008

Pages 176-200

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

the most appropriate initial insulin regime for young patient after being diagnosed with new onset Type1 DM → Meal time Actrapid and insulatard at night.

Insulin side-effects • Hypoglycaemia • Weight gain
• Hypokalemia • Lipodystrophy at the injection site typically presents as atrophy of the subcutaneous fat can be prevented by rotating the injection site

Mixtard- associated nocturnal hypoglycemia • This is because the insulatard component of the Mixtard peaks about 6 h after it has been given. This, along with some residual actrapid activity, gives an excess of insulin in the middle of the night, leading hypoglycaemia.
• Split evening insulin so take actrapid before evening meal and insulatard before bedtime

Hypoglycaemic episodes which occur during the day in a patient takes a basal bolus insulin regime of long-acting insulin (Insulatard®) and short- acting insulin (Actrapid®) with each meal: • the most appropriate next step → Refer for Dose Adjustment For Normal Eating education (DAFNE) • the next step after DAFNE, should hypos persist, would be continuous glucose monitoring, to learn more about fluctuations in serum blood glucose over the course of the day. • those patients who have problems with nocturnal hypoglycaemia → changing insulatard to insulin glargine

What is the most appropriate initial advice with respect to adjusting prandial insulin dose? • 1 unit of insulin per 10 grams of dietary carbohydrate

Glucagon-like peptide-1 (GLP-1)

Incretins increase insulin release and decrease glucagon secretion from the pancreas. DPP-IV metabolizes GLP. Inhibiting DPP-IV maintains high levels of GLP.

Incretin effect
• Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), produced by the L-cells of the ileum →↑ insulin release (more than if the same load is given intravenously), ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight) - this known as the incretin effect. • This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

GLP-1 : Site of synthesis Small intestinal L cells

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

Endocrinolog & Metabolism Glucagon-like peptide-1 (GLP-1) • Production glucagon-like peptide-1 (GLP-1), a hormone produced by the L-cells of the ileum in response to an oral glucose load
• Effects in glucose homeostasis Glucose-dependent stimulation of insulin secretion Reduction of gastric emptying Reduction of inappropriate glucagon secretion Weight loss • Regulation of GLP-1 Increasing GLP-1 levels, either by: administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) OR inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

GLP is a confusing misnomer: Glucagon raises glucose and FFA levels. GLP decreases glucagon.

Glucagon-like peptide-1 (GLP-1) analogs

Agents: Exenatide, Liraglutide
• Liraglutide VS Exenatide
 Liraglutide is given once a day (long-acting) whereas Exenatide is given twice daily (has a half-life of around 2.5 hours)

 Liraglutide can be used in renal impairment with an estimated glomerular filtration rate [eGFR] as low as 30 mL/min/1.73 m2. Exenatide are cleared via renal excretion and is therefore not recommended in patients with an eGFR < 30.

Mechanism of action
• Incretin effect: Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), produced by the L-cells of the ileum →↑ insulin release (more than if the same load is given intravenously), ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight).

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• GLP-1 agonists (Incretin mimetic drugs) →↑GLP-1 levels → ↑ insulin secretion, ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight)

• Metabolic effects increase insulin secretion
 inhibit glucagon secretion.
 inhibits glucose production in the liver slows gastric emptying →Suppresses appetite

Indications • NICE state that: Consider adding exenatide to metformin and a sulfonylurea if: BMI ≥ 35 kg/m in people of European descent and there are problems associated with high weight, or
 BMI < 35 kg/m and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities. Advantages • Improve glycaemic control: lowers HbA1c by 0.5–1.5% over 3 months • No risk of hypoglycemia • Promote weight loss (≈ 6% weight loss over a 6 month period).

Administration • NICE like patients to have achieved a 1% reduction in HbA1c (11 mmol/mol) and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

Adverse effects
• nausea and vomiting (the major adverse effect). • Acute pancreatitis in some patients.

The preferred pathway for glucose management according to the NICE guidelines is to add insulin to the combination of metformin and a sulphonylurea. However, where weight is of particular concern (BMI >35), exenatide may be considered as an alternative. It can also be used where insulin would interfere with a patient's occupation.

When to choose exenatide as an alternative to insulin or sulphonylurea as first choice add-in options to metformin?
• morbid obesity
• or risk of hypoglycaemia, (eg : HGV drivers)

Current NICE guidance suggests the use of GLP-1 mimetics only if BMI is above 35 and there are specific medical or psychological problems associated with high body weight.

Sign guidelines 2017: For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide) should be considered.

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

Endocrinolog & Metabolism Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)

Agents
• Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin and Alogliptin

Action • Incretin effect: Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), produced by the L-cells of the ileum → GLP-1 degradation via the enzyme DPP-4 → end of the GLP-1 effect.

• DPP-4 inhibitors (Incretin mimetic drugs) bind to the GLP-1 receptors inhibiting the DPP-4 that breaks down GLP-1 →↑GLP-1 levels → ↑ insulin secretion, ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight)

Indications • Can be considered as monotherapy in patients who are intolerant of or have contraindications to metformin, or other glucose-lowering agents.
 e.g linagliptin might be a good choice as initial therapy in a patient with chronic kidney disease or who is at particularly high risk for hypoglycemia. • Only recommended as second-line therapy with metformin if patients are at significant risk of hypoglycaemia or its consequences (e.g. older patients, those working at heights or heavy machinery, isolated patients) or if a sulphonylurea is not tolerated or contraindicated.
• can be considered as add-on drug therapy for patients who are inadequately controlled on metformin, a thiazolidinedione, sodium-glucose co-transporter-2 (SGLT2) inhibitor, or a

sulfonylurea.
• NICE guidelines suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

• NICE guidelines recommend: continue DPP-4 inhibitor only if there is a reduction of > 0.5 percentage points in HBA1c in 6 months. Advantages • Oral preparation • Well tolerated with no increased incidence of hypoglycaemia • Do not cause weight gain • We can use them all in CKD but with dose adjustment (Only linagliptin does not need dose adjustment in any stage of CKD) • Linagliptin is preferred in patients with chronic kidney disease [eGFR] <30 mL/min/1.73 m2)

Side effects • GI disturbance (nausea, flatulence, diarrhoea and constipation) (because DPP-4 inhibitor delays gastric emptying). • Acute pancreatitis (insufficient data) - still under investigation but is to be discontinued in the event of pancreatitis. • Saxagliptin associated with increased incidence of heart failure. • Increased risk of upper respiratory tract infections.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Sodium-glucose cotransporter 2 inhibitors (gliflozins)

Examples • Include canagliflozin, dapagliflozin and empagliflozin

Mechanism of action • reversible inhibition of SGLT-2 in the proximal convoluted tubule of the kidney → ↓ glucose reabsorption → glycosuria and polyuria.

