REVIEW ARTICLE

Drug Safety 2007; 30 (3): 215-245
0114-5916/07/0003-0215/$44.95/0

Drug-Induced Endocrine and Metabolic Disorders

Ronald C.W. Ma,[1] *Alice P.S. Kong*,[1,2] *Norman Chan*,[3] *Peter C.Y. Tong*[1] and *Juliana C.N. Chan*[1]

1 Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China
2 Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China
3 Qualigenics Diabetes Centre, Hong Kong, China

Contents

Abstract

Complex interactions exist amongst the various components of the neuroendocrine system in order to maintain homeostasis, energy balance and reproductive function. These components include the hypothalamus-pituitary-adrenal and -gonadal axes, the renin-angiotensin-aldosterone system, the sympathetic nervous system and the pancreatic islets. These hormones, peptides and neurotransmitters act in concert to regulate the functions of many organs, notably the liver, muscles, kidneys, thyroid, bone, adrenal glands, adipocytes, vasculature, intestinal tract and gonads, through many intermediary pathways. Endocrine and metabolic disorders can arise from imbalance amongst numerous hormonal factors. These disturbances may be due to endogenous processes, such as increased secretion of hormones from a tumour, as well as exogenous drug administration. Drugs can cause endocrine abnormalities via different mechanisms, including direct alteration of hormone production, changes in the regulation of the hormonal axis, effects on hormonal transport, binding, and signalling, as well as similar changes to counter-regulatory hormone systems. Furthermore, drugs can affect the evaluation of endocrine parameters by causing interference with diagnostic tests. Common drug-induced endocrine and metabolic disorders include disorders of carbohydrate metabolism, electrolyte and calcium abnormalities, as well as drug-induced thyroid and gonadal disorders. An understanding of the proposed mechanisms of these drug effects and their evaluation and differential diagnosis may allow for more critical interpretation of the clinical observations associated with such disorders, better prediction of drug-induced adverse effects and better choices of and rationales for treatment.

There are complex interactions amongst various components of the neuroendocrine system to maintain homeostasis, energy balance and reproductive function. These components include the hypothalamus-pituitary-adrenal (HPA) and -gonadal axes, the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS) and the pancreatic islets. These hormones, peptides and neurotransmitters act in concert to regulate the functions of many organs, notably the liver, muscles, kidneys,

thyroid, bone, adrenal glands, adipocytes and gonads, through many intermediary pathways. The cellular responses to these hormones in turn are dependent on the number, structure and activity of their respective receptors, binding ligands and downstream signalling pathways. These interacting pathways are tightly regulated at multiple levels that can be influenced by endogenous pathological processes and exogenous drug administration.

The clinical manifestations of endocrine and metabolic disorders can be varied, non-specific and often subclinical, leading to diagnostic challenges. On the other hand, many endocrine diseases are closely, although not invariably, associated. Hence, the drugs used to treat one condition may have effects on other pathways, either unmasking subclinical conditions or giving rise to adverse effects. Many of these endocrine or metabolic conditions require hormone therapy either for replacement or treatment, which can give rise to different clinical effects depending on dosages and host responses.

In this review article, we describe some of the common drug-induced endocrine and metabolic disorders and their underlying mechanisms. Although the list does not aim to be exhaustive, an understanding of the principles underlying these interactions is important for the diagnosis and treatment of these conditions.

1. Intermediary Metabolism

1.1 Insulin

The two principal fuels in the human body are glucose and free fatty acids (FFA), which are stored intracellularly as glycogen and triglycerides, respectively. Insulin is an anabolic hormone secreted mainly during fed-state to promote glycogen synthesis in the liver and muscle and lipid storage in adipocytes. Together with growth hormone (GH), insulin promotes protein synthesis notably in muscle and bone. During starvation or periods of stress, decreased insulin levels contribute to glycogen breakdown, lipolysis, hepatic ketogenesis and protein catabolism. In addition to glucose, other physiological insulin secetagogues include FFA, ketone bodies and amino acids.[1] These primary stimuli for insulin secretion exert their effects by altering fluxes of cations across both the calcium and potassium channels of the β-cell membrane, which result in increased intracellular free calcium, followed by pulsatile release of insulin.[2]

1.2 Counter-Regulatory Hormones

In the presence of hypoglycaemia, counter-regulatory hormones are released to restore euglycemia. Glucagon secreted from α-cells of the pancreatic islets elevates blood glucose levels by stimulating glycogenolysis, gluconeogenesis, and ketogenesis in the liver.[3] The catecholamines, noradrenaline (norepinephrine) and especially adrenaline (epinephrine) enhance glucagon secretion, inhibit the activity of glycogen synthase and stimulate lipolysis, glycogenolysis and gluconeogenesis. Catecholamines have dual actions on insulin release. Stimulation of the α-adrenoceptor mediated principally by noradrenaline limits insulin secretion, whereas that of β-adrenoceptor, mediated mainly by adrenaline, enhances insulin release.[1]

During hypoglycaemia or stress, catecholamines and glucagon rapidly mobilise fuel stores to increase blood glucose and FFA levels. This is followed by the long-term effects of cortisol and GH, which maintain the elevation of blood glucose. Cortisol promotes lipogenesis, increases protein breakdown and stimulates gluconeogensis. Cortisol also increases the synthesis and release of adrenaline from the adrenal medulla, and contributes to the lipolytic and hyperglycaemic state.[4] Long-term administration of glucocorticoids activates glycogen synthase and promotes glycogen deposition in the liver.[5] GH exerts its effects via insulin-like growth factor-I (IGF-I), secreted mainly by the liver and bone to promote cellular growth and differentiation. Under physiological conditions, GH promotes protein synthesis under the influence of insulin. In high dosages, GH inhibits glucose transport and utilisation in peripheral tissues. It also promotes lipolysis and elevates FFA levels as part of counter-regulation.

1.3 Free Fatty Acids and Glucose Metabolism

Increased FFA oxidation impairs glucose uptake and oxidation at peripheral sites.[6-8] This is in part due to impaired activation of the insulin signalling pathway resulting from accumulation of intramyocellular lipids.[9,10] Positive energy balance, especially in the presence of insufficient fat mass, can lead to ectopic fat infiltration, notably in the viscera, muscle, liver and pancreas. These ectopic fat deposits can lead to insulin resistance and β-cell dysfunction. Drugs that promote the differentiation of preadipocytes to mature fat cells re-distribute the ectopic fat to subcutaneous fat depots and improve both lipid and glucose metabolism.[11] Enzymes involved in lipogenesis and lipolysis are sensitive to the actions of insulin, counter-regulatory hormones and sex steroids. Thus, drugs that influence these hormonal actions can lead to abnormal lipid and glucose metabolism.[12,13]

1.4 The Hypothalamus-Pituitary Axis and Regulation of Appetite

In addition to the autonomic nervous system, cross-talk between signals generated by the brain, the gastrointestinal tract and the adipocytes is involved in the regulation of appetite and intermediary metabolism. Several gastrointestinal peptide hormones, including glucose-dependent insulinotropic peptide (GIP), cholecystokinin and glucagon-like-peptide-1 (GLP-1) facilitate the release of insulin from the pancreatic β-cells following a meal.[14,15] Leptin, a hormone produced by adipocytes, regulates fat mass by decreasing appetite and activating the SNS.[16,17] In addition to regulating appetite, the hypothalamus-pituitary gland axis and its surrounding neurons also regulate sleep, mood, libido and reproduction, which are all intimately related to energy metabolism.[18-20]

1.5 Diabetes Mellitus, Obesity and Metabolic Syndrome

Diabetes mellitus is characterised by hyperglycaemia owing to defects in insulin secretion, insulin action or both.[21] Whilst autoimmune destruction of pancreatic β-cells is the primary cause for type 1 diabetes, type 2 diabetes is a heterogeneous condition with varying combinations of insulin resistance and insulin deficiency. Closely associated with type 2 diabetes is the metabolic syndrome, a clustering of cardiovascular risk factors including low high-density lipoprotein-cholesterol (HDL-C) levels, elevated blood pressure, hypertriglyceridaemia, increased adipocytokine levels (proinflammatory and prothrombotic factors), with truncal obesity as the main linking factor.[22,23] Patients with metabolic syndrome a have 3- to 5-fold increased risk of diabetes and premature cardiovascular disease.[24]

Excessive production of GH, cortisol, glucagon and catecholamines may lead to hyperglycaemia in association with acromegaly, Cushing's syndrome, glucagonoma and phaeochromocytoma, respectively.[25] Subtle disturbances of these counter-regulatory hormones may impact on the development of obesity and metabolic syndrome.[4,13,26-28] Activation of stress-related hormones, such as cortisol and catecholamines,[4,13,26-28] and the age-associated decline in levels of sex steroids and GH may lead to reduced muscle mass, increased body fat, insulin resistance and the metabolic syndrome[26,29] (figure 1).

1.6 Drug-Induced Hyperglycaemia and Dyslipidaemia

Many drugs have been associated with hyperglycaemia (table I), especially in patients with diabetes or with risk factors for diabetes, such as a positive family history, obesity, physical inactivity, and a history of gestational diabetes (GDM), polycystic ovary syndrome (PCOS) or other features of the metabolic syndrome.[30] As a result of the frequent coexistence and concomitant treatment of obesity, depression, diabetes and hypertension, drug-induced adverse effects are not uncommon and may have additive effects on the metabolic risk. The corticosteroids are another class of drug commonly associated with hyperglycaemia and dyslipidaemia.[31,32] Other drug and non-drug causes of dyslipidaemia, along with their clinical features, are outlined in table II.

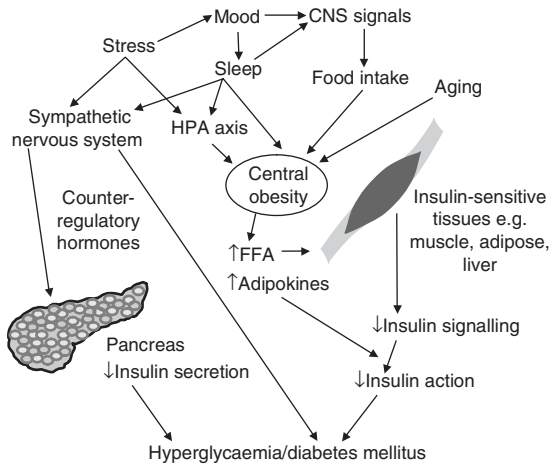

Fig. 1. A schematic diagram showing the interactions of neurohormonal factors in the pathogenesis of central obesity, insulin resistance and hyperglycaemia. Drugs may lead to hyperglycaemia or diabetes mellitus by impacting any part of this complex system. **FFA** = free fatty acids; **HPA** = hypothalamic-pituitary-adrenal; ↓ indicates decrease; ↑ indicates increase.

1.6.1 Antihypertensives

Diabetes and hypertension are frequently associated with each other. Thus, the use of antihypertensive drugs, notably diuretics and β-adrenoceptor antagonists (β-blockers), may unmask diabetes in at-risk patients or worsen glycaemic control in patients with diabetes.[33] In a 6-year prospective study involving 12 550 hypertensive patients, use of β-blockers was associated with a 28% increase in the risk of diabetes, after adjusting for other risk factors.[34] In the ASCOT-BPLA (Blood Pressure-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial), which involved 19 247 hypertensive patients and had a median 5.5 years of follow-up, combination therapy with amlodipine and perindopril was associated with a 30% risk reduction for new-onset diabetes and an 11% risk reduction for mortality compared with the combination of atenolol and thiazide diuretics.[35] In the elderly, sporadic cases of hyperglycaemic hyperosmolar non-ketotic coma have been reported following treatment with indapamide,[36] chlortalidone and bumetanide.[37]

Thiazide diuretics can reduce total-body potassium levels, resulting in decreased insulin secretion and increased insulin resistance by activating the RAAS.[38] These adverse effects can be reversed with potassium supplements[38] or by using a lower dosage.[39] β-Blockers can also increase insulin resistance by increasing bodyweight, altering lipid enzyme activities, increasing vascular resistance and reducing peripheral blood flow.[40] β-Blockers that have intrinsic sympathomimetic activities, such as celiprolol, or possess activities as α-adrenoceptor antagonists (α-blockers), such as carvedilol, have more favourable effects on glucose and lipid metabolism than the other β-blockers.[41-43]

Dyslipidaemia following antihypertensive treatment, especially with thiazide diuretics and β-blockers, may attenuate their cardioprotective effects.[44] There has been much debate regarding the adverse metabolic profile associated with the thiazide diuretics and its potential impact on cardiovascular outcomes. In an earlier review of 12 reported trials that included thiazide-treated patients, only two small studies recorded more coronary heart disease events in thiazide-treated patients than in controls.[45] In the large ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), there was no increased cardiovascular events in the group treated with the thiazide diuretic, chlortalidone, compared with patients randomised to amlodipine or lisinopril after a mean follow-up of 4.9 years.[46] In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC

Table I. Differential diagnosis of hyperglycaemia

Cause	Examples
Nondrug-related	
Type 1 diabetes mellitus (immune mediated or idiopathic)	
Type 2 diabetes	
Genetic defects of β-cell function	Maturity-onset diabetes of the young, mitochondrial DNA mutations
Defects in insulin action	
Pancreatic diseases	Pancreatitis, pancreatectomy, cystic fibrosis, haemochromatosis
Endocrinopathies	Acromegaly, Cushing's syndrome, phaeochromocytoma, hyperthyroidism, somatostatinoma, glucagonoma, aldosteronoma
Infections	
Anti-insulin receptor antibodies	
Other genetic syndromes	Down's syndrome, Turner's syndrome, Prader-Willi syndrome, Lawrence-Moon-Biedl syndrome, myotonic dystrophy
Gestational diabetes	
Drug-related	
Drugs that decrease pancreatic insulin secretion	Diazoxide, thiazide diuretics, β-adrenoceptor antagonists [β-blockers], phenytoin, pentamidine, glucocorticoids, octreotide, streptozocin, ciclosporin, gatifloxacin, alloxan, vacor
Drugs that affect liver glucose metabolism	Nicotinic acid, sex hormones, β-blockers, glucocorticoids
Drugs that increase peripheral tissue insulin resistance	Thiazide diuretics, phenytoin, glucocorticoids, β-sympathomimetics, atypical antipsychotics, protease inhibitors/HAART
Drugs that increase counter-regulatory responses	Corticosteroids, somatropin (growth hormone), diazoxide

HAART = highly active antiretroviral therapy.

