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Retinopathy. http://www.retinalscreening.nhs.uk/pages/ International Diabetes Federation Home Page. http://www.idf.org Mendosa, D. Online Diabetes Resources. http://www.mendosa.com/faq.htm NHS Diabetes. https://www.diabetes.org.uk World Health Organization. Diabetes Programme. https://www.who. int/diabetes/en/ 13.9.2 Hypoglycaemia Mark Evans and Ben Challis ESSENTIALS Hypoglycaemia is a low blood glucose concentration, clinically im- portant because glucose is the main fuel supporting brain metab- olism and function. The commonest causes are as a consequence of insulin or sulphonylurea drugs used to treat diabetes, but there are many rarer causes including insulinoma, toxins (alcohol), organ failure (hepatic), endocrine diseases (adrenal insufficiency, pituitary insufficiency), nonislet cell tumour hypoglycaemia (large mesen- chymal tumours and other malignancies), post bariatric surgery (noninsulinoma pancreatogenous hypoglycaemia syndrome), auto- immune insulin syndrome, factitious or felonious administration of insulin/sulphonylureas, and infections (malaria). Clinical features—typical features include 'autonomic' symptoms (e.g. tachycardia, tremor, and sweating), hunger and neuroglycopenic symptoms related to brain glucose deprivation (e.g. impaired cogni- tive function, blurred vision, drowsiness, and irritation). If blood glu- cose falls sufficiently low, patients may become sleepy, comatose, and/or suffer seizures, cardiac arrhythmias, irreversible cognitive damage, and even death. Recurrent hypoglycaemia can lead to a situation where symptomatic awareness of hypoglycaemia may be lost so that patients are unaware of their falling glucose until already cognitively impaired. Diagnosis—diagnosis in diabetes is usually clinical, with or without confirmation by a point-of-care blood glucose meter. With sus- pected nondiabetic hypoglycaemia, symptoms compatible with hypoglycaemia should occur at a time when a low plasma glucose concentration is documented, and these should be ameliorated fol- lowing correction of hypoglycaemia. Measurement of blood total in- sulin immunoreactivity, C-peptide, and proinsulin, and in some cases β-hydroxybutyrate, alcohol, sulphonylureas, and other hormone as- says may be required for diagnosis. Management—where conscious level is not impaired, the best treatment is oral intake of fast acting carbohydrates, but if the subject is drowsy or unconscious, injection rescue will be needed with intra- venous glucose or, if venous access is not available, intramuscular glucagon. Introduction—the clinical approach to hypoglycaemia The most common clinical scenario where physicians may generally encounter hypoglycaemia is as a consequence of the treatment of

 diabetes with insulin and/or other blood glucose-lowering therapies. Hypoglycaemia is uncommon in otherwise healthy nondiabetic in- dividuals due to existence of a robust counterregulatory hormonal response to falling plasma glucose concentrations. As described next though, there is a gamut of nondiabetes conditions which can result in hypoglycaemia that general physicians need to be aware of. The clinical approaches in these two situations are very different. With diabetes, there is usually less uncertainty about 'diagnosis' (i.e. whether this is hypoglycaemia or not, but the clinical strategy is directed towards minimizing consequences and/or risk of recur- rence). In nondiabetes, the focus is different with the initial goal being to determine whether the patient is truly suffering from hypoglycaemia or not and, if so, then to determine the cause and management needed. In this chapter we first describe hypoglycaemia in diabetes then describe how this is approached systematically in a nondiabetic pa- tient with suspected hypoglycaemia. Hypoglycaemia in diabetes Defining hypoglycaemia in diabetes Despite its undoubted importance, there are no universal criteria for defining hypoglycaemia in diabetes. In general though, hypogly- caemia can be defined either 'biochemically' (i.e. using a glycaemic threshold) or described by the functional consequences of a low blood glucose. For the former, although there is no single agreed blood glucose threshold used

to define hypoglycaemia, it is useful in clinical prac- tice to give advice about glucose levels to guide action. For example, those with insulin-treated diabetes may be told to avoid results of below 4 mM (72 mg/dl) with the intention of reducing the chances of dropping to levels at which cognitive function starts to become impaired (typically below 3 mM or 54 mg/dl). An important point to be aware of is that home devices using capillary ('finger-prick') samples may be inaccurate, particularly in the hypoglycaemic range even when used optimally. In diabetes research, clinical trials in dia- betes will often use biochemical definitions of hypoglycaemia; for example, many studies use a definition of below 3.9 mM (70 mg/dl) although this particular level may be less useful in clinical practice (see description of pathophysiology below). A more pragmatic approach is to use a functional classification of the effects of hypoglycaemia in diabetes, for example, as severe (requiring external assistance for rescue—usually family, friends, or work colleagues but may require paramedic attention) or not. There are limitations; for example, this cannot be used for those who are not independent (e.g. children or patients requiring long- term care) and it may also be difficult to determine whether help was needed or rather was offered and accepted (e.g. by a concerned spouse). This becomes particularly challenging where the definition has medico-legal consequences (e.g. the ability to hold a driving li- cence may depend on whether an episode of hypoglycaemia was judged severe or not). Severe hypoglycaemia even in those at risk is relatively uncommon so an additional definition providing information about the burden of hypoglycaemia might be to ask about moderate hypoglycaemia, defined as events requiring patients to interrupt their activity and treat immediately to avoid severe hypoglycaemia. Aetiology of hypoglycaemia in diabetes Hypoglycaemia is the commonest adverse effect of insulin therapy in diabetes, but it also occurs with other therapies such as treatment with sulphonylurea drugs (which act by increasing insulin secretion from the endogenous pancreas) and/or where insulin is used in combination with other blood glucose-lowering therapies. As a consequence, use of sulphonylurea drugs in type 2 diabetes therapy is starting to fall in many countries. Insulin-treated patients fear hypoglycaemia as much as other complications of diabetes such as amputation or blindness. This means that some will choose to accept worse (higher) overall con- trol of glycaemia to try to minimize hypoglycaemia risk, thus exposing themselves to increased risk of long-term complications of diabetes. Epidemiology of hypoglycaemia in diabetes With increasing rates of type 2 diabetes treated with insulin, the most common presentations of hypoglycaemia to emergency services in developed countries are older patients (over 65 years) treated with insulin. The demography means that there are often coexisting comorbidities other than diabetes. Several observational studies have shown that severe hypoglycaemia in this age group is associated with increased risk of mortality within the following 12 months, although it is unclear whether this is directly related to hypoglycaemia or to the other comorbidities. Hypoglycaemia is also common in hospitalized patients with dia- betes, occurring in 5 to 10%. This may be attributed to multiple fac- tors such as coexisting illness, altered meals and schedule but also sometimes removing the locus of control from a patient who effect- ively self-manages diabetes outside hospital. Increasingly, such pa- tients may be allowed where appropriate (conscious and alert) to continue managing their own diabetes while an inpatient. Independent of age, there is an increased risk of hypoglycaemia seen with increasing duration of diabetes, whether type 1 or type 2 diabetes. The cause is unclear although one possibility for the latter at least is that this reflects the progressive loss of endogenous (glucose-responsive) insulin secretion that typifies type 2 diabetes. Hypoglycaemia is also a particular concern for very young children under the age of 5. This carries multiple additional challenges, for example with dosing small amounts of insulin accurately and unpredictable food intake. Pathophysiology of hypoglycaemia in diabetes Ultimately, hypoglycaemia in diabetes is