Indications • Empagliflozin or canagliflozin may play a role in patients with overt cardiovascular diseases (CVD) or heart failure not reaching glycemic goals with metformin and lifestyle modifications • may have a role as a third agent in those who cannot or will not take insulin, when full doses of metformin and a sulfonylurea have not produced satisfactory metabolic control, or in patients in whom risk of hypoglycemia is high (frail, older adults) or in whom avoidance of weight gain is a priority.

Advantages

• Glycemic efficacy: lowers HbA1c by 0.6% over 3 months • Promotes weight loss (modest calorie spillage into the urine) there for it is better than gliptins in obese patient who does not achieve control by metformin
• ↓ Blood pressure (Sodium loss → fall in BP)
• ↓ Risk of cardiovascular mortality in patients with type 2 DM and cardiovascular disease • Reduce uric acid, which may over the longer term reduce nephropathy progression • Do not usually cause hypoglycemia

Adverse effects • Recurrent infections due to glucosuria Recurrent urinary infections (↑ glucose in the urine (Glycosuria) → predispose to bacterial growth) Genital infection (Vulvovaginal candidiasis): contra-indicated in patients with recurrent thrush.

 Necrotizing fasciitis of the perineum • Diabetic ketoacidosis (patients may present with euglycaemic ketoacidosis) SGLT-2 inhibitors →↑glucagon, →↑lipid oxidation →↑risk of ketoacidosis. • Increased risk of bone fracture
 SGLT-2 inhibitors → ↑PTH →↑ ↑bone turnover →↑ risk of bone fracture. SGLT-2 inhibitors → ↑ fibroblast growth factor (FGF-23) → ↓vitamin D →↑ ↓bone mineralisation.
• Acute kidney injury • Dehydration → weight loss, orthostatic hypotension • Increased total cholesterol, (both HDL and LDL) • ↑ Risk of lower limb amputation: Empagliflozin is preferred rather than canagliflozin. Canagliflozin found to be associated with increased risk of lower limb amputation and fractures.

Empagliflozin has been shown to reduce cardiovascular mortality

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

Endocrinolog & Metabolism

Contraindications • Renal Impairment: eGFR <30 mL/minute/1.73 m2: Use is contraindicated. • Recurrent urinary tract infections (e.g., in patients with anatomical or functional anomalies of the urinary tract)

Alpha-glucosidase inhibitors

Overview
• These are acarbose, miglitol and voglibose. • Not usually used as first-line therapy, because of modest efficacy and poor tolerance.

Mechanism of action • inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides and thereby slow absorption of glucose and reduce postprandial blood glucose concentration.

Advantages • They may be used as part of a combination regimen in people who consume highcarbohydrate diets and have high postprandial glucose levels. • reduction in risk of new onset type 2 diabetes and cardiovascular events.

Side effects
• Abdominal pain, flatulence and diarrhea (Using glucosidase inhibitors is like making a person lactose intolerant). Mechanism of diarrhoea: Alpha-glucosidase inhibitors → block glucose absorption → the sugar remains in the bowel → bacteria eat the glucose, and cast off gas and acid.

Diabetic ketoacidosis (DKA): Overview

Epidemiology • Approximately 25% of patients with type 1 diabetes will first present in diabetic ketoacidosis

Pathophysiology • Osmotic diuresis and hypovolemia Insulin deficiency → hyperglycemia → hyperosmolality → osmotic diuresis and loss of electrolytes → hypovolemia • Metabolic acidosis with increased anion gap
 Insulin deficiency → ↑ lipolysis → ↑ free fatty acids → hepatic ketone production (ketogenesis) → ketosis → bicarbonate consumption (as a buffer) → high anion gap metabolic acidosis Sign guidelines (November 2017): In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit (currently empagliflozin and canagliflozin) should be considered.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 Lack of insulin → ↑cortisol, catecholamines and glucagon → ↑ fatty acid metabolism → ↑ beta-hydroxybutyrate → acetoacetate → urine ketone Insulin withdrawal → initial acute rise in glucagon concentrations → Hepatic glucose production rises rapidly over the first 2 – 4 hours reaching a plateau after around 4 hours.

• Intracellular potassium deficit Insulin deficiency → hyperosmolality → K+ shift out of cells + lack of insulin to promote K+ uptake → intracellular K+ depleted → total body K+ deficit despite normal or even elevated serum K+ (Total body potassium is reduced by up to 500 mmol)

1BWhat is the primary cause of ketoacidosis in type 1 diabetes? • 2BLipolysis

Causes • Precipitating factors leading to diabetic ketoacidosis (DKA) are: Infection (30-40%) The most common precipitating factor Non-compliance with treatment (25%) Newly diagnosed diabetes (10-20%) Alterations to insulin dose (13%) Myocardial infarction (< 1%) • The drugs implicated in precipitating diabetes as well as diabetic ketoacidosis. atypical antipsychotics such as olanzapine
 thiazide diuretics beta sympathomimetics, and steroids. Features • abdominal pain • polyuria, polydipsia, dehydration • Kussmaul respiration (deep hyperventilation) • Acetone-smelling breath ('pear drops' smell) (Fruity odor) • serum sodium is falsely low due to the osmotic load of glucose.
• Blood count: Platelet secretory activity is often increased in DKA, but aggregation decreased.
 Neutrophil count is also commonly raised and correlates with ketone body levels, so does not necessarily imply underlying infection.

Diagnostic criteria: All of these must be present to make the diagnosis: • The ‘D’ – a blood glucose of >11.0 mmol/L or known to have diabetes mellitus • The ‘K’ a capillary or blood ketone of >3.0 mmol/L or significant ketonuria (2+ or more) • The ‘A’ – a bicarbonate of <15.0 mmol/L and/or venous pH <7.3

Association
A raised amylase in the absence of frank pancreatitis is common in patients with diabetic ketoacidosis (DKA), No specific management is required, and amylase falls with rehydration and control of blood glucose.

