1.2–2% over 3 months • Weight loss
• No risk of hypoglycemia • Beneficial effect on dyslipidemia • Reduce macrovascular complications and death (superior to sulphonylureas and insulin in terms of macrovascular risk, e.g. myocardial infarction).

Adverse effects
• Gastrointestinal upsets are common (nausea, anorexia, diarrhoea), intolerable in 20%

commonly occur if not slowly titrated up.
 The BNF advises leaving at least 1 week before increasing the dose. modified release preparations reduce the risk further.
 High dose metformin interfere with the enterohepatic circulation of bile salts, leading to reduced reabsorption of bile salts from the ilieum → chronic diarrhoea .
• Vitamin B12 deficiency
 Associated with long-term treatment with metformin
 The possibility of metformin-associated B12deficiency should be considered in patients on metformin who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia. • Lactic acidosis with severe liver disease or renal failure It is rare, although it remains important in the context of exams
 The patients usually have severe renal impairment. factors increases the risk of metformin lactic acidosis: Tissue hypoxia, e.g. recent myocardial infarction, sepsis, acute kidney injury and severe dehydration.

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 The (BNF) states that there should be a six week "cooling off" period post-MI before the commencement or recommencement of metformin. Contrast radiography. : metformin should be discontinued on the day of the procedure and for 48 hours thereafter Excess alcohol intake Drugs: Cyclosporin, aminoglycosides, cimetidine (Metformin is excreted by the renal tubules and this process can be inhibited by cimetidine, but not the other H2 receptor antagonists). The mainstay of treatment is rehydration. correction of acidosis with 8.4% sodium bicarbonate.
 Patients with resistant acidosis should be considered for haemodialysis, which also clears metformin. Despite aggressive treatment, mortality still 50%.

High dose (> 2 gm daily) interferes with enterohepatic circulation of the bile salts (Bile salt malabsorption) → diarrhoea

Contraindications • Chronic kidney disease:
 NICE recommend that the dose should be reviewed if the creatinine is > 130 mmol/l (or eGFR < 45 ml/min) (reduce the those and monitor renal function every three months) and stopped if the creatinine is > 150 mmol/l (or eGFR < 30 ml/min) (stage four chronic kidney disease (CKD 4) • Alcohol abuse is a relative contraindication→ ↑risk of lactic acidosis • Intravenous iodinated contrast medium
• Heart failure (NYHA III and IV), respiratory failure, shock, sepsis
• Alcoholism

Sulphonylureas

Mechanism of action • Block ATP-sensitive potassium channels (KATP) of the pancreatic β cells → depolarization of the cell membrane → calcium influx → insulin secretion

Side effects • Life-threatening hypoglycemia; increased risk with the following : Age over 65 years Simultaneous intake of CYP2C9 inhibitors (e.g., amiodarone, trimethoprim, fluconazole) Patients with renal failure more common with long acting sulphonylureas such as chlorpropamide and glyburide (glibenclamide). • Weight gain • syndrome of inappropriate ADH secretion (SIADH) • bone marrow suppression • liver damage (cholestatic) • photosensitivity • Hematological changes: granulocytopenia, hemolytic anemia

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159 • Chlorpropamide & tolbutamide → disulfiram-like reaction following alcohol intake (alcohol intolerance). alcohol intake with Chlorpropamide & tolbutamide → inhibits aldehyde dehydrogenase (the enzyme responsible for the metabolism of acetaldehyde) → accumulation of toxic acetaldehyde → disulfiram-like effect (a drug used to treat alcoholism) → (facial flushing, erythema, paraesthesia of the extremities, nausea and vomiting, tachycardia, and hypotension). Contraindications • Pregnancy and breast feeding
• Severe cardiovascular comorbidity
• Severe liver and kidney failure • Obesity • Beta blockers (can mask hypoglycemic symptoms while lowering serum glucose levels)