caused by excess insulin ac- tion in real or absolute terms, whether this is exogenous insulin by injection or endogenous insulin stimulated by secretagogue drugs such as sulphonylureas. Excess insulin action may occur either be- cause of a systematic overtreatment of diabetes with therapy and/or because of a change in circumstances occurring at the time of the event. A useful clinical strategy is to decide whether an event is a 'one-off' with or without an identifiable precipitant or whether part of a recurring pattern needing a systematic change in approach. Common identifiable causes for episodes of hypoglycaemia are • Insulin errors (e.g. accidentally giving a duplicate insulin injec- tion, injecting the wrong insulin, or miscalculating a dose in those who adjust insulin doses). • Less food, particularly carbohydrate intake than anticipated from missed or inadequate meals or snacks. • Exercise or activity which can cause hypoglycaemia either at the time and/or exert a delayed effect in the evening or night following activity.

13.9.2 Hypoglycaemia 2533 • Alcohol—typically exerting a delayed effect to reduce hepatic glu- cose production during the night or even the following morning after consumption. This can occur sometimes even with relatively modest intake. • Hot weather increasing insulin absorption. • Breastfeeding can markedly increase the metabolic demands on mother and many with insulin-treated diabetes have to reduce insulin doses significantly at this time to avoid hypoglycaemia. In addition to these factors which may help explain individual epi- sodes of hypoglycaemia, there may be other risk factors that gener- ally increase the risk of hypoglycaemia: • Insulin injection site problems—overuse of the same insulin injec- tion site can result in a build-up of local fat deposits, lipohypertrophy or, more rarely, loss of fat (lipoatrophy). This can alter the predict- ability of insulin absorption so that blood glucose levels can swing widely without an obvious cause. This is an important and often overlooked cause of glycaemic instability and hypoglycaemia and patients should 'rotate' injection sites so as not to overuse an area and/or avoid injecting into lumpy areas. • Use of inappropriately long needles for insulin injection resulting in deeper insulin delivery into more vascular muscle thus increasing absorption speed. Needle lengths of 4 to 6 mm are appropriate for most patients. • Impaired counterregulation and symptomatic unawareness (see next). • 'Tight' glycaemic control with overly-aggressive attempts to lower average blood glucose levels. An inverse relationship between overall control measured by HbA1c and rates of severe hypogly- caemia was identified in the large and pivotal DCCT (Diabetes Control and Complications Study). In the real world of type 1 diabetes, more recent data suggest that this is not seen with no association between HbA1c and hypoglycaemic risk, perhaps illustrating the differences between clinical studies and everyday clinical practice where patients may be reluctant to intensify gly- caemic control if they start to suffer from hypoglycaemia. • Other medical conditions can predispose such as renal/liver im- pairment and (rarely) coexisting adrenal/pituitary insufficiency. Counterregulatory defences against hypoglycaemia In nondiabetes, a robust series of counterregulatory defences nor- mally prevent hypoglycaemia from occurring (Fig. 13.9.2.1). An early and potent defence is cessation of insulin secretion from the nondiabetic pancreas (typically at a plasma glucose of around 4 mM) to reduce circulating insulin, something that cannot occur in those treated with exogenous insulin or insulin secretagogues such as sulphonylureas. If plasma glucose concentrations continue to fall (for example under experimental conditions in nondiabetes Normal Counter-regulatory Defences against Hypoglycaemia Counter-regulatory Defences against Hypoglycaemia in Type 1 Diabetes Impaired Counter-regulatory Defences against Hypoglycaemia in Subset of Type 1 Diabetes Switch-off endogenous insulin secretion 4 3 2 1 Release of glucagon Release of other counter-regulatory hormones Warning symptoms Cognitive Impairment Lethargy, risk of coma/seizures Glucose (mM) (a) Release of other counter-regulatory hormones Warning

symptoms 4 3 2 1 Cognitive Impairment Lethargy, risk of coma/seizures Glucose (mM) (b) (c) Release of counter-regulatory hormones/warning symptoms 4 3 2 1 Cognitive Impairment Lethargy, risk of coma/seizures Glucose (mM) Fig. 13.9.2.1 Counterregulatory responses to hypoglycaemia. (a) Normal responses with protective defences shown in blue and consequences of brain nueroglycopenic in red. (b) Altered responses in type 1 diabetes. (c) Impaired counterregulatory responses in a subset of patients with type 1 diabetes.