Very high glucose artificially drops sodium level → Pseudohyponatremia

Endocrinolog & Metabolism

Cause of hyperkalemia → transcellular shift of potassium out of the cell in exchange for hydrogen. Cause of ↓ total body K stores → excess loss of solutes with water in the urine. Cause of hypokalemia during DKA treatment → insulin drives potassium into cells with glucose.

Assessment of severity : presence of one or more of the following may indicate severe DKA (suggest intensive care admission): • GCS < 12 • Oxygen saturation <92% on air • Systolic blood pressure <90 mmHg • Tachycardia (˃100) or bradycardia (˂ 60 bpm) • pH < 7 • Blood ketone > 6 mmol/L • Bicarbonate < 5 mmol/L • Anion gap >16 mmol/l. [Anion Gap = (Na+ + K+) – (Cl- + HCO3-)]. Normal values are 8-12 mEq/L. • Potassium < 3.5 mmol/L on admission

Differential diagnosis • Alcoholic ketoacidosis Ketoacidosis without a raised glucose in a person with alcoholism is virtually diagnostic of alcoholic ketoacidosis.
 a careful history needs to be taken to differentiate it from euglycaemic DKA.
 If alcoholic ketoacidosis is suspected, then ß-hydroxybutyrate should be measured and not urine ketones, because acetoacetate production can be suppressed in alcoholic ketoacidosis. • Starvation ketosis
 ↓carbohydrate intake →↓insulin secretion, → lipolysis and ketosis.
 because it is arises over a prolonged period,→ renal compensation → acid base and electrolyte disturbances are often minimal

---

Diabetic ketoacidosis (DKA): Management Fluid replacement • Calculate fluid deficit mild to moderate DKA (indicated by a blood pH of 7.1 or above) → 5% fluid deficit.
 severe DKA (indicated by a blood pH below 7.1) → 10% fluid deficit. Most patients with DKA are deplete around 5-8 litres.
• Calculate maintenance fluid requirement
 if they weigh less than 10 kg, give 2 ml/kg/hour if they weigh between 10 and 40 kg, give 1 ml/kg/hour if they weigh more than 40 kg, give a fixed volume of 40 ml/hour. • Choose appropriate fluids Use 0.9% sodium chloride until the plasma glucose is below 14 mmol/litre. If the glucose falls below 14.0 mmol/L: commence 10% glucose given at 125 ml/ hour alongside the 0.9% sodium chloride solution, so that the insulin infusion can be continued at a sufficient rate to clear ketones (for example, 6 units/hour, monitored for effect).

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 In addition consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr. All fluids (except any initial bolus) administered with 40 mmol/litre potassium chloride unless they have renal failure.

• Rate of fluid replacement JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over:

Fluid Volume 0.9% sodium chloride 1L 1000ml over 1st hour 0.9% sodium chloride 1L with potassium chloride 1000ml over next 2 hours 0.9% sodium chloride 1L with potassium chloride 1000ml over next 2 hours 0.9% sodium chloride 1L with potassium chloride 1000ml over next 4 hours 0.9% sodium chloride 1L with potassium chloride 1000ml over next 4 hours 0.9% sodium chloride 1L with potassium chloride 1000ml over next 6 hours

 Slower infusion may be indicated in young adults (aged 18-25 years →↑risk of cerebral oedema), elderly, heart or kidney failure.

Fluid deficit in DKA Assume a 5% fluid deficit in children and young people in mild or moderate DKA (indicated by a blood pH of 7.1 or above)
 Assume a 10% fluid deficit in children and young people in severe DKA (indicated by a blood pH below 7.1)

Insulin • Insulin type
 Soluble infusion → intravenous infusion at 0.1 unit/kg/hour.
 If patient normally takes long acting insulin analogue (Lantus, Levemir) continue at usual dose and time. In those newly diagnosed, then a long acting basal insulin should be commenced, at a dose of 0.25 units/Kg subcutaneously once daily. • Best time for starting → NICE recommend to start insulin infusion 1–2 hours after beginning intravenous fluid therapy
• Rate of infusion (fixed rate insulin regime, not a sliding scale). 0.1 unit/kg/hr based on estimate of weight 50 units human soluble insulin (Actrapid or Humulin S) made up to 50 ml with 49.5 ml 0.9% sodium chloride solution (i.e. 1 unit /ml). Once the glucose drops to ˂14 mmol/L then in addition to adding a 10% dextrose infusion consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr to avoid the risk of developing hypoglycaemia and hypokalaemia Insulin infusion rate should only be increased if blood ketones are not falling at >0.5 mmol/h, venous bicarbonate not increased by 3.0mmol/L/hour or capillary blood glucose not reduced by 3.0mmol/L/hour.

Correction of hypokalaemia • As a result of both acidosis and insulin deficiency there is a total body potassium deficit of up to 1000 mmol.
• rehydration, insulin replacement and correction of acidosis resulting in further potassium loss with restoration of urine flow • hypokalemia is a major cause of death in ketoacidosis.

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

Endocrinolog & Metabolism

• JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L) Potassium replacement in mmol/L of infusion solution
Over 5.5 Nil 3.5-5.5

Below 3.5 Senior review as additional potassium needs to be given

Other treatment • Bicarbonate The role of bicarbonate in DKA is controversial. Generally not recommended. The acidosis usually corrects itself once the fluid and electrolyte balance is restored. There is no evidence to support bicarbonate use in a patient with a pH greater than 7.0. Intravenous bicarbonate should be given if the blood pH is lower than 6.9. In practice for DKA, sodium bicarbonate is only really considered in the peri-arrest situation.

• Low-molecular weight heparin DKA increased risk of venous thromboembolism because of volume depletion, hyperglycaemia and their decreased conscious level.

Monitoring • Blood glucose should be assessed every hour but testing for urine ketones can be performed every 4 hours.