7), diuretics were still recommended as the first-line treatment for uncomplicated hypertension.[47] In addition, the increased incidence of new-onset diabetes among patients receiving thiazide diuretics is likely to be preventable through the treatment of thiazide-induced hypokalaemia.[48,49]

Agonists and antagonists of adrenoceptors have opposing effects on lipoprotein lipase, lecithin **:** cholesterol acyltransferase and low-density lipoprotein-cholesterol (LDL-C) uptake by low-density lipoprotein (LDL) receptors. Patients treated with β-blockers have increased triglyceride and LDL-C levels, but decreased HDL-C levels.[50] The reverse lipid pattern is observed in patients treated with α-blockers.[50] Thiazide diuretics, partly by altering insulin action, can increase LDL-C, very low-density lipoprotein-cholesterol (VLDL-C) and triglyceride levels.[51] These adverse metabolic effects can be minimised by using low-dose treatment.[43]

Diazoxide, a vasodilator that was once used as an antihypertensive drug, causes hyperglycaemia by reducing insulin secretion and increasing counter-regulatory responses.[52] It also stimulates hepatic glucose production, increases adrenaline secretion and decreases insulin sensitivity. These adverse metabolic effects have been used to treat refractory hypoglycaemia due to insulinoma.[52]

1.6.2 Corticosteroids

Glucocorticoids induce insulin resistance by increasing hepatic gluconeogenesis[53] and inducing the expression of the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR)-γ in adipocytes, leading to obesity.[54] Treatment with glucocorticoids is associated with increased levels of triglycerides, LDL-C, increased HDL-C levels and their subfractions.[55] These lipid abnormalities are in part mediated by insulin resistance and hyperinsulinaemia, reduced uptake of LDL and increased VLDL production in the liver.[31] Long-term corticosteroid use can lead to other adverse effects, including osteoporosis and suppression of adrenal steroid production; the latter can result in adrenal insufficiency following withdrawal of steroid therapy.[56]

1.6.3 Sex Steroids

The use of the oral contraceptive pill (OCP) is associated with an increased risk of impaired glucose regulation, especially in high-risk women such as those who are obese, those with a family history of diabetes and those with a history of GDM.[57] These adverse effects are mainly attributable to the progestogens in the combination types of OCP, with norethisterone having the least, and norgestrel the greatest, hyperglycaemic effect. These effects can be attenuated by the use of newer preparations of OCP that contain a lower concentration of estrogen and progestogens such as levonorgestrel or desogestrel. The triphasic pills that contain low daily doses of levonorgestrel or gestodene are associated with a reduced risk of impaired glucose regulation compared with estrogen-progestin high-dose oral contraceptives.[57]

The use of the OCP is also associated with dyslipidaemia,[58] the occurrence of which is dependent on the estrogen dose relative to the progestin dose as well as any androgen effects of the progestin.[59] Estrogens can increase triglyceride levels, but may reduce LDL-C and increase HDL-C levels. Progestins tend to have the opposite effects i.e. they decrease triglyceride levels, while increasing LDL-C and reducing HDL-C levels.[60,61]

1.6.4 Antipsychotics

The close association between schizophrenia and diabetes is now increasingly recognised although the nature of the relationship between the two disorders remains to be clarified.[62] The use of older

Table II. Causes of dyslipidaemia

Cause	Lipid abnormalities	Other features or mechanism
Nondrug-related		
Familial forms	Variable	
Dietary	Variable	
Diabetes mellitus	↑Triglycerides, ↓HDL-C, ↑VLDL-C	↑Glucose levels
Hypothyroidism	↑LDL-C, ↑triglycerides	Low thyroid hormone levels
Nephrotic syndrome	↑LDL-C, VLDL-C	Proteinuria, ↑VLDL-C production
Chronic liver disease	↑LDL-C	
Cholestasis/biliary obstruction	↑LDL-C	Diversion of biliary cholesterol into circulation
Chronic renal failure	↑Triglycerides, ↑VLDL-C	Renal impairment
Cushing's syndrome	↑Triglycerides	Features of cortisol excess
Hypopituitarism	↑LDL-C, VLDL-C	Pituitary disease/surgery
Anorexia nervosa	↑LDL-C	↓Biliary excretion of cholesterol and bile
Lipodystrophy	↑Triglycerides, ↑VLDL-C	Congenital/acquired
Pregnancy	↑Triglycerides, ↑LDL-C	
Obesity	↑Triglycerides, ↓HDL-C	
Drug-related		
Alcohol	↑VLDL-C, ↑triglycerides	↑VLDL-C production, ↑HDL production
Estrogen	↑VLDL-C, ↑triglycerides ↓LDL-C, ↑HDL-C	↓Lipoprotein lipase activity ↑VLDL-C production, ↑HDL production
Progestogens	↑LDL-C, ↓HDL-C, ↑triglycerides	
Glucocorticoids	↑LDL-C, ↑VLDL-C, ↑triglycerides, ↑HDL-C	(↓Lipoprotein lipase activity) ↑VLDL-C production
Diuretics	↑LDL-C, ↑VLDL-C, ↑triglycerides	↑Insulin resistance
β-Adrenoceptor antagonists (β-blockers) [non-cardioselective]	↓HDL-C, ↑LDL-C, ↑triglycerides	
Androgens	↓HDL-C	
Retinoids	↑LDL-C, ↑VLDL-C, ↑triglycerides	

HDL-C = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **VLDL-C** = very low-density lipoprotein-cholesterol; ↑ indicates increase; ↓ indicates decrease.

Table III. Conditions and drugs that are known to cause hypoglycaemia

Cause	Examples
Nondrug-related fasting hypoglycaemia	
Critical illness	Liver failure, renal failure, cardiac failure, sepsis
Hormonal deficiencies	GH deficiency, cortisol deficiency (Addison's Disease)
Endogenous hyperinsulinaemia	insulinoma, autoimmunity
Insulin-like growth factor-mediated hypoglycaemia	NICTH
Enzymatic defects in carbohydrate, protein or fat metabolism	Glycogen storage diseases, fatty acid oxidation defects
Nondrug-related reactive hypoglycaemia	
Alimentary hypoglycaemia	
Galactosaemia	
Drug-related	
Drugs that increase insulin levels or secretion	Insulin, sulphonylureas, pentamidine, cotrimoxazole (trimethoprim/sulfamethoxazole), β-sympathomimetics, aspirin (acetylsalicylic acid), quinine
Drugs that increase insulin sensitivity	ACE inhibitors, angiotensin II receptor antagonists (angiotensin II receptor blockers), α-adrenoceptor antagonists (α-blockers)
Drugs that decrease the action of counter-regulatory hormones	β-Adrenoceptor antagonists (β-blockers), ACE inhibitors, octreotide, alcohol

GH = growth hormone; **NICTH** = non-islet cell tumour hypoglycaemia.

antipsychotic agents such as phenothiazines[63] and chlorpromazine[64] has been associated with hyperglycaemia, which has been attributed to weight gain or a reduction in insulin secretion.

The use of second-generation antipsychotics, commonly referred to as 'atypical antipsychotics', is gaining popularity as a result of their improved tolerability and efficacy. However, these drugs have also been associated with hyperglycaemia.[65,66] The atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine, ziprasdone and aripiprazole. Since the first report of such a case in 1994,[67,68] a high prevalence of previously undiagnosed hyperglycaemia among patients with schizophrenia receiving treatment with clozapine has been observed.[69] In a study of 82 patients treated with clozapine, 30 patients (36.6%) were diagnosed with diabetes after 5 years of follow-up. The diagnosis of diabetes was associated with weight gain and increased triglyceride levels.[70] In a 10-year follow-up study, 43% of clozapine-treated patients had new-onset diabetes and an associated increased risk of cardiovascular death.[71] In a report on a US FDA drug-surveillance programme for clozapine-associated adverse events, the authors suggested a causal relationship between clozapine and diabetes due to the large number of reports of diabetes, a temporal relationship between the diagnosis of diabetes and initiation of clozapine treatment, the relatively young age of patients and the prompt reversibility of the disease upon drug withdrawal in some patients.[72]

Other atypical antipsychotics, such as olanzapine and risperidone, have also been associated with weight gain and diabetes.[73-78] It has been postulated that antagonism of the serotonin 5-HT_{1A} receptor may inhibit insulin secretion and contribute to the adverse metabolic effects.[79]

Given the high prevalence of obesity and metabolic syndrome in modern societies, risk factors for diabetes and cardiovascular disease should be considered at the time of commencing therapy with second-generation antipsychotics. Patients who are given second-generation antipsychotics should receive appropriate education, baseline screening for metabolic abnormalities, regular monitoring and referral to specialist services when appropriate.[65]

1.6.5 Protease Inhibitors and Highly Active Antiretroviral Therapy

The morbidity and mortality of patients with advanced HIV infection have been significantly reduced by the use of highly active antiretroviral therapy (HAART).[80] However, the protease inhibitors,

and to a lesser extent, nucleoside reverse transcriptase inhibitors, that are employed in such regimens are associated with significant metabolic abnormalities.[81] In a 5-year cohort analysis of 221 HIV-infected patients attending a tertiary care centre, the cumulative incidences of new-onset hyperglycaemia, hypercholesterolemia, hypertriglyceridaemia and lipodystrophy were 5%, 24%, 19% and 13%, respectively, with most of the events occurring after the initiation of treatment with protease inhibitors[82] and in the absence of significant weight gain.[83] These drug-related metabolic changes may be due insulin resistance as a result of lipodystrophy and ectopic fat distribution.[84-87] As part of a long-term health maintenance plan,[88] HIV-infected patients undergoing HAART should receive regular assessment and monitoring of glucose and lipid levels.[89]

1.7 Drug-Induced Hypoglycaemia

A fall in the plasma glucose level, while remaining at a level within the physiological range (>4.6 mmol/L), is accompanied by decreased insulin secretion. A reduction in glucose levels to just outside the physiological range (≤4.6 mmol/L but >3.8 mmol/L) increases the secretion of counter-regulatory hormones. A further decrease in glucose levels to <3.0 mmol/L elicits the symptoms of hypoglycaemia, and a fall to a level <2.7 mmol/L will result in cognitive dysfunction. Although the insulin-antagonistic effects of glucagon and adrenaline are of rapid onset, those of cortisol and GH are only observed after a lag period of several hours.[90]

Hypoglycaemia most commonly results from over-treatment in diabetic patients receiving insulin or sulphonylureas (table III). In patients who present with unexplained hypoglycaemia, the possibility of factitious use of drugs[91] or inadvertent dispensing should always be considered.[92-94] This can be diagnosed by measuring plasma levels of insulin and C-peptide in the setting of hypoglycaemia and levels of the metabolites of sulphonylureas in the urine or blood.[95] Other less common drug-related causes of hypoglycaemia are listed in table IV.

Other common medical causes of hypoglycaemia include renal failure, hepatic failure, sepsis, hyperinsulinaemia due to the presence of an insulinoma, non-islet cell tumour hypoglycaemia (NICTH) and insufficient counter-regulatory responses.[118,119] The evaluation of a patient with unexplained hypoglycaemia requires detailed investigation into the patient's history and a physical examination, followed by a supervised fast and measurement of insulin and C-peptide levels, as appropriate (table V).

Drug-induced hypoglycaemia is fairly common, especially during intensive glucose-lowering therapy. In the DCCT (Diabetes Control and Complications Trial), the overall rate of hypoglycaemia was 18.7 episodes per 100 type 1 diabetic patient-years in the conventionally-treated group and 61.2 epi-

Table IV. Some examples of uncommon causes of drug-related hypoglycaemia and their possible mechanisms

Drug	Potential mechanisms	References
Cotrimoxazole (trimethoprim/sulfamethoxazole)	Stimulation of insulin release	96-98
Lithium	Decreases cAMP levels, thereby enhancing the actions of counter-regulatory hormones	99,100
Disopyramide	Stimulation of insulin release and inadequate adrenergic response	101-105
Cibenzoline	Stimulation of insulin release	106-108
Halothane	Liver damage	109
Selegiline	Hyperinsulinaemia	110
Aluminium phosphide	Hepatic failure	111
Maprotiline	Unknown	112,113
Calcium hopantenate	Liver damage	114
Carbimazole	Autoantibodies to insulin	115
Propoxyphene	Increased levels of counter-regulatory hormones	116,117

cAMP = cyclic adenosine monophosphate (cyclic AMP).

Table V. Diagnostic evaluation of unexplained fasting hypoglycaemia

Diagnosis	Plasma glucose levels	Plasma insulin levels	Plasma C-peptide levels	Plasma hydroxybutyrate levels	Other tests/diagnostic criteria
Oral antihyperglycaemic agents	↓	↑	↑	Absent	Sulphonylureas or their metabolites detectable in plasma or urine
Insulinoma	↓	↑or normal	↑	Absent	Negative for sulphonylureas in the plasma or urine, imaging studies to localise tumour
Autoimmune hypoglycaemia	↓	↑	↑	Absent	Positive insulin antibodies
Exogenous insulin	↓	↑	↓	Absent	Presence of insulin antibodies
Insulin-like growth factors (e.g. NICTH)	↓	↓	↓	Absent	↑'Big' IGF-II, ↑IGF-II/IGF-I ratio, presence of tumour
Non-insulin mediated	↓	↓	↓	Present	Absent response to glucagon
Adrenal insufficiency	↓	↓	↓	Present	Low cortisol level during hypoglycaemia, short synacthen test
Ethanol	↓	↓	↓	Present	Ethanol level, reduced levels of counter-regulatory hormones

IGF = insulin-like growth factor; **NICTH** = non-islet cell tumour hypoglycaemia; ↑ indicates increase; ↓ indicates decrease.

sodes per 100 patient-years in the intensive treatment group.[120] In the UK Prospective Diabetes Study (UKPDS), the incidence of hypoglycaemia in insulin-treated type 2 diabetic patients was 2.3 episodes per 100 patient-years.[121]

Unawareness of hypoglycaemia occurs when there are no warning symptoms prior to the onset of cognitive dysfunction resulting in confusion and coma.[122] This phenomenon is associated with delayed and reduced neuroendocrine responses to falling blood glucose levels.[123,124] In the DCCT, unawareness of hypoglycaemia was common, with up to 36% of the hypoglycaemic episodes occurring without symptoms.[125] Risk factors for unawareness of hypoglycaemia include a long duration of diabetes, intensified glycaemic control, the presence of autonomic neuropathy, pregnancy, increased age, renal and liver impairment and use of β-blockers, which may mask the adrenergic symptoms of hypoglycaemia.[126] Hypoglycaemic unawareness can be prevented by strict avoidance of hypoglycaemia, which may restore counter-regulatory responses and awareness of symptoms such as sweating and palpitation as a result of the activation of the autonomous nervous system.[127]

1.7.1 Insulin

When human insulin was first introduced, the increased number of reports of severe hypoglycaemia associated with it was largely attributed to the intensive glucose control associated with the change in insulin regimen.[128] Compared with unmodified human insulin, rapidly-acting insulin analogues (e.g. lispro) reduce post-prandial glucose excursions and the incidence of nocturnal hypoglycaemia.[129,130] Insulin glargine, a long-acting insulin analogue with a peakless concentration profile is also associated with a lower risk of nocturnal hypoglycaemia compared with insulin suspension isophane (neutral protamine Hagedorn [NPH] insulin).[131] In patients with type 1 diabetes, a basal-bolus regimen with insulin glargine and insulin lispro results in better glycaemic control and fewer episodes of nocturnal hypoglycaemia than are observed with insulin suspension isophane and unmodified human insulin.[132] Lipoatrophy and lipohypertrophy due to long-term insulin injection may also contribute to erratic glycaemic control and hypoglycaemic episodes.[133] These complications can be prevented through patient education and the use of alternating insulin injection sites.