section 13 Endocrine disorders 2534 with insulin infusion), at a plasma glucose level of between 3 and 4 mM, a well-orchestrated release of counterregulatory hor- mones occurs. Glucagon is released from α-cells of the pancreatic islets, acting predominantly to oppose insulin action at the liver. Neurohumoral sympathoadrenal responses with increased sympa- thetic nerve activation and release of adrenaline from the adrenal medulla also exert anti-insulin actions in periphery and at the liver. Cortisol and growth hormone also rise and help counteract the effects of insulin. Associated with this neurohumoral response is the generation of symptoms alerting the patient of a falling glucose. These ‘autonomic’ symptoms include sympatho-adrenal symptoms such as tachy- cardia, palpitations, pallor, anxiety, and tremulousness through ac- tivation of β-adrenergic receptors, whereas cholinergic activation results in sweating and paraesthesia. Hunger is also generated, an important symptom in its own right as it prompts corrective feeding to restore glucose. A major rationale for the existence of such robust counter regulatory defences protecting against hypoglycaemia is because of the reliance of brain on blood glucose to fuel metabolism and support function. Brain has minimal local stores of glycogen and is extremely metabolically active. In adults, brain represents about 2% of body weight yet consumes at least 20% of glucose. As plasma glucose concentrations fall, ‘neuroglycopenic’ symptoms are ac- tivated because of brain glucose deprivation—such as blurred vision, drowsiness, irritation, slurred speech, and behavioural changes. Cognitive function becomes impaired with slowing of re- action times, increased tendency to make errors and loss of judge- ment. This is important as this may mean that patients lose the ability to make appropriate and judicious decisions about treating their hypoglycaemia. Eventually if blood glucose falls sufficiently low for long enough, patients may become sleepy, comatose and/ or suffer seizures. With prolonged deep hypoglycaemia, cardiac arrhythmias, myocardial infarction, stroke, irreversible cognitive damage, and even death may ensue. Impaired counterregulatory defences against hypoglycaemia in diabetes In diabetes, the protective counterregulatory defences described earlier may be altered (Fig. 13.9.2.1). The ability to switch off en- dogenous insulin secretion is lost in those treated with exogenous insulin or secretagogue drugs such as sulphonylureas. Glucagon re- sponses to hypoglycaemia are lost during the first few years of type 1 diabetes and probably also become blunted in those with insulin- treated type 2 diabetes. A subset of people with diabetes develop abnormalities in other counterregulatory defences, particularly catecholamine responses, associated with a loss of symptomatic awareness of hypoglycaemia so that defensive responses become diminished and delayed, occurring after the onset of cognitive dysfunction. This pattern is associated with a markedly increased risk of suffering from severe hypoglycaemia (as described earlier requiring assistance to correct). The mechanisms underpinning this reduction in counterregulatory responses and loss of symptomatic awareness remain unclear, but antecedent hypoglycaemia itself is a major contributor, resulting in blunted responses to subsequent hypoglycaemia (effectively a type of ‘stress desensitization’ where exposure to a repeated stress— here hypoglycaemia—results in reduced responses). The label ‘hypoglycaemia-associated autonomic failure’ (HAAF) is sometimes attached to the loss of counterregulatory neurohumoral responses that follows antecedent hypoglycaemia. Duration of

diabetes is also a risk factor for HAAF/hypoglycaemia unawareness although it is not clear whether this is because of hypoglycaemia exposure or an independent effect of diabetes. Clinical features of hypoglycaemia in diabetes Typical symptoms are as already described, with sympathoadrenal and neuroglycopenic symptoms and also hunger. In those with impaired counterregulation/unawareness, hypoglycaemia may be more apparent to others—family or work colleagues—and may con- sist of the consequences of neuroglycopenia such as irritability and abnormal behaviour or increase in errors at work. Overnight hypoglycaemia is a particular concern for many pa- tients with insulin-treated diabetes (and their carers/parents/rela- tives). During sleep, patients may be slower to recognize symptoms but also counterregulatory defences may be blunted—perhaps related to supine posture. In addition to reduced defences, many people have circadian changes in insulin sensitivity during the hours of darkness. For example, a common pattern is for a relative insulin resistance at the end of the sleep period, sometimes called the ‘dawn phenomenon’. This means that patients may wake with high blood glucose values and lead to the temptation to increase background insulin doses which can increase risk at other times of night. A formerly common description of high morning glu- cose values being caused by rebound after silent overnight hypo- glycaemia (eponymously named as the Somogyi effect) has been largely discredited with modern methods for continuously moni- toring overnight glycaemia. Acute management of hypoglycaemia in diabetes Acute management is aimed at recognizing and taking early cor- rective action to restore blood glucose. Most episodes are self- managed with oral rapid-acting carbohydrates with 15–20 g glucose (e.g. 150–200 ml orange juice, 150 ml cola, four dextrose tablets), repeated if need be. Good practice is to follow up this ini- tial rapid-acting therapy with a more starchy or mixed snack or meal to sustain the restoration in glucose. Highly concentrated glucose gels are commercially available, administered orally by smearing into the inside of the cheek cavity. Although conven- tional teaching was that these were absorbed through the buccal mucosa, current thinking is that the glucose is swallowed and ab- sorbed from the stomach. These should not be used therefore in unconscious patients. Where the level of consciousness is reduced, rescue needs to be by injection of either glucose intravenously or 1 mg glucagon given intravenously or intramuscular/subcutaneous delivery (with future options perhaps including nasal glucagon delivery). Although 50% glucose has often been used, many current protocols suggest that the maximum concentration used is 20% because of the risks of tissue necrosis if there is extravasation. Glucagon carries the potential ad- vantage of not requiring an intravenous cannula for administration. It is available as a kit for emergency use (e.g. to be given at home by partners/parents). Glucagon acts predominantly by mobilizing hep- atic glycogen stores so is likely to be ineffective where these are low (for example after overnight fasting or in the few hours following a previous glucagon injection).