Assessment of treatment
• Targets
 Reduction of the blood ketone concentration by 0.5mmol/L/hour
 Increase the venous bicarbonate by 3.0mmol/L/hour
 Reduce capillary blood glucose by 3.0mmol/L/hour
• If these targets rates are not achieved: always check the insulin infusion pump malfunction (the correct insulin residual volume is present) then the FRIII rate should be increased by 1 unit/hr increments hourly until the targets are achieved. • Expected time of DKA resolution It is unusual for DKA not to have resolved by 24 hours with appropriate treatment • Indicators of DKA resolution: Resolution of DKA is defined as: pH > 7.3 units.
 bicarbonate > 15.0mmol/L; and
 blood ketone level < 0.6mmol/L (rather than < 0.3mmol/L), in order to avoid restarting the FRIII if the ketone level rebounds upon discontinuation of the FRIII • Unreliable indicators of acidosis resolution Glucose level is not an accurate indicator of resolution of acidosis in ketoacidosis, so the acidosis resolution should be verified by venous gas analysis. Do not rely on bicarbonate alone to assess the resolution of DKA due to the possible hyperchloraemia secondary to large volumes of 0.9% sodium chloride infusion. ↑↑ 0.9% sodium chloride infusion →↓HCO_3 →hyperchloremic metabolic acidosis → difficulty is assessing whether the ketosis has resolved.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 hyperchloraemic acidosis may cause renal vasoconstriction → oliguria. Do not rely on urinary ketone clearance to indicate resolution of DKA, because these will still be present when the DKA has resolved. Euglycaemic DKA • Definition: DKA in people known to have diabetes but where the glucose is normal, or not particularly raised. • Causes partial treatment of DKA prior to admission use of the sodium-glucose cotransporter (SGLT) inhibitor drugs (e.g. dapagliflozin, canagliflozin, empagliflozin) • Treatment: treated in exactly the same way as hyperglycaemic DKA.
 1) Initiate glucose 10% straight away at 125 ml/hr because the glucose is ˂ 14 mmol/L 2) Begin with 0.1units/kg/hr insulin rate
 3) If glucose falling despite 10% glucose reduce to 0.5 units/kg/hr to avoid hypoglycaemia SCE-question sample-mrcpuk.org : The non-improvement of the patient’s clinical status and biochemical findings suggest that the metabolic acidosis is due to another reason such as sepsis. The finding of a raised lactate concentration will provide further insights.

Typical deficits in DKA in adults: • Water - 100ml/kg
• Sodium - 7-10mmol/kg
• Chloride - 3-5mmol/kg
• Potassium - 3-5mmol/kg

Resolution of DKA is defined as: • pH > 7.3 units.
• bicarbonate > 15.0mmol/L; and
• blood ketone level < 0.6mmol/L (rather than < 0.3mmol/L), in order to avoid re-starting the FRIII if the ketone level rebounds upon discontinuation of the FRIII At which time, a patient can be converted back to subcutaneous insulin? • After Resolution of DKA

Metabolic treatment targets
• Reduction of the blood ketone concentration by 0.5 mmol/L/hour
• Increase the venous bicarbonate by 3.0 mmol/L/hour
• Reduce capillary blood glucose by 3.0 mmol/L/hour
• Maintain potassium between 4.0 and 5.5 mmol/L If these targets are not achieved, then the fixed rate intravenous insulin infusion (FRIII) rate should be increased by 1 unit/hr increments hourly until the targets are achieved.

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

Endocrinolog & Metabolism

Complications of DKA and its treatment • Cerebral oedema The risk is highest in paediatric (1%) and adolescent patients and is rarer in adults. Mechanism
 Exact pathogenic mechanism remains unknown – multifactorial
 ↑glucose → ↑osmolar gradient results in water shift from the intracellular fluid (ICF) to the extracellular fluid (ECF) space and contraction of cell volume. Correction with insulin and I.V fluids → rapid reduction in osmolarity → reversal of the fluid shift → cerebral edema.
 Features headache agitation or irritability unexpected fall in heart rate increased blood pressure. deterioration in level of consciousness abnormalities of breathing pattern, for example respiratory pauses oculomotor palsies pupillary inequality or dilatation. Treatment
 mannitol (20%, 0.5–1 g/kg over 10–15 minutes) or hypertonic sodium chloride (3% over 10–15 minutes) to induce osmotic fluid shifts. urgent treatment should be started when cerebral oedema is suspected and not be delayed whilst awaiting imaging. • Thromboembolism • Acute respiratory distress syndrome • Arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia • Acute kidney injury (AKI): Transient AKI may occur in up to 50% of adults. • Recovering DKA are at risk of hypophosphataemia weakness following treatment for DKA. often arises as a side effect of insulin with cells forming ATP and taking up free phosphate to achieve this.

Prognosis • The mortality rate associated with the modern management of DKA → 1-2% • Specifically, mortality relates to cerebral oedema.

(SCE- question samples.mrcpuk.org) A 26-year-old woman with DKA. After 24 hours of treatment with intravenous fluids, potassium and insulin, her normal subcutaneous insulin regimen was

resumed. However, she felt nauseated and there was a concomitant increase in blood ketones to 3.5 mmol/L (<0.3). random plasma glucose: 7.3 mmol/L. What is the most appropriate next step in management? • start glucose 10% with fixed-rate intravenous insulin A fixed-rate insulin infusion is recommended for faster resolution of DKA.
 If the blood glucose is below 14 mmol/L, it is necessary to administer intravenous infusion of 10% glucose in order to avoid hypoglycaemia and permit the continuation of fixed-rate intravenous insulin.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Hypoglycaemia

Definition • In patients with diabetes: generally described as ≤ 3.9 mmol/L (≤ 70 mg/dL). • It can be defined as “mild” if the episode is self-treated and “severe” if assistance by a third party is required.