1.7.2 Sulphonylureas

Sulphonylureas bind to sulphonylurea receptors on the β-cell membrane. This is followed by closure of the adenosine triphosphate (ATP)-sensitive potassium channels and membrane depolarisation, which opens the voltage-gated calcium channels, leading to an influx of calcium ions and the subsequent release of insulin.[134] The older sulphonylureas, such as chlorpropamide, have a long half-life and are associated with a high risk of hypoglycaemia, especially in elderly patients or patients with renal or liver impairment.[126] The second-generation sulphonylureas, such as glibenclamide (glyburide), gliclazide, glipizide and gliquidone, have shorter half-lives. Glibenclamide, which is commonly prescribed, has a prolonged action due to active metabolites and is associated with a higher incidence of hypoglycaemia than the other new sulphonylureas.[135] The meglitinide analogues, such as repaglinide and nateglinide, are new insulin secretagogues, which bind to alternative sites on the β-cell membrane and have been shown to be associated with a lower risk of hypoglycaemia than the older sulphonylureas.[136-138] Since many lifestyle factors, such as diet, weight changes, exercise, concurrent medical conditions and medications, can influence blood glucose levels, patient education, self monitoring and regular clinical assessments are important measures to reduce the risk of drug-induced hypoglycaemia.

1.7.3 Drugs that Enhance the Effects of Antihyperglycaemic Drugs

Other antidiabetic drugs, such as the biguanides (metformin), PPAR-γ agonists (thiazolidinediones) and α-glucosidase inhibitors, do not have direct effects on insulin secretion but may enhance the glucose-lowering effects of insulin and the sulphonylureas.[139] According to a review article by Chan et al.,[90] sporadic cases of hypoglycaemia have been reported in association with a large number of drugs. These include β-blockers, salicylates, phenylbutazone, monoamine oxidase inhibitors, sulphonamides, trimethoprim, cotrimoxazole (trimethoprim/sulfamethoxazole), the H_2 receptor antagonists and tricyclic antidepressants. The underlying mechanisms of these adverse drug reactions are not always clear and these reports highlight the complexity of the regulation of glucose homeostasis.[90] In addition, alcohol can precipitate or exacerbate drug-induced hypoglycaemia in the fasting state by inhibiting gluconeogenesis and glycogenolysis. On the other hand, when consumed with a meal containing carbohydrates, alcohol is preferentially metabolised, giving rise to higher post-prandial glucose excursions.[140]

Ciclosporin, an inhibitor of cytochrome P450 (CYP) 3A4 and organic anion transporter 1B1, increases the plasma concentration of repaglinide, which is metabolised by CYP2C8 and 3A4, and thus the risk of hypoglycaemia may be increased if these drugs are coadministered.[141,142]

1.7.4 Renin-Angiotensin-Aldosterone System Inhibitors

Based on a large number of randomised clinical trials, treatment with inhibitors of the RAAS, including the ACE inhibitors and angiotensin II receptor antagonists (angiotensin II receptor blockers [ARBs]), is associated with a reduced incidence of new onset of diabetes compared with placebo or other antihypertensive drugs.[143-145] Apart from improving vascular function and reducing insulin resistance, the presence of the RAAS in the pancreatic islets suggests that these drugs may have direct beneficial effects on β-cell function.[146] Several angiotensin receptor antagonists, including telmisartan and irbesartan, have a partial PPAR-γ agonist effect,[147] which may further enhance insulin sensitivity.[148]

1.7.5 β-Adrenoceptor Antagonists (β-Blockers) and Sympathomimetic Drugs

Insulin release is usually inhibited by the α-adrenergic effects of catecholamines and facilitated by their β-adrenergic effects.[15] The latter can stimulate peripheral glucose production and lipolysis. Except during times of stress, α-adrenergic effects predominate over those due to β-adrenoceptor stimulation.[15] Thus, depending on the pharmacological profiles and host response, β-blockers may cause hyperglycaemia in predisposed patients or mask symptoms of hypoglycaemia in diabetic patients

treated with antihyperglycaemic drugs. Sporadic cases of β-blocker-induced hypoglycaemia in healthy individuals have been reported during exercise[149] and post-operatively,[150] both of which are conditions that are associated with increased secretion of counter-regulatory hormones.

Isoxsuprine and ritodrine are β-sympathomimetics, which relax smooth muscle cells and are used to halt premature labour. Due to their potential stimulatory effects on the pancreatic β-cells, there have been cases of neonatal hyperinsulinaemic hypoglycaemia in infants born to women treated with these drugs.[151-153] Hypoglycaemia following salbutamol (albuterol) overdose has also been reported in some paediatric patients treated with this drug for asthma.[154,155]

1.7.6 Antimalarial Drugs

The incidence of hypoglycaemia in patients with falciparum malaria is high and can be either spontaneous or a result of antimalarial treatment.[156] Risk factors include young age, pregnancy, renal failure and severe infection.[156] Antimalarial drugs such as quinine, chloroquine, hydroxychloroquine and sulfadoxine-pyrimethamine may stimulate insulin release and lead to hypoglycaemia.[156-161] However, not all hypoglycaemia in patients with malaria is due to antimalarial treatment. In a study of Malawian children with severe falciparum malaria, hypoglycaemia was associated with low plasma insulin levels and elevated plasma levels of lactate, alanine and 5′-nucleotidase.[162] These findings suggest that impaired hepatic gluconeogenesis may explain hypoglycaemia in patients who have not yet received antimalarial drugs.

1.7.7 Pentamidine

Pentamidine is an antiprotozoal drug used in the treatment of pneumocystis pneumonia in patients with HIV that may cause acute pancreatitis.[163-165] This can sometimes lead to cytolytic release of insulin, which in turn results in hypoglycaemia.[166-170] The latter may be followed by destruction of the pancreatic β-cells, insulin insufficiency and hyperglycaemia.[166,167] Risk factors for pentamidine-induced dysglycaemia include renal impairment, resulting in drug accumulation, and severe clinical conditions complicated by shock and hypoxia.[171-173] Hypoglycaemia has also been reported in association with inhaled pentamidine therapy.[174]

2. Drug-Induced Electrolyte Abnormalities

2.1 Homeostasis of Fluid and Electrolyte Balance

The kidney is a key organ in the regulation of fluid and electrolyte balance, under the dual influence of the RAAS and antidiuretic hormone (ADH, also know as vasopressin) [figure 2]. In response to reduced renal blood flow, angiotensin II constricts blood vessels and stimulates aldosterone release. Aldosterone promotes sodium retention and urinary potassium loss. The expansion of blood volume restores renal perfusion pressure which suppresses renin, thus completing the feedback loop. Drugs and clinical conditions that reduce renal blood flow can activate the RAAS causing hypokalaemia. These include liver cirrhosis and nephrotic syndrome, due to low albumin levels, and heart failure due to reduced cardiac output.[175]

ADH is produced by neurons that originate in the supraoptic and paraventricular nucleus of the hypothalamus and project through the pituitary stalk to terminate in posterior pituitary gland. The hormone exerts its biological action (reducing the urinary flow rate and increasing reabsorption of solute-free water) through vasopressin (V2) receptors located in the distal and collecting tubules of kidneys. The binding of ADH to V2 receptors increases the permeability of the tubular cells through activation of aquaporin-2, a protein that forms the water channels in tubular cells. The secretion of ADH is stimulated by increased plasma osmolality, reduced circulating blood volume and to a lesser extent, increased arterial pressure, similar to that mediated by angiotensin II.[176] In patients with diabetes insipidus due to ADH deficiency, excessive urinary free water loss is compensated for by increased fluid intake in response to thirst sensation, the latter being regulated

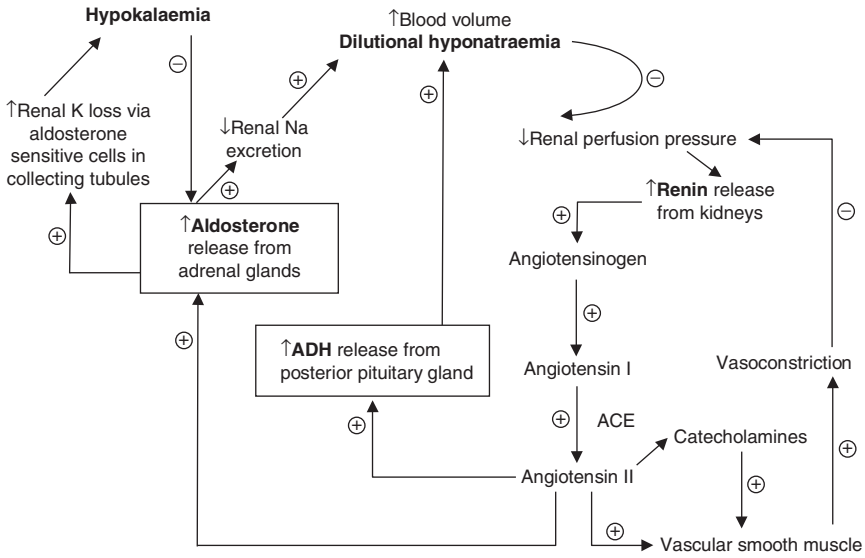

Fig. 2. Feedback control between the renin-angiotensin-aldosterone system and antidiuretic hormone in the regulation of electrolytes and fluid balance. **ACE** = angiotensin converting enzyme; **ADH** = antidiuretic hormone; **K** = potassium; **Na** = sodium; ↑ indicates increase; ↓ indicates decrease; + indicates positive effect; − indicates negative effect.

primarily by hypothalamic osmoreceptors and plasma osmolality.

2.2 Drug-Induced Hyponatraemia and Hypernatraemia

Hyponatraemia can be dilutional (excess water retention) or depletional (excessive loss of sodium with or without water) in nature. Table VI lists examples of drugs that can cause hyponatraemia, with their underlying mechanisms. Diuretics that promote urinary loss of sodium are major causes of depletional hyponatraemia. Thiazides, notably indapamide, can cause severe hyponatraemia and hypokalaemia[177-180] by acting at the distal renal tubules to enhance urinary loss of sodium and potassium. Patients who have polydipsia and weight gain appears to be the most at risk of thiazide-induced hyponatraemia.[181]

Loop diuretics act on the ascending limb of the loop of Henle and inhibit both sodium and water reabsorption.[182] If water intake is high in the setting of excessive urinary sodium loss induced by diuretics, depletional hyponatraemia can occur. Compared with thiazides, loop diuretics are less likely to induce severe hyponatraemia. This is due to the inhibition of sodium chloride transport in the loop of Henle by loop diuretics, which prevents the generation of a counter-current gradient and thereby limits the ability of ADH to induce water retention.[182] As a result, clinicians should consider other causes of hyponatraemia before attributing it to loop diuretics.

Drug-induced causes of dilutional hyponatraemia include the syndrome of inappropriate ADH (SIADH). Drugs can cause dilutional hyponatraemia by enhancing ADH release or its effects (table VI).

Hypernatraemia may be caused by drug-induced diabetes insipidus due to suppression of ADH secretion (e.g. caused by lithium, carbamazepine) or ADH deficiency (e.g. caused by lithium, demeclocycline, methoxyflurane, amphotericin B, rifampicin, cisplatin or foscarnet).[176] Excessive dehydration is usually prevented by stimulation of the thirst centre. Thus, hypernatraemia occurs only in individuals in whom thirst sensation is impaired or water access is not feasible (e.g. elderly patients or those who have had a cerebrovascular accident).

2.3 Drug-Induced Hypokalaemia and Hyperkalaemia

Diuretics increase the delivery of sodium and water to aldosterone-sensitive potassium secreting cells in the collecting tubules and promote urinary potassium wasting. Due to volume contraction, these drugs also activate the RAAS and ADH secretion, which may worsen electrolyte abnormalities.[182] Indapamide, a thiazide-like diuretic, causes severe hypokalaemia and hyponatraemia especially in the elderly population.[178] Laxatives also cause an increased loss of potassium from the gastro-intestinal tract. Laxative- and diuretic-induced hypokalaemia are not uncommon adverse effects in patients treated with slimming pills.[183,184]

Some naturally occurring compounds or pharmacological agents decrease 11β-hydroxysteroid dehydrogenase levels and give rise to hormonal changes that mimic primary hyperaldosteronism, a condition known as 'apparent mineralocorticoid excess'.[185] Due to the similarities in the mineralocorticoid and glucocorticoid metabolic pathways, 11β-hydroxysteroid dehydrogenase is produced by the kidneys to inactivate cortisol by converting it to cortisone.[186] Naturally occurring liquorice, carbenoxolone (a synthetic derivative of glycyrrhizin [glycyrrhizinic acid], which is a constituent of liquorice) and some liquorice-containing chewing tobaccos can inactivate 11β-hydroxysteroid dehydrogenase.[185,186] As a result, there is increased binding of intra-renal cortisol to mineralcorticoid receptors in the distal tubules, leading to excessive water and sodium retention and urinary potassium loss. Liquorice is a common ingredient in many traditional Chinese herbal medicines and Chinese chewing snacks.