 Longer term management of hypoglycaemia in diabetes In addition to acute restoration of glucose, patients and/or their clinical teams should also reflect on the causes for an episode and whether any changes are needed to treatment and/or self- management. Causes to consider were described earlier and listed in Table 13.9.2.1. In type 2 diabetes, sulphonylureas were widely used for many years as an effective therapy for diabetes but use has declined now with the availability of newer agents carrying less risk of hypogly- caemia. For example, therapies acting through the glucagon-like peptide-1 (GLP-1) axis consist of either synthetic GLP-1 agonists or agents which inhibit the breakdown of endogenous GLP-1 by the en- zyme dipeptidyl peptidase IV (DPPIV inhibitors). These mimic the internal GLP-1 signal that primes pancreatic β cells to release insulin but importantly do so in a glucose-responsive fashion, thus

redu- cing the potential for inappropriate insulin release during hypogly- caemia which can occur with nonglucose-responsive therapy (e.g. sulphonylureas). In those using insulin therapy, there may also be adjustments needed to reduce risk of hypoglycaemia. Increasingly insulin re- gimens (in both type 1 and type 2 diabetes) are designed to try to tailor insulin doses to daily variations in diet/activity etc rather than using fixed dosing. Modern insulin analogues are designed to have more rapid onset/offset of action (to be used around mealtimes or for blood glucose corrections) or longer acting analogues for use as background cover. Probably most important is the training and support given to patients to allow them to gauge accurately insulin dosing. Developed from a successful German model, the DAFNE (Dose Adjustment for Normal Eating) programme in the United Kingdom, Ireland, and Australia successfully educates patients in op- timizing insulin dosing and can reduce problematic hypoglycaemia. For those struggling with hypoglycaemia despite optimizing therapy with injections, changing insulin delivery to continuous subcutaneous insulin infusion (CSII or 'insulin pump' therapy) may allow blood glucose to be controlled without hypoglycaemia. Other technologies available, albeit with limited access to date, are devices allowing continuous or semi-continuous glucose monitoring (CGM) from subcutaneously inserted sensors measuring interstitial fluid glucose as a surrogate for blood glucose. CGM can be linked to alarms to warn patients of hypoglycaemia—actual or anticipated if glucose is dropping. CSII can be linked to CGM so that insulin de- livery is automated, including being reduced or suspended if glucose levels are falling or low with the aim of reducing hypoglycaemia risk. Finally, small numbers of patients with recalcitrant and serious/ potentially life-threatening hypoglycaemia may be considered for transplantation of either a whole pancreas or isolated islets. Numbers are limited currently by the availability of donors and the require- ment for potentially toxic long-term immunosuppressive therapy. Consequences of hypoglycaemia in diabetes Acute episodes of profound hypoglycaemia may result in seizures, sudden death, or structural brain damage, although these are un- common. More commonly, acute hypoglycaemia can increase risk of accidents; falls and road accidents for example. Patients with insulin-treated diabetes fear hypoglycaemia and some may respond by deliberately running blood glucose levels high, thus exposing themselves to risks of long-term complications of diabetes. Finding the correct balance between risk of hypoglycaemia and long-term exposure to hyperglycaemia is challenging. Recent large studies examining the benefits of very tight blood glucose control in patients with type 2 diabetes who are at high risk of cardiovascular disease have shown an apparent increase in morbidity with lower glycaemia. The mechanisms are unclear but one possibility is hypoglycaemia. Over the long term, the possible cumulative effects of recurrent hypoglycaemia, particularly on brain and cognitive functioning, including memory, are unclear. Neuropsychological data suggest that in young children, the developing brain may be particularly sensitive to hypoglycaemia exposure. Future approaches to minimizing hypoglycaemia in diabetes Glycaemic management in diabetes is a trade-off between the de- sire to lower average glycaemia to reduce long-term complications and the acute hazard of hypoglycaemia. New therapies for type 1 and type 2 diabetes may allow the former without the latter. For ex- ample, new insulins with more rapid onset/offset, relative hepato- selectivity, or even 'smart' glucose-responsive insulins. Technology described briefly here earlier is advancing rapidly with automated insulin delivery from linked CGM and CSII opening up the real possibility of 'artificial pancreas' technology. This might also allow glucagon as well as insulin to be administered by a pump with delivery targeted to avoid or treat hypoglycaemia. Hypoglycaemia in nondiabetes As outlined previously, the approach to hypoglycaemia or suspected hypoglycaemia in nondiabetes is initially that of confirmation and diagnosis. A diagnosis of hypoglycaemia based on clinical symptoms alone is challenging and often

erroneous due to lack of specificity. Moreover, it is not possible to biochemically define a single glycaemic threshold below which symptoms of hypoglycaemia develop in all individuals.
Table 13.9.2.1 Causes of hypoglycaemia in diabetes Acute causes for individual episodes of hypoglycaemia Increased insulin action Insulin dose too large (relative to carbohydrates/blood glucose) Increased absorption (hot weather, sauna) Injection site lipodystrophy Injections too deep (wrong needles) Insulin error (e.g. duplicate injection or incorrect insulin) Decreased carbohydrates Smaller or low-carbohydrate meal (relative to insulin dose) Missed snack Increased glucose demand Exercise/activity Breastfeeding Alcohol Factors associated with increased background risk of hypoglycaemia Previous problematic hypoglycaemia Long duration of diabetes Hypoglycaemia unawareness Adrenal/pituitary insufficiency