Counter-regulatory responses in patients with hypoglycaemia and threshold for symptoms • There is considerable variability in the serum glucose level at which a person will experience symptoms of hypoglycemia. Usually occurred by the time serum glucose concentration is < 2.8 mmol/L (50 mg/dL). • Response mechanisms against hypoglycaemia in healthy patients: The first response is → insulin release inhibition. This occurs when plasma glucose reaches approximately 4 mmol/L. The second response is → counterregulatory hormone release (glucagon, adrenaline, noradrenaline, cortisol, and growth hormone). Occurs when glucose drops to 3.6-3.9 mmol/L. • Recurrent hypoglycemia in diabetic patients → hypoglycemia-associated autonomic failure (HAAF) → changes in the counterregulatory response (e.g., decreased epinephrine release) → lower glucose threshold needed to trigger symptoms → asymptomatic hypoglycemia (for this reason, the initial symptom of hypoglycemia in patients with HAAF is often confusion.) Epidemiology • between 30 to 40 % of patients with type 2 diabetes experience symptomatic hypoglycaemia. • The prevalence of severe hypoglycaemia is similar in patients with type 2 diabetes receiving insulin for more than 5 years to that in patients with type 1 diabetes Causes Diabetic patients: relative overdose of insulin or a noninsulin drug is the most common cause. • Insulin-related Insulin excess or noninsulin drugs (e.g., sulfonylureas, meglitinides) Increased sensitivity to insulin (weight loss, ↑activity/exercise) Decreased insulin clearance (renal failure) • Glucose-related (missed meals, Exercise) • Acute illness (sepsis, organ failure) Nondiabetic patients • Endogenous hyperinsulinism or IGF (insulinoma, Gastric bypass surgery (late dumping syndrome) • Exogenous hyperinsulinism (self-administration of insulin/sulphonylureas) • Critical illness (sepsis, organ failure) • Liver failure • Hormone deficiencies (hypopituitarism, adrenal insufficiency) • Alcohol • Autoimmune causes Insulin autoimmune syndrome (IAS) Anti-insulin receptor autoantibodies: Usually associated with autoimmune diseases like Sjögren syndrome and SLE. • Drugs that cause hypoglycemia Nonselective beta blockers

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

Endocrinolog & Metabolism

 Antimalarial drugs: quinine, chloroquine Antibiotics: sulfonamides, trimethoprim-sulfamethoxazole, fluoroquinolones Antifungal drugs: pentamidine, oxaline Analgesics: indomethacin, propoxyphene/dextropropoxyphene Antihypertensive drugs: ACE-inhibitors → improve insulin sensitivity. Antiarrhythmics: cibenzoline, disopyramide Low dose aspirin → ↓prostaglandin synthesis → stimulate beta cell Others: IGF-1, lithium, mifepristone, heparin, 6-mercaptopurine

Consider factitious disorder in patients with access to insulin and other diabetes medications (e.g., healthcare professionals), for whom there is no other obvious explanation for hypoglycemia.

Beta blockers can mask signs of hypoglycaemia.

Features
• Neurogenic/autonomic Increased sympathetic activity: tremor, pallor, anxiety, tachycardia, sweating, and palpitations Increased parasympathetic activity: hunger, paresthesias, nausea, and vomiting • Neuroglycopenic
 Agitation, confusion, behavioral changes Fatigue Seizure, focal neurological signs
 Nocturnal hypoglycaemia →vivid dreams →REM sleep disruption → daytime weakness and somnolence. Somnolence → obtundation → stupor → coma → death

Diagnosis → Whipple triad: Low plasma glucose concentration
 Signs or symptoms consistent with hypoglycemia Relief of symptoms when plasma glucose increases after treatment

Standard work-up for hypoglycaemia:
• Laboratory (not test-strip) blood glucose measurement • Insulin and C-peptide levels taken during the hypoglycaemic attack Hypoglycaemia + hyperinsulinaemia → insulin is the cause of hypoglycaemia. External insulin does not contain C-peptide, which is released from pancreatic islet with endogenous insulin. ↑ Insulin + ↓ C-Peptide → insulin abuse
 ↑ Insulin + ↑ C-Peptide → endogenous hyperinsulinism (e.g insulinoma, sulphonylurea) • Sulphonylurea level (serum or urine) • Liver function tests to rule out significant liver dysfunction • Blood alcohol and alcohol history • Cortisol levels, with or without Synacthen testing • Chest X-ray to exclude occult malignancy

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Work-up for hypoglycaemia is not indicated in two occasions
• If the Whipple triad is not confirmed, no further workup is indicated.
• Hypoglycemia in diabetic patients is almost always due to acute illness and/or medications (e.g., insulin) and further workup is generally not indicated.

If both C-peptide and insulin are raised → Suggests endogenous insulin secretion.
• Request a plasma sulfonylurea screen is the most appropriate next step, and depending on the result of this, further investigation may be required.

↑ Insulin with ↓ C-Peptide level points to a diagnosis of insulin abuse →Exogenous insulin administration (as the C peptide is released with endogenous insulin).
C-Peptide level ↑ with Sulfonylurea abuse

Management • For patient who are able to swallow: Oral glucose 15–20 g (Fast-acting carbohydrates such as glucose tablets, candy, or juice) Chocolate is not recommended as it contains fat which shown to slow the absorption of quick acting carbohydrate. Repeat capillary blood glucose measurement 10-15 minutes later. If it is still less than 4.0mmol/L, repeat step 1 (no more than 3 treatments in total). If blood glucose remains less than 4.0mmol/L after 30-45 minutes or 3 cycles, Consider: 150-200ml of 10% I.V glucose over 15 minutes
 Once blood glucose is above 4.0mmol/L and the patient has recovered, give a long acting carbohydrate (e.g. Two biscuits, One slice of bread/toast, 200-300ml glass of milk, Normal meal if due. • For patient who are unable to swallow (e.g. Glasgow Coma Scale Score ˂ 13): If intravenous access can be obtained. I.V glucose: 10% or 20% glucose solutions are preferred options: give 75-100ml of 20% glucose over 15 minutes. Repeat capillary blood glucose measurement 10 minutes later. If it is still less than 4.0mmol/L, repeat. give 150-200ml of 10% glucose over 15 minutes. Repeat capillary blood glucose measurement 10 minutes later. If it is still less than 4.0mmol/L, repeat 50% intravenous dextrose is not recommended by Joint British Diabetes Societies (JBDS): (hyperosmolarity →↑risk of extravasation injury, venous endothelium destruction and phlebitis). if no intravenous access can be obtained → Glucagon (1 mg intramuscularly) Glucagon acts on the liver by Activates adenylate cyclase → ↑ glycogenolysis and gluconeogenesis → rapid correction of hypoglycaemia