The combination of beta-blockers and hypoglycemia should be avoided: • Beta-blockers may mask the warning signs of hypoglycemia (e.g., tachycardia) and decrease serum glucose levels even further. Agents
• Glibenclamide
 long-acting sulfonylurea
 associated with a greater risk of hypoglycaemia, therefore, should be avoided in the elderly, and shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead Renally excreted: renal impairment →↑ risk of hypoglycaemia
• Gliclazide
 intermediate half-life of around 11 hours.
 causes less hypoglycemia than other sulfonylureas.
 extensively metabolised within the liver by CYP2C9. Renal clearance accounts for only 4% of total drug clearance. In CKD stage 1, 2, 3 (eGFR > 30 mL/min) gliclazide can be used safely. in patients with severe CKD → reduced dose can be used
 gliclazide action can be potentiated predominantly by two mechanisms: Displacement of the drug from plasma proteins to give freer (unbound) drug - some agents such as aspirin can do this, and Interference with the hepatic metabolism of the drug.(e.g fluconazole) • Glipizide
 metabolized by the liver into inactive metabolites and therefore, renal insufficiency does not affect the drug's clearance.
 the best choice of sulfonylureas in a patient with renal impairment (no need for dose adjustment).
• Chlorpropamide
 has a higher side effect profile may produce a syndrome of inappropriate anti-diuretic hormone (ADH) secretion.

Sulphonylurea provide microvascular benefits, but NO benefit was demonstrated for macrovascular outcomes (cardiovascular disease), in contrast to metformin.

Sulphonylurea overdoses: In sulphonylurea overdoses, if the patient remains hypoglycaemic despite infusion of sufficient glucose, consider administration of octreotide (a somatostatin analogue which lowers insulin levels and thus raised blood glucose)

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Meglitinides

Meglitinides (nateglinide and repaglinide) → increase postprandial insulin release specifically

Agents • Repaglinide • Nateglinide

Action → closure of the β-cell K+-ATP channel. • Short-acting insulin secretagogues • Blockage of ATP-sensitive potassium (KATP) channels of the pancreatic beta cells → depolarization of the cell membrane → calcium influx → insulin secretion • Act like sulfonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site of the pancreatic channel.

Indications • useful for post-prandial hyperglycaemia or an erratic eating schedule, as patients take them shortly before meals

Advantages • The shorter action of duration result in less weight gain compared to sulphonylureas.
• Nateglinide is useful for shift workers and patients who tend to fast for a period of time because doses can be skipped when meals are missed. In these patient groups there may be a lower incidence of hyperglycaemia.
• Repaglinide can be used even in CKD stages 4 and 5 without dose reduction.

Adverse effects • weight gain and hypoglycaemia (less so than sulfonylureas)

Thiazolidinediones (glitazones, insulin sensitizers)

Mechanism of action: Peroxisome Proliferator Activated Receptor (PPAR) gamma agonists → increase peripheral insulin sensitivity

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Agents • Pioglitazone • Rosiglitazone: was withdrawn in 2010 following concerns about cardiovascular side-effect profile. Pioglitazone metabolism
• mainly by CYP2C8 cytochrome P450 enzyme pathway

Mechanism of action
• Agonists to the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) receptor → ↑ transcription of genes involved in glucose and lipid metabolism → ↑ levels of adipokines such as adiponectin and insulin sensitivity → ↑ storage of fatty acids in adipocytes, ↓ products of lipid metabolism (e.g., free fatty acids) → ↓ free fatty acids in circulation → ↑ glucose utilization and ↓ hepatic glucose production. Metformin also boosts insulin sensitivity, but pioglitazone has more effect on peripheral insulin resistance. PPAR-gamma receptor • an intracellular nuclear receptor. • Its natural ligands are free fatty acids • it is thought to control adipocyte differentiation and function. • activated by free fatty acids and thiazolinediones such as pioglitazone.