section 13 Endocrine disorders 2536 For example, in healthy individuals hypoglycaemic symptoms may develop at plasma glucose concentrations approximating 3.0 mmol/L whereas in patients with antecedent hypoglycaemia, symptoms may occur at lower glycaemic thresholds due to an attenuated or absent physiologic response to hypoglycaemia. Therefore, a diagnosis of hypoglycaemia depends on satisfying Whipple's triad. This man- dates that symptoms compatible with hypoglycaemia occur at the time a low plasma glucose concentration is documented and are ameliorated following correction of hypoglycaemia. Only after these criteria are fulfilled should further investigations to determine the aetiology of a hypoglycaemic disorder be embarked upon. Initial work-up of a patient suspected of having a hypoglycaemic disorder involves detailed history, clinical examination, and scru- tiny of biochemical data. A history of hypoglycaemia should be interrogated for timing, duration, and nature of specific symptoms with special attention given to the temporal association of precipi- tants such as fasting, exercise, and medications, or relieving fac- tors including carbohydrate ingestion. Establishing the presence of comorbid conditions is critical as many diseases may manifest as hypoglycaemia including disorders of the liver and kidney, sepsis, nonislet cell tumours, and endocrine deficiency (cortisol and growth hormone). Eliciting a medication history is vital as many drugs, in addition to insulin and insulin secretagogues, cause drug-induced hypoglycaemia. Moreover, ascertaining accessibility to diabetic medications may identify surreptitious, accidental, or rarely, malicious causes of hypoglycaemia. Finally, establishing a family history of hypoglycaemia is relevant for identifying con- genital hyperinsulinism syndromes, inborn errors of metab- olism, or inherited tumour syndromes that may predispose to hypoglycaemia. Aetiology of nondiabetic hypoglycaemia The principal causes of nondiabetic hypoglycaemia are presented in Table 13.9.2.2. Hypoglycaemic disorders may be classified into those that produce hypoglycaemia due to inappropriately elevated plasma insulin levels or those that result in symptomatic hypogly- caemia in association with appropriately suppressed plasma insulin levels (Table 13.9.2.3). Although many hypoglycaemic disorders in neonates and infants are recognized, the remainder of this chapter focuses primarily on hypoglycaemic disorders encountered in adults with reference to paediatric syndromes that may present for the first time in adulthood. Drug-induced hypoglycaemia Several pharmacological agents and toxins predispose to hypogly- caemia. Unsurprisingly, the most common cause of drug-induced hypoglycaemia is insulin followed by insulin secretagogues such as sulfonylureas and meglitinides. Few drugs cause hypoglycaemia in the absence of concomitant antidiabetic therapy usage and of these, ethanol, β-adrenergic antagonists, sulphonamides, somatostatin analogues, and salicylates have been reported. Ethanol is a common cause of noniatrogenic hypoglycaemia and frequent causative agent in hypoglycaemia-related deaths. Ethanol induces hypoglycaemia through inhibition of gluconeogenesis due to increased hepatic alcohol dehydrogenase activity and

subsequent depletion of NADH. As a consequence of a reduced NADH/NAD+ ratio conversion of lactate to pyruvate, the main gluconeogenic substrate, is minimized resulting in impaired hepatic glucose output. In a fasted or malnourished patient con- suming alcohol, fasting hypoglycaemia may occur following de- pletion of hepatic glycogen stores. Biochemically, hypoglycaemia is associated with increased plasma β-hydroxybutyrate levels and suppressed insulin, C-peptide, and proinsulin together with de- tectable levels of blood ethanol. Because glycogen stores have been depleted and gluconeogenesis inhibited, glucagon administration is not an effective therapy and oral or intravenous glucose are the treatments of choice. Noncardioselective β-blockers, such as propranolol, increase the risk of fasting hypoglycaemia due to their ability to impair hepatic and renal gluconeogenesis, reduce glucagon secretion, and mask autonomic symptoms of hypoglycaemia. Cholinergic symptoms such as hunger and sweating are not affected, however, and in an unaware patient may serve as clinical indicators of hypoglycaemia. Through undefined mechanisms, sulphonamides stimulate insulin secretion while salicylates both inhibit hepatic glucose production and promote insulin secretion thereby inducing hypoglycaemia. Insulinoma Insulinomas are insulin-secreting tumours of the pancreatic islets of Langerhans. Although rare, insulinoma is the most common cause of spontaneous fasting hypoglycaemia in an otherwise healthy adult and occurs with an annual incidence of 1–2 per million population. Insulinomas may appear at any age, although they most typically present in the fourth to sixth decades with a slight female prepon- derance reported in some case series. Table 13.9.2.2 Causes of nondiabetic hypoglycaemia Hypoglycaemia with suppressed endogenous insulin Drugs Insulin Ethanol β-adrenoceptor antagonists, salicyclates, others Critical illness Sepsis Chronic kidney disease Cirrhosis Congestive cardiac failure Malaria Endocrine deficiencies Cortisol deficiency Growth hormone deficiency Nonislet cell tumour-associated hypoglycaemia (NICTH) Surreptitious, accidental, or malicious hypoglycaemia Inborn errors of metabolism Hypoglycaemia with inappropriately elevated endogenous insulin Drugs Insulin secretagogues Neuroendocrine tumours Insulinoma GLP-1oma Postgastric bypass surgery Noninsulinoma pancreatogenous hypoglycaemia syndrome Postprandial (reactive) hypoglycaemia Autoimmune Hirata disease (anti-insulin antibody) Type B insulin resistance (anti-insulin receptor antibody) Congenital hyperinsulinism syndromes