Hypoglycaemic symptoms with normal blood glucose level • Adults who have poor glycaemic control may start to experience symptoms of hypoglycaemia above 4.0mmol/L.
• adults who are experiencing hypoglycaemia symptoms but have a blood glucose level greater than 4.0mmol/L – treat with a small carbohydrate snack only e.g. 1 medium banana, a slice of bread or normal meal if due. (diabetologists-abcd.org.uk)

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

Endocrinolog & Metabolism

MRCPUK-part-1-September 2011 exam: An 18-year-old girl is admitted with hypoglycaemia (RBS: 1.9 mmol). her father who has type 2 DM describes a number of similar episodes. Insulin15 mg/ml (6-10 mg/ml)Proinsulin22% (22-24%) C-peptide 0.15 nmol/l (0.2-0.4 nmol/l).What is the most likely diagnosis? Insulin abuse (The raised insulin with low c-peptide level points to a diagnosis of insulin abuse. C-peptide levels would be raised in a patient following sulfonylurea abuse)

Hypoglycaemic episodes after regular exercise in patient who takes BD mixed insulin: • the most appropriate next step in his management is → transfer to a basal bolus regime where he can alter his short acting insulin dose just prior to planning exercise.

Diabetes mellitus: early morning hyperglycemia Overview
• The most common causes of morning hyperglycemia are nocturnal growth hormone secretion

and hypoinsulinaemia. • There is no evidence to support the existence of Somogyi effect (nocturnal hypoglycemia leading to a surge of counterregulatory hormones, leading to hyperglycemia in the morning). The opposite is typically found, ie, patients with morning hyperglycemia typically have high, not low, blood glucose concentrations at night.

Dawn phenomenon • Definition: A physiological increase of growth hormone (GH) levels in the early morning hours stimulates hepatic gluconeogenesis and leads to early-morning hyperglycemia • Diagnosis: measurement of nocturnal blood glucose → normal nocturnal glycemia, with early-morning hyperglycemia • Treatment: Long-acting insulin dose may be given later or increased under careful glycemic control.

Hypoglycaemia unawareness (HU) Definition • Hypoglycemia unawareness (HU) is defined as onset of neuroglycopenia before the appearance of autonomic warning symptoms.
Incidence
• Occurs in approximately 40% of people with type 1 diabetes mellitus (T1DM) and with less frequency in T2DM. Mechanism
• Recurrent hypoglycaemia → hypoglycemia-associated autonomic failure (HAAF) → failure of counter-regulatory hormones → inability to recognise impeding hypoglycaemia by symptoms. • Impaired awareness of the symptoms of plasma glucose levels below 3 mmol/litre is associated with a significantly increased risk of severe hypoglycaemia. • more common in patients with intensively controlled diabetes of long duration, leading to recurrent hypoglycaemia.
• Alcohol inhibits gluconeogenesis, decreases peripheral hypoglycaemic responses and impairs perception of symptoms of hypoglycaemia.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Symptoms and signs associated with progressive hypoglycemia

Treatment • Optimizing insulin treatment, flexible insulin therapy using basal–bolus regimens → Avoidance of hypoglycemia • avoid hypoglycaemia in adults with type 1 by offering insulin pump and real- time continuous glucose monitoring. • In recurrent severe hypoglycaemia that has not responded to other treatments refer to islet cell transplantation. • NICE advise to avoid relaxing individualised blood glucose targets to address impaired hypoglycaemia awareness → use the recommended targets • The patient demonstrating hypoglycemia unawareness is required to stop driving for 3 months after a second episode of hypoglycaemia.

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

Endocrinolog & Metabolism

Hyperosmolar hyperglycaemic state (HHS)

Pathophysiology • Severe hyperglycemia → ↑ serum osmolality → osmotic diuresis → severe dehydration • In general, there is enough insulin in patients with type 2 diabetes to suppress

ketogenesis, but insufficient to prevent hyperglycaemia and the hepatic resistance to glucagon.

Overview
• Occurs most commonly in elderly people with type 2 diabetes • Infection is the commonest precipitating factor (80%). • Mortality is higher than DKA (5% to 15%).
Features
• Osmotic features : Polyuria, polydipsia,
• Dehydration: dry mucous membranes, poor skin turgor, hypotension. • Acute cognitive impairment (lethargy, disorientation, stupor) is common Diagnostic criteria • Hypovolaemia • Hyperglycemia (≥ 30 mmol/L) • ↑ Serum osmolality (> 320 mOsm/kg) • Normal serum pH and ketones (pH >7.3, bicarbonate >15mmolL and no significant ketonenaemia <3mmol/L)

Management
• Fluids Fluid losses in HHS are estimated to be between 100 - 220 ml/kg (e.g. 10-22 litres in an individual weighing 100 kg). The fluid of choice is 0.9% sodium chloride (NaCL)
 Only switch to 0.45% (NaCL) if the osmolality is not declining despite adequate positive fluid balance. An initial rise in sodium is expected and is not itself an indication for hypotonic fluids. Fluid replacement alone with 0.9% sodium chloride solution will result in falling blood glucose.
 IV fluid replacement should aim to achieve a positive balance of 3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within the next 12 hours. • Insulin
 Low dose IV insulin (0.05 units/kg/hr) should only be commenced once the blood glucose is no longer falling with IV fluids alone OR immediately if there is significant ketonaemia (3β-hydroxy butyrate greater than 1 mmol/L or urine ketones greater than 2+)(e.g. mixed DKA / HHS picture). • Potassium
 Patients with HHS are potassium deplete, decreased intracellular K+ (normal or increased serum K+). less common problem in HHS than DKA but monitoring and replacement are essential Potassium should be replaced or omitted as required If potassium level in first 24 hr (mmol/L)→ No potassium replacement
 If K : 3.5 – 5.5 → 40 mmol/L If K below 3.5 → senior review as additional potassium required • Prophylactic anticoagulation: low molecular weight heparin (LMWH)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Targets • The fall in blood glucose should be no more than 5 mmol/L/hr • The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours. • Rapid changes of serum osmolarity are dangerous and can result in cardiovascular collapse and central pontine myelinolysis (CPM). • Measure or calculate osmolality (2Na+ + glucose + urea) frequently to monitor treatment response

Complication • Thrombotic events such as myocardial infarction, stroke or peripheral arterial thrombosis.
• Cerebral oedema, seizures secondary to rapid reduction in serum osmolality.
• Rapid correction of hyponatraemia, may lead to cerebral pontine myelinolysis

---

_Diabetes mellitus: hypertension management

Antihypertensive therapy is the single intervention most likely to reduce the overall risk of both microvascular and macrovascular events. • Lipid lowering therapy → prevent macrovascular events, but has no effect on microvascular events. • Lowering HbA1c only prevent → microvascular events.