Indications
• may be considered as monotherapy in patients with severe renal failure and/or contraindications for insulin • NICE guidance advice that: only continue thiazolidinediones if there is a reduction of > 0.5 percentage points in HbA1c in 6 months

Advantages • Glycemic efficacy: lowers HbA1c by 1% in 3 months • Favorable effect on lipid metabolism: ↓ triglyceride, ↓ LDL, ↑ HDL • No risk of hypoglycemia • associated with the lowest rate of secondary beta-cell failure. Sulfonylureas are associated with the highest rate Side effects • ↑ Risk of heart failure • ↑ Risk of bone fractures (osteoporosis). due to reduced osteoblast activity → reduced bone mineral density. • Fluid retention and edema the risk of fluid retention is increased if the patient also takes insulin , or other drugs that cause fluid retention (for example, NSAIDs, calcium antagonists)
• Weight gain • Rosiglitazone: ↑ risk of cardiovascular complications like cardiac infarction or death • Bladder cancer • liver impairment: monitor LFTs Contraindications • Congestive heart failure (NYHA III or IV) • Liver failure • Pioglitazone: history of bladder cancer or active bladder cancer; macrohematuria of unknown origin

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Insulin: Basics
Structure • Insulin is a peptide hormone , composed of 51 amino acids. It is a dimer of an A-chain and a B-chain, which are linked together by disulfide bonds. Production
• Insulin is produced in the pancreatic beta cell by proteolytic cleavage from pro-insulin resulting in c-peptide which is secreted together with insulin in a 1:1 molar ratio. Secretion • Insulin is stored in secretory granules • Released by beta cells as a result of increased intracellular calcium. • Released in pulses about every 9-13 minutes.
 This pulsing release mechanism is important because it is thought that this keeps cells sensitive to insulin.
 this is one of the first things that disappears when insulin sensitivity disappears. • Secreted in response to hyperglycaemia C-peptide • a protein cleaved from proinsulin when it is activated.
• has a longer half-life than insulin, and thus is a useful measure of insulin secretion (it is more accurate than measuring insulin itself).
• The level of this can be measured in the urine. Insulin and C peptide are ↑ in insulinoma and

sulfonylurea use, whereas exogenous insulin lacks C-peptide.

Functions • Insulin binds to insulin receptors (a type of tyrosine kinase receptor) located in various tissues in the body → acts as an anabolic hormone in target tissues (e.g., liver, skeletal muscle, adipose tissue).
• Carbohydrate metabolism

 Stimulate Glycogenesis (glycogen synthesis from glucose by glycogen synthase, and glycogen branching enzyme. Triggered by high serum insulin concentrations.) in muscle and liver Stimulate Glycolysis (converts glucose to pyruvate and produces ATP and NADH as byproducts.) in adipose and muscle Inhibits Glycogenolysis (breakdown of glycogen by glycogen phosphorylase) Inhibits Gluconeogenesis (produces glucose from noncarbohydrate substances such as amino acids, triglycerides, and glycerol.) (Insulin inhibit pyruvate carboxylase which used in gluconeogenesis) Inhibits Production and release of glucagon • Lipid metabolism Stimulate Lipid synthesis and triglyceride storage in adipose tissue Inhibits Lipolysis (breakdown of lipids) Inhibits Ketogenesis (production of ketone bodies by HMG-CoA synthase). Thiazolidinediones are associated with an increased risk of bladder cancer Pioglitazone may cause fluid retention

• Protein metabolism Stimulate Protein synthesis in muscle tissue Stimulate Uptake of amino acids Inhibits Proteolysis

• Increases cellular uptake of potassium (via stimulation of Na+/K+ ATPase pump)