 Signs and symptoms Insulinoma may present, initially, with fatigue, weight gain, altered mental state, and/or autonomic symptoms that rapidly improve fol- lowing carbohydrate ingestion. Because of the nonspecific and subtle nature of these symptoms the interval between symptom onset and diagnosis is often 3–5 years with a delayed diagnosis of more than 20 years reported in some instances. With frequent hypoglycaemia patients with insulinoma may develop hypoglycaemia unawareness. Thus, for many patients, neuroglycopenic symptoms such as loss of consciousness, disorientation, behavioural changes and/or seizure may dominate the clinical presentation and occur at times of ex- ercise or fasting with a minority of patients reporting postprandial symptoms alone. Pathology Most insulinoma are sporadic, small (<1 cm), solitary and be- nign tumours with less than 10% exhibiting malignant potential. Multiple insulinomas occur in less than 10% of cases, and most often in association with multiple endocrine neoplasia (MEN)- 1, an inherited tumour syndrome characterized by pancreatic neuroendocrine tumours in conjunction with primary hyper- parathyroidism and pituitary tumours. Tumours occurring in the setting of MEN1 are associated with loss of function of menin, the protein product of the tumour suppressor gene MEN1. Loss of heterozygosity at the MEN1 locus has been demonstrated in MEN1-associated insulinomas; however, the mechanism(s) by which menin loss

promotes tumourigenesis remain unclear. Although single-copy deletion and somatic mutations in MEN1 have been identified in small subset of sporadic (nonfamilial) insulinoma, understanding the genetic events that underlie these tumours has, until recently, been less forthcoming. Through the use of whole exome sequencing several investigators have recently identified a recurrent somatic mutation in the transcription factor Ying Yang 1 (YY1) in one-third of sporadic insulinomas. The recurrent YY1 mutation (YY1T372R) alters the DNA binding speci- ficity of the transcription factor resulting in neomorphic activity and marked changes in tumoural gene expression which collectively contribute to disease pathogenesis by promoting constitutive insulin secretion from tumour cells. The main pathophysiological feature of insulinoma is the in- ability of tumour cells to adequately suppress insulin secretion as plasma glucose concentrations fall to hypoglycaemic levels. Hypoglycaemia, therefore, results from reduced rates of glucose production due to relative insulin excess for a given plasma glucose concentration. That 95% of patients with insulinoma have elevated fasting proinsulin plasma concentrations and tumour cells contain an elevated proinsulin-to-insulin ratio as well as reduced insulin content compared with normal β-cells suggests that dysregulated insulin biosynthesis and secretion also contribute to the dysfunc- tion of tumourous islets. Diagnosis A 72-hour fast is the investigation of choice to establish diag- nosis of insulinoma. During the fast, biochemical diagnosis is es- tablished when hypoglycaemia (<3 mmol/litre), in the presence of Whipple's triad, is associated with inadequately suppressed concentrations of plasma insulin (≥18 pmol/litre), C-peptide (≥0.2 nmol/l), proinsulin (≥5 pmol/litre), reduced plasma concentrations of β-hydroxybutyrate (≤2.7 mmol/litre) and nega- tive plasma or urine sulfonylurea screen. An increase in plasma glucose concentration of at least 1.4 mmol/litre following intravenous glucagon indicates maintenance of glycogen stores and provides further evidence for excess insulin-like activity. Using these criteria two-thirds of patients with insulinoma will be diagnosed within 24 hours of fasting, 95% of patients within 48 hours, and 99% by 72 hours. Conventional noninvasive imaging modalities such as com- puted tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound will detect up to 80%, 85%, and 90% of insulinomas, respectively (Fig. 13.9.2.2). However, a small number of insulinomas remain elusive following conventional imaging. To facilitate localization of these smaller tumours, se- lective arterial calcium stimulation with hepatic venous sam- pling for insulin quantification regionalizes insulinoma with high sensitivity (>90%); however, this method is invasive, technically challenging, and poses a risk for complications. Due to reduced expression of somatostatin receptor 2 (SSTR2) in insulinoma somatostatin receptor scintigraphy detects only 20–50% of be- nign tumours. In contrast, GLP1 receptors are highly expressed in insulinomas leading to development of GLP1-like radioligands that, when used in combination with whole planar body imaging and single photon emission CT (SPECT), may provide an alter- native, noninvasive method for safely and successfully localizing occult insulinomas. Table 13.9.2.3 Biochemical interpretation of a 72-hour fast Diagnosis Glucose (mmol/litre) Insulin (pmol/litre) C-peptide (nmol/litre) Proinsulin (pmol/litre) β-hydroxybutyrate (mmol/litre) IGF2:IGF1 ratio Oral agent screen Anti-insulin receptor antibody Normal <3 <18 <0.2 <5

> 2.7 <10 – – Exogenous insulin <3 18 <0.2 <5 <2.7 <10 – – Sulfonylurea <3 18 0.2 5 <2.7 <10

-

– Insulinoma <3

> 18 0.2 5 <2.7 <10 – – Nonislet cell tumour <3 <18 <0.2 <5 <2.7 10 – – Autoimmune disorder <3 18 0.2 5 <2.7 <10 –