In our body compartment, sodium is the main extracellular cation and potassium is the main intracellular cation. Thus, energy-dependent transmembrane cation exchange systems, such as the sodium-

Table VI. Examples of drugs and conditions that cause hyponatraemia

Cause	Examples
Nondrug-related dilutional hyponatraemia	
Excessive water intake	
Increased water resorption	Cirrhosis, congestive heart failure, nephrotic syndrome
Reduced renal excretion of water load	SIADH (can also be caused by drugs), glucocorticoid deficiency
Drug-related dilutional hyponatraemia	
Exogenous ADH	Vasopressin used in the control of GI bleeding; desmopressin used in the treatment of diabetes insipidus, platelet dysfunction, nocturia
Drugs that cause inappropriate ADH secretion	Antipsychotics (phenothiazines, such as haloperidol, thioridazine), antidepressants (tricyclic antidepressants such as amitriptyline; monoamine oxidase inhibitors; SSRIs, such as fluoxetine and sertraline), chemotherapeutic agents (vincristine, vinblastine, cisplatin, cyclophosphamide), amiodarone, bromocriptine, nicotine, methylenedioxymethamfetamine ('ecstasy'), ciprofloxacin
Drugs that cause increased sensitivity to ADH in the collecting tubular cells	Oxcarbazepine, carbamazepine
Drugs that cause expression of increased numbers of ADH receptors in collecting tubular cells	Chlorpropamide
Nondrug-induced depletional hyponatraemia	
Renal salt loss	Tubulointerstitial nephritis, polycystic kidney disease, analgesic nephropathy
GI salt loss	Fistulae
Skin loss	
Drug-induced depletional hyponatraemia	
Drugs that cause excessive urinary sodium loss	Thiazide diuretics, loop diuretics

ADH = antidiuretic hormone; **GI** = gastrointestinal; **SIADH** = syndrome of inappropriate ADH; **SSRIs** = selective serotonin reuptake inhibitors.

potassium adenosine triphosphatase (Na-K-ATPase), pump sodium out of the cells in exchange for potassium influx, in order to maintain the correct electrolyte gradient for normal cellular function. Drugs that increase activity of the Na-K-ATPase can lead to increased potassium entry into the cells and cause hypokalaemia.[187] These include catecholamines, β_2-adrenoceptor agonists (such as salbutamol, terbutaline or dopamine), insulin, levothyroxine sodium (thyroxine) and theophylline.[188] These drug effects may be exacerbated in stressful situations, such as acute coronary syndromes and sepsis, which are associated with increased endogenous production of catecholamines.[189]

Hyperkalaemia can be induced by drugs that decrease Na-K-ATPase activity leading to potassium leakage from cells. Non-selective β-blockers, such as propranolol, selective β_1-blockers, such as atenolol or metoprolol, digoxin (digitalis) overdose,[190] calcineurin-inhibitors, diazoxide, minoxidil, anaesthetics such as isoflurane, suxamethonium chloride (succinylcholine chloride) and arginine can cause hyperkalaemia via this mechanism.[191,192]

Drugs that induce aldosterone deficiency or resistance can also cause hyperkalaemia. ACE inhibitors, NSAIDs and ciclosporin can cause aldosterone deficiency whereas amiloride, spironolactone, triamterene, trimethoprim and pentamidine can induce aldosterone resistance, causing hyperkalaemia. Hypertonic mannitol can induce hyperkalaemia through elevation of plasma osmolality and potassium efflux through a passive gradient and solvent drag.[192] Since ADH promotes solute-free water retention while aldosterone has effects on sodium, water and potassium handling, patients receiving the aforementioned medications may develop hyponatraemia or hypokalaemia or both, depending on dietary intake of sodium and potassium, concomitant medications and clinical conditions. Other patients at high risk for drug-induced electrolyte abnormalities include those with renal artery stenosis or defective autoregulation, such as diabetic patients with autonomic neuropathy. These conditions may coexist in the same patient, such as elderly diabetic patients who have cardiovascular and renal complications and who are receiving multiple medications.[193,194]

2.4 Other Drug-Induced Electrolyte Abnormalities

Drugs that act on the renal tubules, such as loop diuretics, can induce other electrolyte abnormalities, e.g. hypomagnesaemia. In a review article,[195] 50 medications were listed that can cause hypomagnesaemia. Of these, 17 drugs were considered to be clinically important. These included cisplatin, amphotericin B and ciclosporin. In patients receiving these drugs, routine monitoring of serum magnesium levels and prophylactic administration of magnesium may be indicated.

3. Drug-Induced Abnormalities in Calcium Balance

Calcium is a major intracellular signal that mediates many biological actions; these actions are dependent on the maintenance of a steady extracellular calcium level. Over 98% of the body's calcium store and 85% of the phosphate are present in bone as hydroxyapatite. In the plasma, about 40% of calcium is bound to albumin and 15% is associated with phosphate, citrate or sulphate. The remaining 45% is in the form of free (ionised) calcium, which is physiologically active.[196]

The extracellular or serum calcium level is tightly regulated through interaction of the actions of vitamin D and parathyroid hormone (PTH) on their target organs, notably the intestine, kidneys and bone (figure 3). A decreased level of ionised calcium stimulates the release of PTH. In the presence of vitamin D, PTH increases the serum calcium level by stimulating bone resorption and promoting the release of calcium phosphate from bone. In the kidneys, PTH increases the active reabsorption of calcium and enhances production of 1,25-dihyhydroxyvitamin D3 (calcitriol). In the intestine, calcium absorption is augmented by calcitriol. Collectively, these processes raise the serum calcium level and restore homeostasis. Calcitonin is synthesised and secreted by the parafollicular cells

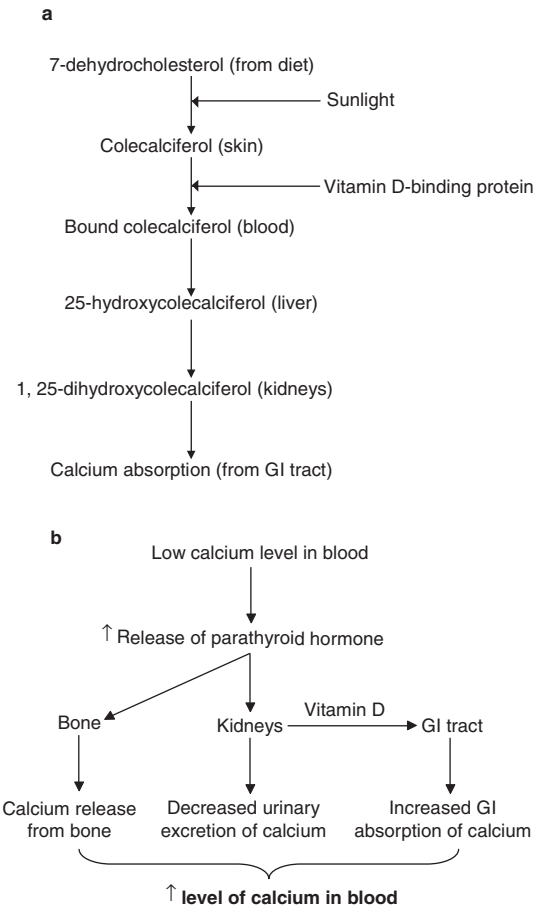

Fig. 3. Schematic diagram of (**a**) vitamin D metabolism and (**b**) calcium metabolism showing the tight regulation of serum calcium levels through interactive effects of parathyroid hormone and vitamin D on the bone, intestine and kidneys. **GI** = gastrointestinal; ↑ indicates increase.

of the thyroid gland in response to high calcium levels. Calcitonin antagonises the actions of PTH, although its effects are only transient.[197]

Vitamin D3 (colecalciferol) is from dietary sources or synthesised in the skin is hydroxylated first in the liver and then in the kidney to form the most active form of vitamin D, calcitriol. Under the influence of calcitriol and PTH, calcium is reabsorbed from the renal tubules to regulate the serum calcium level. In patients with renal failure, in whom the synthesis of calcitriol is impaired, normal serum calcium levels are maintained by secondary hyperparathyroidism, which may result in hypercalcaemia due to tertiary hyperparathyroidism.[197]

A variety of drugs can cause imbalances between bone mineralisation and resorption, as well as between calcium absorption and excretion. Drug-induced hypercalcaemia is more likely to occur in immobilised patients, and in those with malignant conditions or renal impairment, whereas drug-induced hypocalcaemia may occur in institutionalised or malnourished patients.[198]

3.1 Drug-Induced Hypocalcaemia

3.1.1 Antiepileptic Drugs

Patients receiving long-term antiepileptic treatment are at risk of developing vitamin D deficiency. Phenytoin, carbamazepine and phenobarbitone induce up-regulation of hepatic microsomal enzymes, which increase the turnover of 25 hydroxyvitamin D. The reduction in calcitriol causes hypocalcaemia, resulting in secondary hyperparathyroidism.[199] The lack of vitamin D impairs the ability of PTH to normalize the serum calcium level. Eventually, patients may develop antiepileptic-induced bone disease, which is characterised by marked elevation in levels of serum alkaline phosphatase and rickets or osteomalacia.[200]

3.1.2 Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclastic activity and thereby reduce the serum calcium level. Indications for bisphosphonate therapy include hypercalcaemia of malignancy and treatment of osteoporosis and multiple myeloma.[201] Bisphosphonates are also used in prophylaxis against metastatic bone disease and for the treatment of Paget's disease of the bone. Bisphosphonates are usually well tolerated, with minor adverse effects of transient arthralgia or flu-like symptoms. These drugs are rapidly excreted via the kidney and toxicity may occur in the patients with renal failure. Zoledronic acid is a new intravenous bisphosphonate, which is about 1000 times more potent than pamidronate, alendronate or etidronate. Cases of severe hypocalcaemia have been reported

in association with intravenous zoledronic acid therapy.[202,203]

Because of a compensatory increase in the secretion of PTH, most patients receiving intravenous bisphosphonate therapy do not develop hypocalcaemia. In patients with occult vitamin D deficiency, hypomagnesaemia or renal failure, compensatory mechanisms may not be effective.[204,205] Hence, in patients with normocalcaemia or hypercalcaemia with low urinary calcium excretion, caution should be exercised to prevent hypocalcaemia during intravenous bisphosphonate therapy.

3.1.3 Miscellaneous

Ionised calcium levels may be reduced by increased calcium deposition in the tissue or by intravascular binding. The use of phosphate enema for the treatment of faecal retention has been associated with hyperphosphataemia and hypocalcaemic tetany.[206,207] Calcium is deposited with phosphate in the bone and in extra-skeletal tissues, resulting in hypocalcaemia. In patients receiving massive blood transfusions, rapid plasma exchange or leukapheresis, the large amount of citrate may chelate calcium and reduce ionised calcium levels.[208] Hypocalcaemia is also a known complication of chelation therapy. Deaths associated with hypocalcaemia have been reported in patients who developed cardiac arrest after receiving edetic acid (disodium ethylenediaminetetraacetate [Na_2EDTA]) for the treatment of lead poisoning.[209] In patients with refractory cytomegalovirus and herpes infections, the use of the antiviral agent foscarnet has been associated with hypocalcaemia.[210]

Magnesium depletion causes PTH resistance and reduced PTH secretion, resulting in hypocalcaemia. Hypomagnesaemia is a known complication in patients receiving diuretics.[211] In addition, aminoglycosides[211] and cisplatin can cause urinary magnesium wasting, thereby causing hypomagnesaemia and sometimes hypocalcaemia.[212]

In patients with ethylene glycol poisoning, ethylene glycol is metabolised to oxalate. Widespread deposition of calcium oxalate in various organs leads to reduced levels of ionised calcium, resulting in hypocalcaemia.[213] Other examples of drugs that are associated with hypocalcaemia include colchicine,[214] which is postulated to cause inhibition of bone resorption,[215] and intravenous diltiazem.[216]

Other conditions that can cause hypocalcaemia include hypoparathyroidism (e.g. resulting from destruction of the parathyroid glands by irradiation or from a failure of parathyroid development), increased uptake of calcium into the bone (e.g. hungry bone syndrome following surgical treatment of prolonged hyperparathyroidism) and abnormal vitamin D metabolism (e.g. renal failure and following acute pancreatitis).[198]

3.2 Drug-Induced Hypercalcaemia

With the widespread use of automated multichannel analysers, hypercalcaemia is a common incidental finding. The major causes of hypercalcaemia are malignancy and hyperparathyroidism, which can be differentiated by their clinical presentations and the measurement of PTH levels.[217] Drugs are another important cause of hypercalcaemia. Enhanced calcium absorption and increased bone turnover is evident in patients taking high doses of either vitamin D or calcifediol (calcidiol) and the topical vitamin D analogue, calcipotriol (calcipotriene), for skin lesions.[218] Hypervitaminosis A[219] or the use of tretinoin (retinoic acid) for the treatment of acne and certain haematological malignancies[220] can cause hypercalcaemia by increasing bone resorption. Thiazide diuretics stimulate renal tubular calcium reabsorption and may lead to hypercalcaemia, especially in patients with risk factors such as immobilisation or subclinical hyperparathyroidism.[217]

Excessive intake of calcium, in the form of calcium carbonate, may lead to hypercalcaemia,[221] alkalaemia, nephrocalcinosis and renal failure. The incidence of hypercalcaemia appears to be increasing as more people take calcium supplements for osteoporosis, peptic ulcers, gastritis, gastroesophageal reflux and chronic kidney disease.[222]

Lithium treatment may cause hypercalcaemia by altering the set point at which calcium suppresses the secretion of PTH.[223] Increased SNS activity due to over-treatment with levothyroxine sodium or

sympathomimetics, such as theophylline, stimulates osteoclastic bone resorption and cause mild hypercalcaemia, which may be attenuated by β-blocker treatment.[224,225]

4. Drug-Induced Thyroid Disorders

4.1 Regulation of Thyroid Metabolism

Thyroid hormones are the only iodine-containing hormones in vertebrates. The synthesis of thyroid hormones is dependent on the intake of iodine (or iodide [I-], in its ionised form), as this the rate-limiting substrate in the process. Iodide uptake into thyroid follicular cells is the first step in thyroid hormone synthesis. After iodide enters the thyroid, it is oxidised by thyroid peroxidase, and this is followed by iodination of thyroglobulin, resulting in the formation of the mono- and di-iodotyrosines. Two iodotyrosines are coupled to form thyroxine (T_4), whilst triiodothyronine (T_3) can be formed by the coupling of one mono-iodotyrosine and one di-iodotyrosine within a thyroglobulin molecule. However, most T_3 is produced by extrathyroidal deiodination of T_4.[226]

Without iodine, there is no synthesis of the thyroid hormones. Thyroid hormone synthesis can be transiently blocked by the inhibitory effect of high dose iodide on intrathyroidal iodine uptake; the so called Wolff-Chaikoff effect.[227] However, with continued exposure to excess iodide, there is usually escape from this effect. This is due to decreased transport of iodide into the thyroid by the sodium/iodide transporter, thereby lowering intracellular iodide levels to those that are insufficient to maintain the inhibitory effect.[228,229]