First-line antihypertensive drug • For most diabetics regardless the age → ACE inhibitor. • For African or Caribbean family origin: ACE inhibitor plus either a diuretic or a generic calcium-channel blocker. • For a woman for whom, there is a possibility of becoming pregnant → calcium-channel blocker
• Because ACE-inhibitors have a renoprotective effect in diabetes they are the first-line antihypertensives recommended
• If an ACE inhibitor or ARB cannot be used, alternative first-line agents include calcium channel blockers and diuretics. However, in patients with severely increased albuminuria, nondihydropyridine agents (eg, diltiazem, verapamil) are generally preferred over dihydropyridine drugs (eg, amlodipine, felodipine), since nondihydropyridine calcium channel blockers can reduce albuminuria. • The routine use of beta-blockers in uncomplicated hypertension should be avoided, particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycaemia.

Targets: NICE recommend the following blood pressure (BP) targets for type 2 diabetics: • If end-organ damage (e.g. renal disease, retinopathy) < 130/80 mmHg • If NO end-organ damage < 140/80 mmHg

ACE inhibitors are first-line for hypertension in diabetics, irrespective of the patients age

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

Endocrinolog & Metabolism

Post prandial pain in diabetics

Macrovascular atherosclerosis in diabetes → Post prandial pain • Diabetes, especially Type 2 diabetes, is associated with macrovascular disease. • Smoking is a further risk factor for macrovascular atherosclerosis. • After a meal splanchnic blood flow is increased. If the mesenteric artery is occluded the lack of blood flow to the bowel will produce ischaemic type pain.

Diabetic retinopathy

Definition • Diabetic retinopathy is the retinal consequence of chronic progressive diabetic microvascular leakage and occlusion.

Epidemiology • The most common cause of visual impairment and blindness in adults aged 25-65 yearsold. • About 80% of patients with type I diabetes will have retinopathy 10 years after presentation. By contrast, in type II diabetes, where the time of onset is uncertain, up to 25% of patients will have retinopathy at the time of diagnosis. • Features of retinopathy usually do not

appear in patients with type 1 diabetes for up to 5 years following diagnosis.

Causes of rapid worsening of diabetic retinopathy • Pregnancy
• Rapid improvement in blood glucose
 suddenly dropped glucose levels → retinal artery vasoconstriction → rapid deterioration of retinopathy. • The risk of diabetic retinopathy significantly increased in smokers with type 1 diabetes while significantly decreased in smokers with type 2 diabetes (a meta-analysis published in 2018).

Pathogenesis
• Hyperglycaemia → ↑ retinal blood flow & abnormal metabolism in the retinal vessel walls → damage to endothelial cells & pericytes Endothelial dysfunction → ↑ vascular permeability → exudates (seen on fundoscopy).
 Pericyte dysfunction → predisposes to the formation of microaneurysms.
 Retinal ischaemia → production of growth factors → Neovasculization

Which factor has been shown to have an important role in regulating retinal capillary blood flow? • Contractile action of pericytes. • DM →↓ retinal pericytes (normally contractile action of pericytes regulates retinal capillary blood flow) → disordered blood flow regulation → ↑ retinal blood flow → ↑ shear stress on the vessel walls → retinopathy.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

The most likely cause of blurred vision in a newly diagnosed diabetic who was previously fit and well is → Osmotic changes in the lens.

Features • Asymptomatic until very late stages of disease • Visual impairment • Progression to blindness

Classification The earliest sign of diabetic retinopathy is the presence of microaneurysms on fluorescein angiography. Recently a new classification system has been proposed, dividing patients into those with nonproliferative diabetic retinopathy (NPDR) and those with proliferative retinopathy (PDR):

Traditional classification New classification Background retinopathy • microaneurysms (dots) • blot haemorrhages (≤ 3) • hard exudates

Pre-proliferative retinopathy • cotton wool spots (soft exudates; ischaemic nerve fibres) •

> 3 blot haemorrhages • venous beading/looping • deep/dark cluster haemorrhages • more common in Type I DM, treat with laser photocoagulation Mild NPDR • 1 or more microaneurysm Moderate NPDR • microaneurysms • blot haemorrhages • hard exudates • cotton wool spots, venous beading/looping and intra-retinal microvascular abnormalities (IRMA) less severe than in severe NPDR

> Severe NPDR • blot haemorrhages and microaneurysms in 4 quadrants • venous beading in at least 2 quadrants • IRMA in at least 1 quadrant

Non-Proliferative Diabetic Retinopathy (NPDR) • Subtypes Mild NPDR 1 or more microaneurysm Moderate NPDR Microaneurysms blot haemorrhages hard exudates cotton wool spots, venous beading/looping and intra-retinal microvascular abnormalities (IRMA) less severe than in severe NPDR Severe NPDR blot haemorrhages and microaneurysms in 4 quadrants venous beading in at least 2 quadrants IRMA in at least 1 quadrant • Management regular observation if severe/very severe consider panretinal laser photocoagulation

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

Endocrinolog & Metabolism

Proliferative retinopathy • Features More common in Type I DM, 50% blind in 5 years Normal visual acuity is seen in proliferative retinopathy
 Retinal neovascularisation (new vessels)- may lead to vitrous haemorrhage • Management Urgent referral to an ophthalmologist (seen within one week)
 laser photocoagulation: 90% effective in preventing loss of vision in type 1 diabetes. Intravitreal anti-vascular endothelial growth factor (VEGF) injection If severe or vitreous haemorrhage: vitreoretinal surgery.