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section 13 Endocrine disorders 2538 Treatment Surgical resection remains the treatment of choice for insulinomas and is curative for benign and solitary lesions. Prevention of recur- rent hypoglycaemia is the goal of medical therapy and following dietary modification, diazoxide, a potent inhibitor of insulin se- cretion, is first-line treatment for patients with inoperable, meta- static disease, or those who are poor surgical candidates. Adverse effects of diazoxide include hirsutism, oedema, or gastric irritation, which may prove intolerable and necessitate transition to an alter- native therapy. Owing to their inhibitory effect on insulin secretion, calcium channel blockers, such as nifedipine or verapamil, may be tried. Insulinomas are largely insensitive to traditional somatostatin analogues, such as octreotide, due to reduced expression of SSTR2 on insulinoma cells. In patients with metastatic disease, emboliza- tion, or surgical debulking of hepatic metastases to reduce disease volume may produce remission. Malignant insulinomas generally respond poorly to traditional cytotoxic chemotherapeutic agents al- though rapamycin and everolimus, oral inhibitors of the mamma- lian target of rapamycin (mTOR), have proved beneficial in some patients with metastatic insulinoma and refractory hypoglycaemia. Hypoglycaemia and gastric bypass surgery Roux-en-Y gastric bypass (RYGB) surgery is the most effective and commonly employed method for long-term weight loss. An increas- ingly recognized complication of RYGB surgery is noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS), a rare dis- order of hyperinsulinaemic hypoglycaemia that typically presents with severe neuroglycopaenia 1 to 3 hours following a meal. NIPHS occurs with an estimated postoperative prevalence of less than 1% with a median time of 2.7 years reported from surgery to first occur- rence of inpatient treatment for hypoglycaemia. Diagnosis In accordance with Whipple’s triad, at the time of hypoglycaemia patients have elevated insulin, C-peptide, and proinsulin levels and symptoms rapidly improve following correction of a low plasma glucose level. Conventional imaging modalities are not helpful; however, selective arterial calcium stimulation tests may identify pancreatic regions responsible for hyperinsulinism if partial or sub- total pancreatic resection is being considered. Pathophysiology Initially, NIPHS was thought to be due to nesidioblastosis, a con- dition largely limited to newborns and rarely found in adults, based on histopathological findings of β-cell hypertrophy, islet hyperplasia and increased β-cell mass, following examination of pancreata resected from affected individuals. However, subse- quent studies have suggested alternative pathologic causes due to the absence of nesidioblastosis in some patients with postoperative hyperinsulinism. Enhanced levels of incretin hormones such as glucagon-like peptide 1 (GLP-1) and, to a lesser extent, gastric in- hibitory peptide potentiate postprandial insulin secretion following RYGB surgery, may increase β-cell mass and have been implicated in the aetiology of hyperinsulinaemic hypoglycaemia. Treatment Carbohydrate restriction or postoperative delivery of nutrients to the bypassed proximal intestine by gastrostomy tube may be used to alleviate postprandial hypoglycaemia. When dietary strategies fail, medical therapy with diazoxide, somatostatin analogues, or α-glucosidase inhibitors may be considered. Partial pancreatectomy has been advocated for some patients with refractory hypoglycaemia and

life-threatening neuroglycopenia. Nonislet cell induced hypoglycaemia Persistent hypoinsulinaemic hypoglycaemia occurs in the very rare circumstance of nonislet cell tumour-associated hypoglycaemia (NICTH). NICTH is most commonly a late manifestation of large mesenchymal tumours, such as fibrosarcomas or mesotheliomas, that are capable of secreting large amounts of incompletely pro- cessed insulin-like growth factor-II (IGF-II) precursor proteins (so-called big proIGF-II). Other tumour types reported to produce IGF-II include hepatocellular carcinoma, gastrointestinal stromal tumours (GISTs), adrenocortical carcinoma, germ-cell tumour, and renal cell carcinoma. Pathophysiology Elevated IGF-II activity suppresses hepatic glucose production and increases glucose uptake by skeletal muscle. Attenuated secretion of counterregulatory hormones including growth hormone (GH) and glucagon is also a consequence of increased plasma IGF-II (a) (c) (b) Fig. 13.9.2.2 Radiological localization of insulinoma by (a) computed tomography (CT), (b) magnetic resonance imaging (MRI) and
(c) endoscopic ultrasound (EUS). (a) 13 mm insulinoma localized to head of pancreas. (b) 12 mm hypervascular insulinoma localized to head
of pancreas. (c) 10 mm well circumscribed homogenous insulinoma.

 concentrations, thereby further increasing susceptibility to hypogly- caemia. Resultant GH suppression results in low plasma IGF-1 and reduced binding of IGF-II by high-molecular weight protein com- plexes allowing for elevated free plasma IGF-II levels. Diagnosis A biochemical diagnosis of NICTH is established by confirming hypoglycaemia in association with suppressed insulin, proinsulin, C-peptide, β-hydroxybutyrate and abnormally elevated IGF-II to IGF-1 ratio (>10). Once confirmed biochemically, conventional cross-sectional imaging will localize most tumours. Treatment Initial therapy should focus on immediate correction of hypogly- caemia with further treatment directed against the underlying tu- mour. Surgical resection is the mainstay of treatment for benign tumours and may be curative for hypoglycaemia if complete re- section is achieved. In selected cases, reduction of tumour burden by subtotal resection, selective ablation of hepatic metastases, radiotherapy, or systemic chemotherapy may improve NICTH. In unresectable or metastatic disease, administration of oral or intra- venous glucose and/or artificial nutrition may be sufficient in re- lieving hypoglycaemia. Often, however, additional medical therapy is required and may include high-dose glucocorticoids (i.e. prednis- olone 30–60 mg/day), recombinant human growth hormone, and/ or intravenous glucagon. There is no role for diazoxide or somato- statin analogues in the management of NICTH. Autoimmune causes of hypoglycaemia Autoimmune insulin syndrome Insulin autoimmune syndrome (IAS), or Hirata disease, is a rare cause of spontaneous hypoglycaemia with over 90% of cases re- ported among individuals of Japanese ethnicity. IAS is associ- ated with specific HLA class II alleles and commonly occurs following exposure to sulphydryl-containing medications including methimazole, carbimazole, and penicillamine. Association with other autoimmune disorders such as systemic lupus erythematous, rheumatoid arthritis, polymyositis as well as plasma cell dyscrasias and multiple myeloma is also recognized. Hypoglycaemia typically occurs 3–4 hours after a meal subse- quent to a period of early postprandial hyperglycaemia. Insulin secreted early in response to a meal is sequestered by insulin auto- antibodies, usually of IgG isotype, that react with endogenous in- sulin to render it temporarily inactive. Subsequent dissociation of the insulin-antibody complex produces inappropriately elevated free plasma insulin level resulting in hypoglycaemia. In most cases, hypoglycaemia remits spontaneously within 3– 6 months of diagnosis. Dietary modification is the most effective im- mediate treatment strategy with frequent, low-carbohydrate meals encouraged to avoid excessive postprandial insulin secretion. In a limited number of cases prednisolone has