The thyroid hormones secreted from thyroid gland are over 99% protein-bound, with T_3 being less tightly bound than T_4.[230] Only free thyroid hormones are biologically active. Thyroid hormones exert their end-organ effects through binding to nuclear receptors, with T_3 having 10–15 times greater affinity than T_4. Conversion from T_4 to T_3 in peripheral tissues is mediated by 5′-monodeiodinase. The actions of this enzyme can be affected by many medications (table VII). Thyroid hormone synthesis and secretion is under feedback control by thyrotropin (TSH) released from the pituitary gland. Hence, drugs that modify TSH secretion may also affect thyroid function. The symptoms of thyrotoxicosis, such as palpitation, tachycardia, hypertension,

Table VII. Examples of drugs affecting thyroid function and their underlying mechanisms

Mechanisms	Examples of drugs
Decreased TSH secretion	Dopamine, glucocorticoids, somatostatin, levothyroxine sodium (thyroxine) or any exogenous thyroid hormones, amiodarone
Increased TSH secretion	Antipsychotics, metoclopramide, theophylline
Intrinsic effects on the thyroid and thyroid hormone synthesis	Amiodarone, lithium, organic iodine, radiographic contrast agents, amfetamine, thionamides, thalidomide, interferon-α, traditional Chinese herbal medicines with high iodine content
Decreased peripheral tissue conversion from T_4 to T_3	Amiodarone, propranolol, glucocorticoids, sodium iopodate, iopanoic acid
Decreased TBG binding	Androgens, glucocorticoids, diuretics (very large intravenous dose)
Increased TBG binding	Estrogen therapy or estrogen-containing oral contraceptives, tamoxifen, heroin, methadone, phenothiazines
Altered TBG binding	NSAIDs, phenytoin
Interference with assays of thyroid function tests	Monoclonal antibodies, tiratricol (triiodothyroacetic acid [TRIAC]), levothyroxine sodium or its analogues
Altered hepatic metabolism of thyroid hormones	Phenytoin, phenobarbital, carbamazepine, rifampicin, any drugs that can increase the activity of cytochrome P450 enzymes
Decreased absorption of T_4 (of clinical relevance in hypothyroid patients who need regular T_4 replacement therapy)	Calcium carbonate, cholestyramine, colestipol, aluminium hydroxide, ferrous sulphate, sucralfate, dietary soy proteins and fibres

TBG = thyroxine-binding globulin; **TSH** = thyrotropin; **T_3** = triiodothyronine; **T_4** = thyroxine.

sweating and diarrhoea, are mediated through activation of the autonomic nervous system. Medications, including β-blockers, may mask the symptoms of thyrotoxicosis and lead to delayed or missed diagnosis.[231]

4.2 Drug-Induced Hyper- and Hypothyroidism

4.2.1 Thionamides

The thionamides are the main antithyroid drugs, and these include propylthiouracil, carbimazole and methimazole (an active metabolite of carbimazole). These drugs inhibit thyroid peroxidase and thus, the synthesis of the thyroid hormones.[231]

4.2.2 Amiodarone

Amiodarone therapy can cause both hyper- and hypothyroidism.[232] This drug is widely used as a class III anti-arrhythmic drug and has a high iodide content (75mg per 200mg tablet). After hepatic metabolism, about 6mg of iodine per 200mg of amiodarone is released into the circulation.[233] This is compared with the WHO recommendation of a daily iodine intake of 150μg for adults.[234] Hence, amiodarone significantly increases the body iodine load. Dietary iodine content partly predicts amiodarone-induced thyroid dysfunction, with hypothyroidism being more common in iodine-sufficient areas and hyperthyroidism being more common in iodine-deficient regions.[235,236] This reflects the fact that the clinical effects of amiodarone and iodine in an individual depend on the underlying status of the thyroid gland. Excess iodine causes hypothyroidism due to a transient inhibitory effect on intrathyroidal iodine uptake. Populations with chronically high iodine intake have a higher prevalence of autoimmune thyroid disease.[237] Such patients with underlying autoimmune thyroid disease appear to be particularly sensitive to the inhibitory Wolff-Chaikoff effect and are sometimes unable to escape from these inhibitory effects. As a result, excess iodine or amiodarone will result in increased goitre and hypothyroidism in patients with Hashimoto thyroiditis. Conversely, in patients from areas of iodine deficiency who have endemic goitre, iodine and amiodarone administration may result in hyperthyroidism.[236] This effect is also seen in patients from iodine-sufficient areas who have nodular goitre containing autonomously functioning thyroid nodules, and is due to increased substrate provision after escape from the Wolff-Chaikoff effect (type 1 amiodarone-induced thyrotoxicosis).[236] In addition, amiodarone can also cause a destructive thyroiditis, thereby causing transient thyrotoxicosis (type 2 amiodarone-induced thyrotoxicosis).[236]

Amiodarone can also induce hypothyroidism by inhibiting 5′-monodeiodinase resulting in a decreased T_3 level,[238] by reducing T_3 binding to its receptor, by antagonising the effects of the thyroid hormones[236] and by suppressing TSH secretion. All of these mechanisms contribute to the wide range of thyroid dysfunction associated with amiodarone therapy.

4.2.3 Lithium

Lithium is used as treatment for manic-depressive disorders. Due to its inhibitory effect on thyroid hormone synthesis, it was used as an anti-thyroid drug in early 1970s.[239] It is still occasionally used as a second-line therapy or an interim measure before definitive treatment in thyrotoxic patients who are allergic or not responsive to thionamides. Approximately 1–3% of patients treated with lithium develop goitre, typically diffuse, with or without thyroid dysfunction.[240] Lithium has multiple actions resembling those of iodine, but the exact mechanisms of lithium-induced thyroid dysfunction remain to be clarified. Lithium can block thyroid hormone release from thyroglobulin,[241] inhibit adenylate cyclase and prevent TSH or thyroid stimulating antibodies from activating thyroid cells via the TSH receptor.[242] As with amiodarone, lithium may precipitate or adversely affect thyroid function in individuals with autoimmune thyroid diseases.[243]

4.2.4 Levothyroxine Sodium (Thyroxine) and its Analogues

Levothyroxine sodium is used as replacement therapy in patients with hypothyroidism. However, due to its weight-loss effect, levothyroxine sodium and its analogues or metabolites (e.g. tiratricol

[3,5,3′-triiodothyroacetic acid or TRIAC], a physiological metabolite of T_3) have been used for slimming purposes, often by young women.[244] Although T_3 has been used by some doctors to treat obesity, this clinical approach remains controversial.[245] Since levothyroxine sodium and tiratricol can cross-react with T_3 assays,[244] the possibility of inappropriate use of levothyroxine sodium or its analogues should be considered in patients with spurious thyroid function tests.

4.2.5 Traditional Chinese Herbal Medicines

Goitre and hypothyroidism due to iodine deficiency are a worldwide health problem, particularly in iodine deficient areas. Some traditional Chinese herbal medicines with claims to treat thyroid disease have a high iodine content, which can induce thyroid dysfunction.[246] In patients with thyrotoxicosis who are refractory to thionamide therapy despite good drug compliance, the concomitant use of iodine-rich substances should be considered. These include traditional Chinese herbal medicines or foods with high iodine contents (e.g. seafood, seaweeds, fish), which are not uncommonly taken by patients who may mistakenly think that dietary iodine insufficiency is a contributory factor for their conditions.

4.2.6 Interferon-α

Interferon-α can induce both hyper- and hypothyroidism, with the latter being more common, especially during treatment for chronic hepatitis C infection.[247] Interferon-α-induced thyroid dysfunction is usually transient, although prolonged effects have been reported.[248] The exact mechanism is not fully understood. In addition to direct effects on the thyroid gland, interferon-α can lead to increased levels of anti-thyroid antibodies and expression of major histocompatability class I antigens.

5. Drug-Induced Gonadal Dysfunction

5.1 Reproductive Physiology and the Hypothalamus-Pituitary-Gonadal Axis

In women, normal ovulation and menstruation requires intact functioning of the hypothalamus and pituitary, as well as the ovaries and endometrium (figure 4a). Gonadotropin-releasing hormone (GnRH), secreted in a pulsatile manner, is transported via the portal circulation to the pituitary. In women, the secretion of GnRH is under negative feedback control by estrogen and progesterone, and is also regulated by other neuropeptides, such as prolactin and serotonin. Follicle-stimulating hormone (FSH) promotes ovarian follicular maturation, whereas lutenising hormone (LH) stimulates production of estrogen and plays an important role in ovulation. During follicular growth, the granulosa and thecal cell layers in the ovary work in synchrony to produce estradiol from the steroid precursor pregnenolone, a process stimulated by LH. A posi-

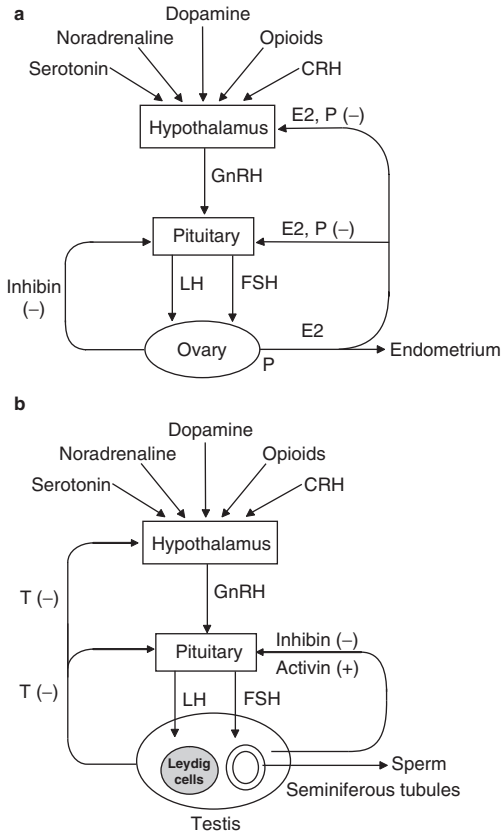

Fig. 4. Regulation of the hypothalamic-pituitary-gonadal axis in the (**a**) female and (**b**) male. **CRH** = corticotropin-releasing hormone; **E2** = estradiol; **FSH** = follicle-stimulating hormone; **GnRH** = gonadotropin-releasing hormone; **LH** = lutenising hormone; **P** = progesterone; **T** = testosterone; **–** indicates inhibitory effect; **+** indicates stimulatory effect.

tive feedback mechanism is present whereby LH and FSH surge mid-cycle in response to increasing estrogen secretion, leading to ovulation. LH then promotes the production of progesterone from the corpus luteum following ovulation. In addition to estradiol, the ovary produces androgens and progesterone, a process involving the conversion of a cholesterol substrate to pregnenolone via multiple enzyme pathways that are regulated by gonadotropin stimulation.

A similar pathway operates in men (figure 4b), whereby testicular function is regulated by LH and FSH from the pituitary. FSH stimulates spermatogenesis and plays an indirect role in androgen biosynthesis by inducing maturation of the Leydig cells during development. LH acts on the Leydig cells to promote androgen synthesis from cholesterol steroid precursors. A feedback loop operates whereby the pituitary and hypothalamus are under negative feedback control by androgens produced in the Leydig cells and inhibin from the seminiferous tubules, as well as positive control via the production of activin.

Sexual development is regulated by activity of the hypothalamus-pituitary-gonadal axis, whereby an increase in episodic secretion of GnRH and increased secretion of gonadotropins in puberty trigger progressive development of secondary sexual characteristics and initiate spermatogenesis in men and ovulation in women.

Whilst estradiol is the predominant female sex hormone and testosterone is the predominant male hormone, low levels of androgens are also present in women and similarly, estrogens in men. Androgens are produced in both the adrenal glands and the gonads. Subsequent peripheral conversion produces 17β-estradiol from testosterone and estrone from androstenedione. Thus, in men, estradiol arises from plasma testosterone, and estrone is derived from andostenedione, with some direct secretion of these estrogens from the testes.[249] Imbalances between these hormonal factors can manifest in disorders such as gynaecomastia.

In addition to affecting the hypothalamus-pituitary-gonadal axis, drugs can interfere with sexual function by altering libido and other physiological functions. Libido, or sex drive, is influenced by sex hormones and emotions. Sexual arousal leads to erection in men and swelling of the vagina, labia minora and clitoris in women. The control of erection and the corresponding female changes involve vascular changes that are mediated by parasympathetic and sympathetic outflow to the peripheral organs. The brainstem and spinal cord, where the neurons that innervate the cardiovascular system and penis arise from, play an important role in this circuit.[250] The dopaminergic and serotoninergic pathways, as well as neurotransmitters such as noradrenaline, acetylcholine and GABA, are also involved. Nitric oxide is the key molecule in the final pathway in this process, whereby, upon its release from endothelial cells and neurons, it acts as a vasodilator causing penile engorgement and erection.[251]

5.2 Drug-Induced Alterations in Gonadotropin Secretion

Disorders of the reproductive axes can be due to drugs affecting pituitary hormone secretion, gonadal function or the relative balance of androgens and estrogens. Long-acting GnRH analogues are used in the treatment of precocious puberty, endometriosis, and prostate and breast carcinoma. These drugs abolish the pulsatile GnRH stimulation, leading to pituitary desensitisation with reduced gonadotropin and sex hormone production. Hence, treatment with these drugs may lead to menopausal symptoms, reduced libido and osteoporosis in female patients or impotence and reduced libido in male patients.[252] Chronic glucocorticoid excess can inhibit LH and FSH secretion, resulting in reduced spermatogenesis or ovulation and lowering of gonadal sex hormone levels.[253] Anti-androgens, such as cyproterone, inhibit the action of adrenal and testicular androgens by competitive antagonism at the target organ receptors. Their progestogenic activity also reduces gonadotropin secretion leading to gynaecomastia, reduced testosterone levels and sperm count.[254]

Table VIII. Differential diagnosis of gynaecomastia

Cause	Examples
Nondrug-related	
Physiological	Puberty (onset at adolescence), idiopathic
Hypogonadism (low testosterone levels)	Primary (history of injury to the testicles?), secondary (history of pituitary disease?)
Estrogen, hCG or aromatase-producing tumours (↑estrogen ↓testosterone ↑hCG levels)	Testicular cancer, adrenal cancer, lung cancer
Endocrine disorders	Thyrotoxicosis, acromegaly, androgen insensitivity due to androgen receptor defects
Cirrhosis (↑SHBG levels)	
Renal failure (↓testosterone; ↑LH, FSH levels)	
Obesity	
Klinefelter's syndrome (↑FSH, LH; ↓testosterone)	
Drug-related	
Drugs that increase estrogenic activity	Conjugated and synthetic estrogens, digoxin (digitalis), oral contraceptives
Drugs that stimulate estrogen secretion	Anabolic steroids, hCG, LHRH, menopausal gonadotropins
Drugs that reduce the effects or synthesis of testosterone	Antiandrogens (e.g. cyproterone, flutamide, finasteride), cimetidine, cytotoxic agents, spironolactone, phenytoin, ketoconazole, reserpine
Drugs that cause gynaecomastia by an unknown mechanism	Calcium channel antagonists, methadone, marijuana, methyldopa

FSH = Follicle-stimulating hormone; **GH** = growth hormone; **hCG** = human chorionic gonadotropin; **LH** = lutenising hormone; **LHRH** = lutenising hormone release hormone; **SHBG** = sex hormone-binding globulin; ↑ indicates increase; ↓ indicates decrease.