Maculopathy • More common in Type II DM • May occur in all stages of NPDR and PDR • Macular oedema is a common form of maculopathy: Occurs when there is abnormal leakage and accumulation of fluid in the macula from damaged blood vessels in the nearby retina. • Mechanism: Retinal vessel microangiopathy → blood leaks → retinal hemorrhages → retinal infiltration with lipids and fluid → macular edema • Features Macular oedema, Hard exudates and macular ischemia. The exudates can be arranged in a ring (circinate exudates) surrounding a point of capillary leakage.
• Diagnosis: Can be shown on fluorescein angiography
• Management check visual acuity responds to laser treatment at the point of leakage. If there is a change in visual acuity then intravitreal vascular endothelial growth factor (VEGF) inhibitors.

Cotton wool spots (CWS) is a pre-proliferative feature: represent infarcts of the nerve fibre layer of the retina.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Diabetic Eye Screening Programme (NHS-2015) • Screening for diabetic retinopathy is offered to all people aged 12 and over with type 1 or type 2 diabetes. • Intervals between screening tests
 For diabetics at low risk of sight loss: one year to two years.
 For those at high risk of sight loss: one-year Treatment • Glycaemic control

 Achievement of target HbA1c of 47.54 mmol/mol (6.5%) would be associated with significantly reduced progression of retinopathy. Should be done gently and gradually (over several weeks) because suddenly drop glucose levels → retinal artery vasoconstriction → rapid deterioration of retinopathy. • Hypertensive control has been shown to be more effective than glycaemic control at reducing progression. • Indications for emergency referral to ophthalmologist: sudden loss of vision rubeosis iridis pre-retinal or vitreous haemorrhage retinal detachment.

• Indication for urgent referral to the ophthalmologist (seen within one week)
 Hard exudates in the macular region (evidence of clinically significant macular oedema) proliferative retinopathy Vitreous haemorrhage

Prognosis
• The percentage of irreversible loss of vision within 5 years if not treated: 3% in those with background retinopathy 20% for those with exudative
 30% for those with pre-proliferative,
 50% for those with proliferative retinopathy.

Asymmetric diabetic retinopathy

Asymmetric DM Retinopathy → suspect ocular ischemia (carotid artery disease) • Asymmetric diabetic retinopathy should always raise the suspicion that there is some other cause of ocular ischaemia on the worst-affected side, such as unilateral or asymmetrical carotid artery disease → do Carotid Doppler.

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

Endocrinolog & Metabolism

Hypertensive retinopathy

The presence of flame and blot haemorrhages, cotton wool spots and blurring of the optic disc margins are typical of the retinal changes that are seen in advanced hypertensive retinopathy. Whilst some of these findings are also observed in diabetic eye disease (e.g. dot and blot haemorrhages, cotton wool spots), the absence of other features (e.g. hard exudates, venous beading) should alert the clinician to other possible diagnoses.

Diabetic retinopathy during pregnancy

Diabetic retinopathy may rapidly deteriorate during pregnancy; therefore needs dilated fundoscopy or photography every trimester (3 monthly).
• Because of the increased risk of progression of the disease in pregnancy, conception should be delayed till the ocular disease is treated and stabilized and good diabetic control.

Diabetic neuropathy

Mechanism of neuropathy in diabetes (Nerve ischemia)
• Diabetes damages small blood vessels, which supply the nerve leads to nerve ischaemia.

Overview • Chronic hyperglycaemia damages small blood vessels, which supply the nerve leads to nerve ischaemia.
• Distal symmetric polyneuropathy is the most common form.
• Sensory nerves are affected more than motor so often reflexes remain intact. • Diabetic peripheral neuropathy usually goes in parallel with retinopathy and nephropathy. • It is also slowly progressive and affects mainly the spinothalamic pathway. • The most distal portion of the longest nerves is affected first.
Risk factors • poorly controlled hyperglycaemia • prolonged duration of diabetes (e.g., >10 years)
• Older age (e.g., >70 years) • Tall stature (longer fibres are more vulnerable to injury). • Hypertension • Smoking
• Dyslipidaemia with elevated triglycerides • co-existence of multiple CVD risk factors (type 2 diabetes)

Features • Asymptomatic (Up to 50%), but the physical examination reveals mild to moderately severe progressive symmetric loss of sensation in the distal lower extremities (stocking glove sensory loss) • Pain is the most common symptom induced by the involvement of small fibres

• Loss of sensation → painless injuries over pressure points, most commonly on the foot, over the metatarsal heads. • Autonomic features
Symptoms and signs of distal symmetric polyneuropathy (DSPN)

Large, myelinated nerve fibers Small, myelinated nerve fibers Function Pressure, balance Nociception, protective sensation Symptoms Numbness, tingling, poor balance Pain: burning, electric shocks, stabbing Ankle reflexes: reduced/absent Examination Vibration perception: reduced/absent (clinically 10 g monofilament (light pressure): diagnostic) reduced/absent Proprioception: reduced/absent

Treatment: First-line: duloxetine, amitriptyline, gabapentin or pregabalin Large fiber involvement in neuropathy results in reduced proprioception, light pressure and vibration sensation and is the earliest clinically identifiable feature of peripheral sensory motor neuropathy.
Short fiber neuropathy is a later manifestation of diabetic peripheral neuropathy, with symptoms including hyperparesthesia and superficial pain. Examination findings indicative of short fiber neuropathy include impaired thermosensation, reduced sweating and a cold foot • Duloxetine
 Action: serotonin-norepinephrine reuptake inhibitor (SNRI) Duloxetine is preferred to amitriptyline because it is associated with a lower risk of urinary retention. Contraindications: history of glaucoma
 patients already taking a serotonergic agent, such as tramadol, because of the associated risk of serotonin syndrome. • Amitriptyline
 recommended by NICE as second line if duloxetine is unsuitable.
 Contraindications: glaucoma and left bundle branch block • Pregabalin or gabapentin
 Action: voltage-gated calcium channel modulator considered as second or third line monotherapy or in combination.
 If there is renal impairment, pregabalin is preferable over gabapentin. • If the first-line drug

treatment does not work try one of the other 3 drugs

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Thermal (cold/hot) discrimination: reduced/absent Pinprick sensation: reduced/absent

---

Revision #1
Created 2026-01-06 17:51:15 UTC by Omar Ayman
Updated 2026-01-06 17:51:15 UTC by Omar Ayman