been successfully used to lower insulin antibody titres. Insulin receptor autoantibodies Hypoglycaemia may occur as part of the type B insulin resistance syndrome in which circulating antibodies to the insulin receptor are present. Hypoglycaemia in this setting is rare, with most reported cases occurring in patients with a background of autoimmune illness or as a paraneoplastic manifestation of malignancy. Since in- sulin degradation is normally receptor-mediated, circulating plasma insulin concentrations may be elevated during hypoglycaemia. Patients may demonstrate severe insulin resistance with acanthosis nigricans, alternating episodes of hyperglycaemia with postpran- dial hypoglycaemia or rarely, severe fasting hypoglycaemia due to insulin-mimetic effects of stimulatory autoantibodies on insulin re- ceptors. Demonstrating the presence of anti-insulin receptor anti- bodies confirms the diagnosis. Remission occurs in most patients with time, however severe hypoglycaemia requires immediate treatment with variable success reported with generalized immunosuppressant agents (glucocortic- oids, rituximab, cyclophosphamide, azathioprine, cyclosporine) or plasmapheresis. Factitious hypoglycaemia In factitious hypoglycaemia individuals surreptitiously induce hypoglycaemia with exogenous glucose-lowering therapies. Self-induced hypoglycaemia may occur for several reasons with underlying psychiatric disturbances at the forefront. A diagnosis of factitious hypoglycaemia should be considered in any individual with access to glucose-lowering therapy and recognition of this differential may avoid unnecessary investigation for an insulin- producing tumour. Biochemically, factitious insulin-induced hypoglycaemia dem- onstrates high plasma insulin concentrations in association with low C-peptide and proinsulin concentrations at the time of hypo- glycaemia. Synthetic insulin analogues are undetectable with con- ventional insulin immunoassays and next generation insulin ELISA immunoassays capable of detecting insulin analogues may be re- quired to confirm the diagnosis. Plasma or urine samples should be screened for sulfonylureas if surreptitious use of these medications is suspected. The diagnosis is made by confirming the presence of hypoglycaemia in association with elevated plasma insulin and C-peptide levels in the presence of a sulfonylurea. Congenital hyperinsulinism Persistent congenital hyperinsulinism (CHI) is rare, occurring in 1:50 000 births and increasing to 1:2500 births in areas with high rates of consanguinity. CHI is a heterogeneous group of genetic disorders characterized by inappropriate insulin secretion from pancreatic β-cells for a given plasma blood glucose concentration. CHI presents with a spectrum of clinical phenotypes, typically in neonates but, as discussed next, rare subtypes may manifest in late child- or adulthood. Adults with undiagnosed CHI are most com-monly identified through predictive genetic screening following identification of an affected neonate although some may present as the index case. To date, CHI has been attributed to genetic mutations in nine different genes which may be broadly divided into defects affecting the pancreatic β-cell ATP sensitive potassium channel or those af- fecting intracellular metabolic pathways. Of these, recessive mu- tations in the KATP channel genes (ABCC8 and KCNJ11) are most common. Relative to other forms of CHI, these ‘channelopathies’ present in early life with severe hypoglycaemia that is unresponsive

 to diazoxide therapy and pancreatectomy is often required for nor- malization of plasma glucose levels. Glucokinase (GCK) is an important regulator of glucose homeostasis that serves as both the glucose sensor in pancreatic β-cells and rate-limiting enzyme regulating hepatic glycolysis. Heterozygous inactivating GCK mutations result in a subtype of maturity onset diabetes of the young (GCK-MODY), while rare, dominant activating mutations cause familial hyperinsulinaemic hypoglycaemia (GCK-HH). GCK-HH is characterized by a spec- trum of clinical phenotypes that most commonly present in neo- nates but may also go unrecognized until later child- or adulthood. Adults with undiagnosed GCK-HH may meet diagnostic

bio- chemical criteria for endogenous hyperinsulinism prompting unsuccessful and sometimes prolonged searches for an insulin- secreting tumour. Suggestive clinical features of GCK-HH are stability of hypoglycaemia during fasting and exacerbation of hypoglycaemia by an oral glucose load. Importantly, absence of family history does not necessarily exclude a diagnosis of GCK- HH given the associated phenotypic heterogeneity and potential for de novo mutations. Exercise-induced hyperinsulinism (EIHI) is a rare hypogly- caemic disorder due to autosomal dominant mutations in the SLC16A1 gene that encodes for the monocarboxylate transporter subtype 1 (MCT1). MCT1 expression is normally low or absence in pancreatic β cells and gain-of-function genetic mutations within the SLC16A1 gene promoter induce ectopic MCT1 expres- sion. This permits pyruvate uptake into β-cells, most commonly during aerobic exercise or in response to an intravenously admin- istered pyruvate load, resulting in pyruvate-stimulated insulin secretion. EIHI may present in child- or adulthood. Affected pa- tients are diazoxide-responsive and avoidance of strenuous exer- cise is advised. FURTHER READING Amiel SA (2014). Banting memorial lecture 2013. A life in balance: wandering the pathways of control. Diabet Med, 31, 382–92. Bodnar TW, Acevedo MJ, Pietropaolo M (2014). Management of non- islet-cell tumor hypoglycemia: a clinical review. J Clin Endocrinol Metab, 99, 713–22. Brown E, et al. (2018). Multidisciplinary management of refractory insulinomas. Clin Endocrinol (Oxf), 88, 615–24. Cryer PE, et al. (2009). Evaluation and management of adult hypogly- cemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 94, 709–28. Elliott J, et al. (2014). Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emer- gency treatment lead to reduced costs after structured education in adults with type 1 diabetes. Diabet Med, 31, 847–53. Elwen FR, et al. (2015). An observational study of patient characteris- tics and mortality following hypoglycemia in the community. BMJ Open Diabetes Res Care, 3, e000094. Placzkowski KA, et al. (2009). Secular trends in the presentation
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