5.3 Chemotherapy-Induced Gonadal Dysfunction

Cytotoxic chemotherapy and radiotherapy can cause significant gonadal damage in both men and women.[255] The risk is particularly high with alkylating agents such as cyclophosphamide, chlorambucil, procarbazine and busulfan. Cisplatin-based chemotherapy causes temporary azoospermia in most men, with recovery to normospermia in 80% by 5 years.[256] Ovarian failure occurs in at least 50% of women treated with alkylating agent monotherapy.[257]

5.4 Environmental Toxin-Induced Endocrine Disruption

Both naturally occurring phytoestrogens[258] and synthetic compounds, such as organochlorine pesticides, polychlorinated biphenyls, phenolic compounds and phthalate esters, may mimic the actions of sex hormones and interfere with the reproductive axes.[259-261] Such 'endocrine disruptors' may possess estrogenic or anti-androgenic properties and have been implicated in male fertility disorders, congenital malformations of the reproductive tract and early onset of puberty in children.[262]

5.5 Drug-Induced Virilisation

In utero exposure to androgens can lead to masculinisation of the female fetus. Exposure to excess androgens during development can lead to precocious puberty in children.[263] Increased androgen levels in women can result in hirsutism, clitoromegaly, deepening of the voice and increased muscle development. Anabolic steroids are known to cause interrupted growth and virilisation in children, birth defects in the unborn child and severe virilisation in women.[264] In men, these drugs can cause testicular atrophy and reduced gonadotropin and testosterone levels.[264] Similar effects are observed with agents such as danazol, stanozolol, methyltestosterone[265] and, to a lesser extent, oxandrolone.[266]

Hyperandrogenism and chronic anovulation are common endocrine abnormalities that affect women of reproductive age. Some of these women fulfill the diagnostic criteria for PCOS and may have polycystic ovaries upon ovarian ultrasonography.[267] The use of anticonvulsants, such as valproic acid (sodi-

um valproate), has been associated with the development of PCOS, although the mechanism is not entirely clear.[268]

5.6 Drug-Induced Gynaecomastia

Gynaecomastia is the enlargement of the male breast due to increased glandular and stromal tissues. It usually results from an imbalance between the effects of testosterone and the estrogens. Common conditions and drugs that cause gynaecomastia are listed in table VIII.

5.7 Drug-Induced Hyperprolactinaemia

Secretion of prolactin from the anterior pituitary is usually inhibited by the hypothalamic dopaminergic system and stimulated by the serotonergic system. Prolactin secretion can also be stimulated by thyrotrophin-releasing hormone, as seen in hypothyroidism. Estrogens also act directly on the pituitary to enhance prolactin secretion. Elevated levels of prolactin impact the reproductive axes by altering LH-releasing hormone and gonadotropin production and by interfering with the actions of LH and FSH. Clinical manifestations include galactorrhoea, amenorrhoea and infertility in women, and impotence and loss of libido in men. A variety of drugs can cause hyperprolactinaemia, predominantly by inhibiting the action of dopamine, and possibly via enhancing the effect of serotonin in the hypothalamus (table IX).[269]

5.8 Drug-Induced Alterations in Sexual Function

Drugs can affect sexual function by altering libido, which may be secondary to changes in sex hormone levels or through direct effects on neurochemical pathways, mood or physiological changes relevant to penile erection.[270] Agents with such effects in men include antipsychotic drugs, antidepressants, lithium[270,271] and antihypertensive agents such as β-blockers, diuretics and centrally acting sympathetic antagonists.[272] Few data are available regarding adverse effects of antihypertensives on sexual function in women, although clonidine, methyldopa, guanethidine and reserpine may have such effects.[230] Disorders that reduce nitric oxide synthesis or release in the erectile tissue commonly manifest as erectile dysfunction.[273] Increased understanding of the pathophysiology of erectile dysfunction has led to development of pharmacological agents, including phosphodiesterase-5 inhibitors (e.g. sildenafil), for the treatment of erectile dysfunction.[274]

Table IX. Examples of conditions and drugs that cause hyperprolactinaemia

Cause	Examples (diagnostic features)
Physiological	Pregnancy (positive pregnancy test), lactation (resolves after cessation of lactation), stress
Prolactin-secreting adenoma	
Lesions of the hypothalamus or pituitary	Hypothalamic lesions (diabetes insipidus is often present), lesions of the pituitary stalk (hypopituitarism), non-functioning pituitary tumours (hypopituitarism and mass effect), acromegaly (elevated GH, IGF-I levels)
Hypothyroidism (↑TRH)	
Chronic renal failure	
Idiopathic	
Drug-related	
Dopamine receptor antagonists	Phenothiazines, haloperidol, domperidone, metoclopramide, risperidone, sulpiride
Catecholamine inhibitors	Reserpine, methyldopa
Drugs that cause hyperprolactinaemia by a miscellaneous or unknown mechanism	Verapamil, cimetidine, opioids, estrogens

GH = growth hormone; **IGF-I** = insulin-like growth factor-I; **LH** = lutenising hormone; **TRH** = thyrotropin-releasing hormone.

6. Diagnostic Approaches in Endocrine Disorders

Endocrine disorders can arise from imbalances amongst numerous hormonal factors. These disturbances may be due to endogenous processes, such as increased secretion from a tumour, or exogenous drug administration. Since many hormones are secreted in a pulsatile manner, confirmation of hyper- or hyposecretion often requires stimulation or suppression tests, e.g. a dexamethasone suppression test for suspected Cushing's syndrome or a synacthen test for suspected hypoadrenalism. This is followed by further investigations to identify the cause. Using Cushing's syndrome as an example, having excluded exogenous corticosteroid ingestion, excess endogenous glucocorticoid production is confirmed by a lack of suppression of production by exogenous dexamethasone. This is then followed by other tests, including measurement of corticotropin levels, which will be elevated in individuals with pituitary lesions or suppressed in those with adrenal lesions.[275]

In general, increased hormone levels may be due to abnormal secretion from endocrine tumours, which can be localised using imaging studies or other such techniques. Hormone deficiency states may be due to destruction of the endocrine gland by tumours, infection, irradiation, autoimmunity or genetic defects resulting in inadequate hormone production or actions. In addition, disorders of hormone receptors or hormone transport and metabolism can result in endocrine disorders. Thus, endocrine disorders are unique, in that all disorders are diagnosed mainly on the basis of measurement of hormone levels. This has important implications in the diagnosis of drug-induced endocrine or metabolic disorders, which usually mediate their effects by altering hormone levels or their regulation. Thus, in establishing a diagnosis of drug-induced endocrine disorder, a careful drug history, with particular emphasis on the temporal relationship between drug ingestion and disease presentation, is extremely important. Sometimes, drug withdrawal followed by rechallenge may be needed to establish the diagnosis.

Another diagnostic pitfall that is unique to drug-induced endocrine disorders is the ability of drugs to interfere with diagnostic tests, including the measurement of hormone levels, thus giving rise to erroneous results or misdiagnosis. For example, carbamazepine interferes with the measurement of urinary cortisol levels by high-performance liquid chromatography methods[276] and agents such as tiratricol can interfere with the measurement of thyroid hormone levels.[244] A large number of drugs, such as antidepressants, antipsychotic agents, levodopa, methyldopa and labetalol, are known to interfere with the measurement of urinary catecholamine or metanephrine levels, which are commonly used to screen for the presence of phaeochromocytomas.[277,278] Other examples include enhanced metabolism of dexamethasone by CYP450-inducing drugs such as isoniazid, phenytoin and carbamazepine, leading to false-positive dexamethasone suppression tests in the diagnostic evaluation for Cushing's syndrome.[279]

7. Conclusion

Endocrine and metabolic disorders are common conditions observed in both inpatient and outpatient settings. Although diabetes and thyroid diseases account for the majority of patients with endocrine disorders, other conditions such as pituitary or adrenal diseases carry significant morbidity and mortality. Many asymptomatic conditions such as abnormalities of electrolyte levels or thyroid function tests are frequently encountered as part of routine clinical assessments. Drug-induced disturbances of carbohydrate metabolism are commonly encountered by clinicians, and of particular importance given the current epidemic of obesity and diabetes. As illustrated in this review, many drugs have potential adverse effects on various components of the endocrine system. Thus, clinicians should be alert to the possibility of drug effects when evaluating patients with endocrine disorders. Many patients with endocrine or metabolic diseases require long-term medications, including hormone therapy. Understanding the complexity of these hormonal pathways and their interactions with host responses and drug ac-

tions should not only improve clinical management but also alert clinicians to aberrant observations, which may bring new insights into the regulation of the neuroendocrine systems.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Cavaghan ML, Polonsky KS. Insulin secretion in vivo. In: Kahn CR, Weir GC, King GL, editors. Joslin's diabetes mellitus. Boston (MA): Lippincott Williams and Wilkins, 2005: 109-24
2. Henquin JC. Pathways in beta-cell stimulus-secretion coupling as targets for therapeutic insulin secretagogues. Diabetes 2004; 53 Suppl. 3: S48-58
3. Jiang G, Zhang BB. Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab 2003; 284 (4): E671-8
4. Axelrod J, Reisine TD. Stress hormones: their interaction and regulation. Science 1984; 224 (4648): 452-9
5. Stalmans W, Laloux M. Glucocorticoids and hepatic glycogen metabolism. Monogr Endocrinol 1979; 12: 517-33
6. Randle PJ, Garland PB, Hales CN, et al. The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963; I: 785-9
7. McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. Diabetes 2002; 51 (1): 7-18
8. Boden G, Chen X, Ruiz J, et al. Mechanisms of fatty acid-induced inhibition of glucose uptake. J Clin Invest 1994; 93 (6): 2438-46
9. Krssak M, Falk Petersen K, Dresner A, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia 1999; 42 (1): 113-6
10. Dresner A, Laurent D, Marcucci M, et al. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. J Clin Invest 1999; 103 (2): 253-9
11. Ferre P. The biology of peroxisome proliferator-activated receptors: relationship with lipid metabolism and insulin sensitivity. Diabetes 2004; 53 Suppl. 1: S43-50
12. Deeb SS, Zambon A, Carr MC, et al. Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, gender, and diet. J Lipid Res 2003; 44 (7): 1279-86
13. Brindley DN. Role of glucocorticoids and fatty acids in the impairment of lipid metabolism observed in the metabolic syndrome. Int J Obes Relat Metab Disord 1995; 19 Suppl. 1: S69-75
14. Holst JJ. Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. Diabetologia 2006; 49 (2): 253-60
15. Ahren B. Autonomic regulation of islet hormone secretion: implications for health and disease. Diabetologia 2000 Apr; 43 (4): 393-410
16. Saladin R, De Vos P, Guerre-Millo M, et al. Transient increase in obese gene expression after food intake or insulin administration. Nature 1995; 377 (6549): 527-9
17. Seals DR, Bell C. Chronic sympathetic activation: consequence and cause of age-associated obesity? Diabetes 2004; 53 (2): 276-84
18. Bruning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. Science 2000; 289 (5487): 2122-5
19. Chehab FF. A broader role for leptin. Nat Med 1996; 2 (7): 723-4
20. Schwartz MW, Woods SC, Porte D, et al. Central nervous system control of food intake. Nature 2000; 404 (6778): 661-71
21. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006; 29 Suppl 1: S43-8
22. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005; 112 (17): 2735-52
23. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome - a new worldwide definition. Lancet 2005; 366 (9491): 1059-62
24. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365 (9468): 1415-28
25. Emmer M, Gorden P, Roth J. Diabetes in association with other endocrine disorders. Med Clin North Am 1971 Jul; 55 (4): 1057-64
26. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev 2001; 2 (2): 73-86
27. Lee ZS, Chan JC, Yeung VT, et al. Plasma insulin, growth hormone, cortisol, and central obesity among young Chinese type 2 diabetic patients. Diabetes Care 1999; 22 (9): 1450-7
28. Lee ZS, Critchley JA, Tomlinson B, et al. Urinary epinephrine and norepinephrine interrelations with obesity, insulin, and the metabolic syndrome in Hong Kong Chinese. Metabolism 2001; 50 (2): 135-43
29. Tong PC, Ho CS, Yeung VT, et al. Association of testosterone, insulin-like growth factor-I, and C-reactive protein with metabolic syndrome in Chinese middle-aged men with a family history of type 2 diabetes. J Clin Endocrinol Metab 2005; 90 (12): 6418-23
30. Pandit MK, Burke J, Gustafson AB, et al. Drug-induced disorders of glucose intolerance. Ann Intern Med 1993 Apr 1; 118 (7): 529-39
31. Sholter DE, Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. Can J Cardiol 2000; 16 (4): 505-11
32. Leaming RD, Prince MJ. Endocrine and pharmacologic causes of insulin resistance. In: Chrousos GP, Olefsky JM, Samols E, editors. Hormone resistance and hypersensitivity states. Philadelphia (PA): Lippincott Williams and Wilkins, 2002
33. Yudkin JS. Factors influencing threshold and choice of treatment for hypertension in NIDDM: cardiovascular factors. Diabetes Care 1991; 14 Suppl. 4: 27-32
34. Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus: atherosclerosis Risk in Communities Study. N Engl J Med 2000; 342 (13): 905-12
35. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366 (9489): 895-906