Insulin therapy Insulin types • Rapid-acting insulin analogues (Aspart, Lispro, Glulisine) Onset: 5 mins Peak: 1 hour Duration: 3-5 hours Reduces the chance of between-meal hypoglycaemia. Useful for reducing postprandial hypoglycaemia because their profile is more in keeping with physiological insulin release. If there is a pre-lunch hyperglycaemia, that means there is a significant postbreakfast peak in glucose levels. As such, the best management → breakfast time injection of rapid acting insulin. • Short-acting insulins (Actrapid, Humulin S) Onset: 30 mins Peak: 3 hours Duration: 6-8 hours may be used as the bolus dose in 'basal-bolus' regimes “Standard insulin” for lowering blood glucose levels in an acute setting Intravenous therapy available

• Intermediate-acting insulins (Isophane [NPH]) Onset: 2 hours Peak: 5-8 hours Duration: 12-18 hours NICE guidelines advise that, in general, a humane isophane insulin is the firstline recommended insulin in type 2 diabetic.
• Long-acting insulins (Determir, Glargine) Onset: 1-2 hours Peak: Flat profile Duration: Up to 24 hours The main advantage → Reduced nocturnal hypoglycaemia might be useful in someone who struggles to inject a twice a day NPH insulin to reduce the frequency of injections to once a day (e.g. someone who requires assistance to inject from a career or district nurse). suitable for providing a basal level of insulin which attempts to mimic the normal physiological state. In which situations does insulin glargine have the clearest advantage over isophane? In patients with type-1 diabetes who have significant nocturnal hypoglycaemia on isophane NICE

only recommends use of insulin glargine in patients who have significant hypoglycaemia on isophane insulin Detemir is the only long-acting insulin that is soluble in the bottle as well as under the skin, possibly allowing for more consistent absorption.

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 Detemir can be administered with other forms of insulin, unlike insulin glargine, which cannot be mixed with other insulins or IV fluids due to its acid vehicle. Degludec a long-acting insulin. Onset: ~1 hour Half-life elimination: ~25 hours (has the highest half-life) Time to peak: 9 hours

Rapid-acting insulins are your favorite GAL (Glulisine, Aspart, Lispro).

Intravenous insulin is the optimal management of high blood sugar in acute myocardial infarction.

Insulin prescription • Starting dose The guidelines recommend starting with either morning or evening long-acting insulin, or with bedtime intermediate acting insulin. 0.2 U/kg or a flat dose of 10 U is the recommended starting dose for intermediate acting insulin. • Targets Fasting and pre-prandial glucose levels → 4-7 mmol/L . Post-prandial glucose levels : less than 10 mmol/L. In hospitalised patients the Joint British Diabetes Societies for Inpatient care (JBDS) suggest a target blood glucose of 6-10mmol/L • Monitoring If patients are not using insulin, sulphonylureas or glinides (repaglinide or netaglinide), then the ADA/EASD consensus does not recommend selfmonitoring of blood glucose levels. Once daily long-acting insulin taken at night is monitored using pre-breakfast fasting glucose measurements. If fasting levels are in range yet the HbA1c is elevated, postprandial monitoring is recommended. • Dose adjustment Pre-prandial glucose: Mainly affected by the basal insulin dose Postprandial glucose is mainly affected by meal intake and prandial insulin dose. At least three consecutive, self-monitored fasting glucose readings should be used to adjust doses (i.e. three days minimum between dose adjustments).
 Up-titration
 increase 2 U of insulin every three days until fasting glucose is in the target range of 3.9-7.2 mmol/L. If the fasting plasma glucose is ˃10 mmol/L, → uptitration schedule of 4 U every three days can be used. Down-titration
 Reduce insulin dose in steps of 20% if hypoglycaemia occurs. • Insulin in renal failure The dose of exogenous insulin is reduced 25% when eGFR is 10-50 mL/min and 50% when eGFR is < 10 mL/min Degludec
A patient with recurrent admissions for DKA secondary to missing doses can be started on degludec to reduce readmission rate. Degludec has a much higher half-life than Detemir and therefore maintains a basal insulin level when the patient omits or forgets doses. This can prevent DKA.