36. Fonseca V, Phear DN. Hyperosmolar non-ketotic diabetic syndrome precipitated by treatment with diuretics. BMJ (Clin Res Ed) 1982; 284 (6308): 36-7
37. Hall S. Hyperosmolar non-ketotic diabetic syndrome precipitated by treatment with diuretics. BMJ (Clin Res Ed) 1982; 284 (6316): 665-6
38. Helderman JH, Elahi D, Andersen DK, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 1983; 32 (2): 106-11
39. Neutel JM. Metabolic manifestations of low-dose diuretics. Am J Med 1996; 101 (3A): 71S-82S
40. Jacob S, Rett K, Henriksen EJ. Antihypertensive therapy and insulin sensitivity: do we have to redefine the role of beta-blocking agents? Am J Hypertens 1998; 11 (10): 1258-65
41. Preuss HG, Burris JF. Adverse metabolic effects of antihypertensive drugs: implications for treatment. Drug Saf 1996; 14 (6): 355-64
42. Bell DS. Advantages of a third-generation beta-blocker in patients with diabetes mellitus. Am J Cardiol 2004; 93 (9A): 49B-52B
43. Weir MR, Moser M. Diuretics and beta-blockers: is there a risk for dyslipidemia? Am Heart J 2000; 139 (1 Pt 1): 174-83
44. Leren P. Effects of oral antihypertensive agents on blood lipid levels. Clin Ther 1986; 8 (3): 309-19
45. Freis ED. The cardiotoxicity of thiazide diuretics: review of the evidence. J Hypertens Suppl 1990; 8 (2): S23-32
46. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288 (23): 2981-97
47. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289 (19): 2560-72
48. Zillich AJ, Garg J, Basu S, et al. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. Hypertension 2006; 48 (2): 219-24
49. Helderman JH, Elahi D, Andersen DK, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 1983; 32: 106-11
50. Rabkin SW. Mechanisms of action of adrenergic receptor blockers on lipids during antihypertensive drug treatment. J Clin Pharmacol 1993; 33 (3): 286-91
51. Weidmann P, Gerber A. Effects of treatment with diuretics on serum lipoproteins. J Cardiovasc Pharmacol 1984; 6 Suppl. 1: S260-8
52. Goode PN, Farndon JR, Anderson J, et al. Diazoxide in the management of patients with insulinoma. World J Surg 1986; 10 (4): 586-92
53. Bernal-Mizrachi C, Weng S, Feng C, et al. Dexamethasone induction of hypertension and diabetes is PPAR-alpha dependent in LDL receptor-null mice. Nat Med 2003; 9 (8): 1069-75
54. Vidal-Puig AJ, Considine RV, Jimenez-Linan M, et al. Peroxisome proliferator-activated receptor gene expression in human tissues: effects of obesity, weight loss, and regulation by insulin and glucocorticoids. J Clin Invest 1997; 99 (10): 2416-22
55. Ettinger WH Jr, Hazzard WR. Prednisone increases very low density lipoprotein and high density lipoprotein in healthy men. Metabolism 1988 Nov; 37 (11): 1055-8
56. Trence DL. Management of patients on chronic glucocorticoid therapy: an endocrine perspective. Prim Care 2003; 30 (3): 593-605
57. Harvengt C. Effect of oral contraceptive use on the incidence of impaired glucose tolerance and diabetes mellitus. Diabetes Metab 1992; 18 (2): 71-7
58. Henkin Y, Como JA, Oberman A. Secondary dyslipidemia: inadvertent effects of drugs in clinical practice. JAMA 1992; 267 (7): 961-8
59. Lipson A, Stoy DB, LaRosa JC, et al. Progestins and oral contraceptive-induced lipoprotein changes: a prospective study. Contraception 1986 Aug; 34 (2): 121-34
60. Seibert C, Barbouche E, Fagan J, et al. Prescribing oral contraceptives for women older than 35 years of age. Ann Intern Med 2003; 138 (1): 54-64
61. LaRosa JC. Effects of oral contraceptives on circulating lipids and lipoproteins: maximizing benefit, minimizing risk. Int J Fertil 1989; 34 Suppl.: 71-84
62. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. Am J Psychiatry 2003; 160 (2): 284-9
63. Arneson GA. Phenothiazine derivatives and glucose metabolism. J Neuropsychiatr 1964; 5: 181-5
64. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001; 62 Suppl. 27: 15-26; discussion 40-1
65. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004; 27 (2): 596-601
66. Luna B, Feinglos MN. Drug-induced hyperglycemia. JAMA 2001; 286 (16): 1945-8
67. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. Am J Psychiatry 1994; 151 (10): 1520-1
68. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine. Am J Psychiatry 1994; 151 (9): 1395
69. Sernyak MJ, Gulanski B, Leslie DL, et al. Undiagnosed hyperglycemia in clozapine-treated patients with schizophrenia. J Clin Psychiatry 2003; 64 (5): 605-8
70. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000; 157 (6): 975-81
71. Henderson DC, Nguyen DD, Copeland PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. J Clin Psychiatry 2005; 66 (9): 1116-21
72. Koller E, Schneider B, Bennett K, et al. Clozapine-associated diabetes. Am J Med 2001; 111 (9): 716-23
73. Bonanno DG, Davydov L, Botts SR. Olanzapine-induced diabetes mellitus. Ann Pharmacother 2001; 35 (5): 563-5
74. Wirshing DA, Pierre JM, Eyeler J, et al. Risperidone-associated new-onset diabetes. Biol Psychiatry 2001; 50 (2): 148-9
75. Smith RC, Lindenmayer JP, Bark N, et al. Clozapine, risperidone, olanzapine, and conventional antipsychotic drug effects on glucose, lipids, and leptin in schizophrenic patients. Int J Neuropsychopharmacol 2005; 8 (2): 183-94
76. Sumiyoshi T, Roy A, Anil AE, et al. A comparison of incidence of diabetes mellitus between atypical antipsychotic drugs: a survey for clozapine, risperidone, olanzapine, and quetiapine. J Clin Psychopharmacol 2004; 24 (3): 345-8
77. Moisan J, Gregoire JP, Gaudet M, et al. Exploring the risk of diabetes mellitus and dyslipidemia among ambulatory users of atypical antipsychotics: a population-based comparison of ris-

peridone and olanzapine. Pharmacoepidemiol Drug Saf 2005; 14 (6): 427-36
78. Caro JJ, Ward A, Levinton C, et al. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. J Clin Psychiatry 2002; 63 (12): 1135-9
79. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced glucose dysregulation. Ann Pharmacother 2000; 34 (7-8): 865-7
80. Crum NF, Riffenburgh RH, Wegner S, et al. Comparisons of causes of death and mortality rates amoung HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. J Acquir Immune Defic Syndr 2006 Feb 1; 24 (2): 194-200
81. Hardy H, Esch LD, Morse GD. Glucose disorders associated with HIV and its drug therapy. Ann Pharmacother 2001; 35 (3): 343-51
82. Tsiodras S, Mantzoros C, Hammer S, et al. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. Arch Intern Med 2000; 160 (13): 2050-6
83. Mulligan K, Grunfeld C, Tai VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. J Acquir Immune Defic Syndr 2000; 23 (1): 35-43
84. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. Lancet 1999; 353 (9170): 2093-9
85. Walli R, Herfort O, Michl GM, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. AIDS 1998; 12 (15): F167-73
86. Yarasheski KE, Tebas P, Sigmund C, et al. Insulin resistance in HIV protease inhibitor-associated diabetes. J Acquir Immune Defic Syndr 1999; 21 (3): 209-16
87. Unger RH. Minireview: weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. Endocrinology 2003; 144 (12): 5159-65
88. Hadigan C. Diabetes, insulin resistance, and HIV. Curr Infect Dis Rep 2006; 8 (1): 69-75
89. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. J Acquir Immune Defic Syndr 2002; 31 (3): 257-75
90. Chan JC, Cockram CS, Critchley JA. Drug-induced disorders of glucose metabolism. Mechanisms and management. Drug Saf 1996; 15 (2): 135-57
91. Moore GL, McBurney PL, Service FJ. Self-induced hypoglycemia: a review of psychiatric aspects and report of three cases. Int J Psychiatry Med 1973; 4 (3): 301-11
92. Gordon MR, Flockhart D, Zawadzki JK, et al. Hypoglycemia due to inadvertent dispensing of chlorpropamide. Am J Med 1988; 85 (2): 271-2
93. Shumak SL, Corenblum B, Steiner G. Recurrent hypoglycemia secondary to drug-dispensing error. Arch Intern Med 1991; 151 (9): 1877-8
94. Moore DF, Wood DF, Volans GN. Features, prevention and management of acute overdose due to antidiabetic drugs. Drug Saf 1993; 9 (3): 218-29
95. Service FJ. Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metab Clin North Am 1999; 28 (3): 519-32, vi
96. Schattner A, Rimon E, Green L, et al. Hypoglycemia induced by co-trimoxazole in AIDS. BMJ 1988; 297 (6650): 742
97. Johnson JA, Kappel JE, Sharif MN. Hypoglycemia secondary to trimethoprim/sulfamethoxazole administration in a renal transplant patient. Ann Pharmacother 1993; 27 (3): 304-6
98. Mathews WA, Manint JE, Kleiss J. Trimethoprim-sulfamethoxazole-induced hypoglycemia as a cause of altered mental status in an elderly patient. J Am Board Fam Pract 2000; 13 (3): 211-2
99. Shah JH, DeLeon-Jones FA, Schickler R, et al. Symptomatic reactive hypoglycemia during glucose tolerance test in lithium-treated patients. Metabolism 1986; 35 (7): 634-9
100. Hunt NJ. Hypoglycemic effect of lithium. Biol Psychiatry 1987; 22 (6): 798-9
101. Smith RC, Sullivan M, Geller J. Inadequate adrenergic response to disopyramide-induced hypoglycemia. Ann Pharmacother 1992; 26 (4): 490-1
102. Croxson MS, Shaw DW, Henley PG, et al. Disopyramide-induced hypoglycaemia and increased serum insulin. N Z Med J 1987; 100 (827): 407-8
103. Cacoub P, Deray G, Baumelou A, et al. Disopyramide-induced hypoglycemia: case report and review of the literature. Fundam Clin Pharmacol 1989; 3 (5): 527-35
104. Strathman I, Schubert EN, Cohen A, et al. Hypoglycemia in patients receiving disopyramide phosphate. Drug Intell Clin Pharm 1983; 17 (9): 635-8
105. Reynolds RM, Walker JD. Hypoglycaemia induced by disopyramide in a patient with type 2 diabetes mellitus. Diabet Med 2001; 18 (12): 1009-10
106. Bertrand G, Gross R, Petit P, et al. Evidence for a direct stimulatory effect of cibenzoline on insulin secretion in rats. Eur J Pharmacol 1992; 214 (2-3): 159-63
107. Jeandel C, Preiss MA, Pierson H. Hypoglycaemia induced by cibenzoline. Lancet 1988; I: 1532-3
108. Gachot BA, Bezier M, Cherrier JF, et al. Cibenzoline and hypoglycaemia. Lancet 1988; 2 (8605): 280
109. Bichel T, Canivet JL, Damas P, et al. Malignant hyperthermia and severe hypoglycemia after reexposure to halothane. Acta Anaesthesiol Belg 1994; 45 (1): 23-7
110. Rowland MJ, Bransome ED Jr, Hendry LB. Hypoglycemia caused by selegiline, an antiparkinsonian drug: can such side effects be predicted? J Clin Pharmacol 1994; 34 (1): 80-5
111. Singh B, Gupta S, Minocha SK, et al. Hypoglycaemia in aluminium phosphide poisoning. J Assoc Physicians India 1994; 42 (8): 663
112. Isotani H, Kameoka K. Hypoglycemia associated with maprotiline in a patient with type 1 diabetes. Diabetes Care 1999; 22 (5): 862-3
113. Zogno MG, Tolfo L, Draghi E. Hypoglycemia caused by maprotiline in a patient taking oral antidiabetics. Ann Pharmacother 1994; 28 (3): 406
114. Otsuka M, Akiba T, Okita Y, et al. Lactic acidosis with hypoglycemia and hyperammonemia observed in two uremic patients during calcium hopantenate treatment. Jpn J Med 1990; 29 (3): 324-8
115. Wong ST, Ng WY, Thai AC. Case report: autoimmune insulin syndrome in a Chinese female with Graves' disease. Ann Acad Med Singapore 1996; 25 (6): 882-5
116. Wiederholt IC, Genco M, Foley JM. Recurrent episodes of hypoglycemia induced by propoxyphene. Neurology 1967; 17 (7): 703-6
117. Florez LR, Rozanski J, Castro A, et al. Propoxyphene-induced hypoglycemia. J Fla Med Assoc 1977; 64 (3): 163-4

118. Service FJ. Hypoglycemic disorders. N Engl J Med 1995; 332 (17): 1144-52
119. Ma RC, Tong PC, Chan JC, et al. A 67-year-old woman with recurrent hypoglycemia: non-islet cell tumour hypoglycemia. CMAJ 2005; 173 (4): 359-61
120. Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes 1997; 46 (2): 271-86
121. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352 (9131): 837-53
122. Maran A, Lomas J, Macdonald IA, et al. Lack of preservation of higher brain function during hypoglycaemia in patients with intensively-treated IDDM. Diabetologia 1995; 38 (12): 1412-8
123. Amiel SA, Tamborlane WV, Simonson DC, et al. Defective glucose counterregulation after strict glycemic control of insulin-dependent diabetes mellitus. N Engl J Med 1987; 316 (22): 1376-83
124. Boyle PJ, Kempers SF, O'Connor AM, et al. Brain glucose uptake and unawareness of hypoglycemia in patients with insulin-dependent diabetes mellitus. N Engl J Med 1995; 333 (26): 1726-31
125. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. Am J Med 1991; 90 (4): 450-9
126. Cryer PE. Hypoglycemia: pathophysiology, diagnosis, and treatment. New York: Oxford University Press, 1997
127. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993; 42 (11): 1683-9
128. Amiel SA. Human insulin in hypoglycemia: a new arena? Diabetes 1995; 44 (3): 257-60
129. Anderson JH, Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. Diabetes 1997; 46 (2): 265-70
130. Holleman F, Schmitt H, Rottiers R, et al. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. The Benelux-UK Insulin Lispro Study Group. Diabetes Care 1997; 20 (12): 1827-32
131. Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. Clin Ther 2003; 25 (6): 1541-77, discussion 1539-40
132. Ashwell SG, Amiel SA, Bilous RW, et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. Diabet Med 2006; 23 (3): 285-92
133. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. Am J Clin Dermatol 2003; 4 (10): 661-7
134. Jackson JE, Bressler R. Clinical pharmacology of sulphonylurea hypoglycaemic agents: part 2. Drugs 1981; 22 (4): 295-320
135. Chan TY. Anti-diabetic drugs as a cause of hypoglycaemia among acute medical admissions in Hong Kong and Singapore--relationship to the prescribing patterns in diabetic patients. Singapore Med J 1998; 39 (4): 186-8
136. Goldberg RB, Einhorn D, Lucas CP, et al. A randomized placebo-controlled trial of repaglinide in the treatment of type 2 diabetes. Diabetes Care 1998; 21 (11): 1897-903
137. Malaisse WJ. Pharmacology of the meglitinide analogs: new treatment options for type 2 diabetes mellitus. Treat Endocrinol 2003; 2 (6): 401-14
138. Rosenstock J, Hassman DR, Madder RD, et al. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. Diabetes Care 2004; 27 (6): 1265-70
139. Scheen AJ. Drug interactions of clinical importance with antihyperglycaemic agents: an update. Drug Saf 2005; 28 (7): 601-31
140. van de Wiel A. Diabetes mellitus and alcohol. Diabetes Metab Res Rev 2004; 20 (4): 263-7
141. Kajosaari LI, Niemi M, Neuvonen M, et al. Cyclosporine markedly raises the plasma concentrations of repaglinide. Clin Pharmacol Ther 2005; 78 (4): 388-99
142. Hatorp V, Hansen KT, Thomsen MS. Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. J Clin Pharmacol 2003; 43 (6): 649-60
143. Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus: part 1. A meta-analysis of randomised clinical trials. Diabetes Metab 2004; 30 (6): 487-96
144. Scheen AJ. Prevention of type 2 diabetes mellitus through inhibition of the renin-angiotensin system. Drugs 2004; 64 (22): 2537-65
145. Kjeldsen SE, Lyle PA, Tershakovec AM, et al. Targeting the renin-angiotensin system for the reduction of cardiovascular outcomes in hypertension: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Expert Opin Emerg Drugs 2005; 10 (4): 729-45
146. Leung PS, Carlsson PO. Pancreatic islet renin angiotensin system: its novel roles in islet function and in diabetes mellitus. Pancreas 2005; 30 (4): 293-8
147. Schupp M, Janke J, Clasen R, et al. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation 2004; 109 (17): 2054-7
148. Miura Y, Yamamoto N, Tsunekawa S, et al. Replacement of valsartan and candesartan by telmisartan in hypertensive patients with type 2 diabetes: metabolic and antiatherogenic consequences. Diabetes Care 2005; 28 (3): 757-8
149. Holm G, Herlitz J, Smith U. Severe hypoglycaemia during physical exercise and treatment with beta-blockers. BMJ (Clin Res Ed) 1981; 282 (6273): 1360
150. Brown DR, Brown MJ. Hypoglycemia associated with preoperative metoprolol administration. Anesth Analg 2004; 99 (5): 1427-8
151. Brazy JE, Pupkin MJ. Effects of maternal isoxsuprine administration on preterm infants. J Pediatr 1979; 94 (3): 444-8
152. Musci MN Jr, Abbasi S, Otis C, et al. Prolonged fetal ritodrine exposure and immediate neonatal outcome. J Perinatol 1988; 8 (1): 27-32
153. Epstein MF, Nicholls E, Stubblefield PG. Neonatal hypoglycemia after beta-sympathomimetic tocolytic therapy. J Pediatr 1979; 94 (3): 449-53
154. Ozdemir D, Yilmaz E, Duman M, et al. Hypoglycemia after albuterol overdose in a pediatric patient. Pediatr Emerg Care 2004; 20 (7): 464-5
155. Wasserman D, Amitai Y. Hypoglycemia following albuterol overdose in a child. Am J Emerg Med 1992; 10 (6): 556-7
156. Okitolonda W, Delacollette C, Malengreau M, et al. High incidence of hypoglycaemia in African patients treated with intra-

venous quinine for severe malaria. BMJ (Clin Res Ed) 1987; 295 (6600): 716-8
157. Davis TM, Pukrittayakamee S, Supanaranond W, et al. Glucose metabolism in quinine-treated patients with uncomplicated falciparum malaria. Clin Endocrinol (Oxf) 1990; 33 (6): 739-49
158. Fairhurst RM, Sadou B, Guindo A, et al. Case report: life-threatening hypoglycaemia associated with sulfadoxine-pyrimethamine, a commonly used antimalarial drug. Trans R Soc Trop Med Hyg 2003; 97 (5): 595-6
159. Shojania K, Koehler BE, Elliott T. Hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polyarthritis. J Rheumatol 1999; 26 (1): 195-6
160. Abu-Shakra M, Lee P. Hypoglycemia: an unusual adverse reaction to chloroquine. Clin Exp Rheumatol 1994; 12 (1): 95
161. Goyal V, Bordia A. The hypoglycemic effect of chloroquine. J Assoc Physicians India 1995; 43 (1): 17-8
162. Taylor TE, Molyneux ME, Wirima JJ, et al. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. N Engl J Med 1988; 319 (16): 1040-7
163. Foisy MM, Slayter KL, Hewitt RG, et al. Pancreatitis during intravenous pentamidine therapy in an AIDS patient with prior exposure to didanosine. Ann Pharmacother 1994; 28 (9): 1025-8
164. Pais JR, Cazorla C, Novo E, et al. Massive haemorrhage from rupture of a pancreatic pseudocyst after pentamidine-associated pancreatitis. Eur J Med 1992; 1 (4): 251-3
165. Villamil A, Hammer RA, Rodriguez FH. Edematous pancreatitis associated with intravenous pentamidine. South Med J 1991; 84 (6): 796-8
166. Perronne C, Bricaire F, Leport C, et al. Hypoglycaemia and diabetes mellitus following parenteral pentamidine mesylate treatment in AIDS patients. Diabet Med 1990; 7 (7): 585-9
167. Bouchard P, Sai P, Reach G, et al. Diabetes mellitus following pentamidine-induced hypoglycemia in humans. Diabetes 1982; 31 (1): 40-5
168. Sattler FR, Waskin H. Pentamidine and fatal hypoglycemia. Ann Intern Med 1987; 107 (5): 789-90
169. Stahl-Bayliss CM, Kalman CM, Laskin OL. Pentamidine-induced hypoglycemia in patients with the acquired immune deficiency syndrome. Clin Pharmacol Ther 1986; 39 (3): 271-5
170. Spadafora MP, Roberts JR. Hypoglycemic coma from pentamadine in an AIDS patient. Am J Emerg Med 1986; 4 (4): 384
171. Assan R, Perronne C, Assan D, et al. Pentamidine-induced derangements of glucose homeostasis. Determinant roles of renal failure and drug accumulation. A study of 128 patients. Diabetes Care 1995; 18 (1): 47-55
172. Waskin H, Stehr-Green JK, Helmick CG, et al. Risk factors for hypoglycemia associated with pentamidine therapy for Pneumocystis pneumonia. Jama 1988; 260 (3): 345-7
173. Comtois R, Pouliot J, Gervais A, et al. High pentamidine levels associated with hypoglycemia and azotemia in a patient with Pneumocystis carinii pneumonia. Diagn Microbiol Infect Dis 1992; 15 (6): 523-6
174. Karboski JA, Godley PJ. Inhaled pentamidine and hypoglycemia. Ann Intern Med 1988; 108 (3): 490
175. Henriksen JH, Moller S. Liver cirrhosis and arterial hypertension. World J Gastroenterol 2006; 12 (5): 678-85
176. Robertson GL. Antidiuretic hormone. Normal and disordered function. Endocrinol Metab Clin North Am 2001 Sep; 30 (3): 671-94
177. Chan TY. Indapamide-induced severe hyponatremia and hypokalemia. Ann Pharmacother 1995; 29 (11): 1124-8
178. Chapman MD, Hanrahan R, McEwen J, et al. Hyponatraemia and hypokalaemia due to indapamide. Med J Aust 2002; 176 (5): 219-21
179. Chow KM, Szeto CC, Wong TY, et al. Risk factors for thiazide-induced hyponatraemia. QJM 2003; 96 (12): 911-7
180. Chow KM, Kwan BC, Szeto CC. Clinical studies of thiazide-induced hyponatremia. J Natl Med Assoc 2004; 96 (10): 1305-8
181. Friedman E, Shadel M, Halkin H, et al. Thiazide-induced hyponatremia: reproducibility by single dose rechallenge and an analysis of pathogenesis. Ann Intern Med 1989; 110 (1): 24-30
182. Rose BD. Diuretics. Kidney Int 1991 Feb; 39 (2): 336-52
183. Henry RC. Weight reduction pills. JAMA 1967; 201 (11): 895-6
184. Kruger J, Galuska DA, Serdula MK, et al. Attempting to lose weight: specific practices among U.S. adults. Am J Prev Med 2004; 26 (5): 402-6
185. Stewart PM. Mineralcorticoid hypertension. Lancet 1999 Apr 17; 353 (9161): 1341-7
186. Funder JW. 11 beta-Hydroxysteroid dehydrogenase: new answers, new questions. Eur J Endocrinol 1996 Mar; 134 (3): 301-7
187. Clausen T, Flatman JA. Effects of insulin and epinephrine on Na+-K+ and glucose transport in soleus muscle. Am J Physiol 1987; 252 (4 Pt 1): E492-9
188. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. N Engl J Med 1983; 309 (23): 1414-9
189. Di Giantomasso D, Bellomo R, May CN. The haemodynamic and metabolic effects of epinephrine in experimental hyperdynamic septic shock. Intensive Care Med 2005; 31 (3): 454-62
190. Reza MJ, Kovick RB, Shine KI, et al. Massive intravenous digoxin overdosage. N Engl J Med 1974; 291 (15): 777-8
191. Sterns RH, Cox M, Feig PU, et al. Internal potassium balance and the control of the plasma potassium concentration. Medicine (Baltimore) 1981 Sep; 60 (5): 339-54
192. Preston RA, Hirsh MJ, Oster MD Jr, et al. University of Miami Division of Clinical Pharmacology therapeutic rounds: drug-induced hyperkalemia. Am J Ther 1998 Mar: 5 (2): 125-32
193. Tuck M, Sambhi M, Levin L. Hyporeninemic hypoaldosteronism in diabetes mellitus. Diabetes 1979; 28: 237-41
194. Williams GH. Hyporeninemic hypoaldosteronism. N Engl J Med 1986; 314 (16): 1041-2
195. Atsmon J, Dolev E. Drug-induced hypomagnesaemia: scope and management. Drug Saf 2005; 28 (9): 763-88
196. Parfitt AM. Calcium homeostasis. In: Mundy GR, Martin JJ, editors. Physiology and phamacology of bone. Berlin: Springer-Verlag, 1993: 1-6
197. Brown EM, Hebert SC. Calcium-receptor-regulated parathyroid and renal function. Bone 1997 Apr; 20 (4): 303-9
198. Bohannon AD, Lyles KW. Drug-induced bone disease. Clin Geriatr Med 1994 Nov; 10 (4): 611-23
199. Bouillon R, Reynaert J, Claes JH, et al. The effect of anticonvulsant therapy on serum levels of 25-hydroxy-vitamin D, calcium, and parathyroid hormone. J Clin Endocrinol Metab 1975; 41 (6): 1130-5
200. Hahn TJ, Birge SJ, Scharp CR, et al. Phenobarbital-induced alterations in vitamin D metabolism. J Clin Invest 1972; 51 (4): 741-8
201. Devogelaer JP. Clinical use of bisphosphonates. Curr Opin Rheumatol 1996; 8 (4): 384-91

202. Peter R, Mishra V, Fraser WD. Severe hypocalcaemia after being given intravenous bisphosphonate. BMJ 2004; 328 (7435): 335-6
203. Henley D, Kaye J, Walsh J, et al. Symptomatic hypocalcaemia and renal impairment associated with bisphosphonate treatment in patients with multiple myeloma. Intern Med J 2005; 35 (12): 726-8
204. Rosen CJ, Brown S. Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency. N Engl J Med 2003; 348 (15): 1503-4
205. Hahn TJ, Hendin BA, Scharp CR, et al. Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol levels in adults. N Engl J Med 1972; 287 (18): 900-4
206. Craig JC, Hodson EM, Martin HC. Phosphate enema poisoning in children. Med J Aust 1994; 160 (6): 347-51
207. Korzets A, Dicker D, Chaimoff C, et al. Life-threatening hyperphosphatemia and hypocalcemic tetany following the use of fleet enemas. J Am Geriatr Soc 1992; 40 (6): 620-1
208. Bolan CD, Cecco SA, Wesley RA, et al. Controlled study of citrate effects and response to i.v. calcium administration during allogeneic peripheral blood progenitor cell donation. Transfusion 2002; 42 (7): 935-46
209. Deaths associated with hypocalcemia from chelation therapy--Texas, Pennsylvania, and Oregon, 2003-2005. MMWR Morb Mortal Wkly Rep 2006; 55 (8): 204-7
210. Jacobson MA, Gambertoglio JG, Aweeka FT, et al. Foscarnet-induced hypocalcemia and effects of foscarnet on calcium metabolism. J Clin Endocrinol Metab 1991; 72 (5): 1130-5
211. Atsmon J, Dolev E. Drug-induced hypomagnesaemia: scope and management. Drug Saf 2005; 28 (9): 763-88
212. Lyman NW, Hemalatha C, Viscuso RL, et al. Cisplatin-induced hypocalcemia and hypomagnesemia. Arch Intern Med 1980; 140 (11): 1513-4
213. Barceloux DG, Krenzelok EP, Olson K, et al. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol 1999; 37 (5): 537-60
214. Heath DA, Palmer JS, Aurbach GD. The hypocalcemic action of colchicine. Endocrinology 1972; 90 (6): 1589-93
215. Frayha RA, Tabbara Z, Berbir N. Acute colchicine poisoning presenting as symptomatic hypocalcaemia. Br J Rheumatol 1984; 23 (4): 292-5
216. Vinson DR, Burke TF, Sung HM. Rapid reversal of life-threatening diltiazem-induced tetany with calcium chloride. Ann Emerg Med 1999; 34 (5): 676-8
217. Bilezikian JP, Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. N Engl J Med 2004 Apr 22; 350 (17): 1746-51
218. Hoeck HC, Laurberg G, Laurberg P. Hypercalcaemic crisis after excessive topical use of a vitamin D derivative. J Intern Med 1994; 235 (3): 281-2
219. Ragavan VV, Smith JE, Bilezikian JP. Vitamin A toxicity and hypercalcemia. Am J Med Sci 1982; 283 (3): 161-4
220. Akiyama H, Nakamura N, Nagasaka S, et al. Hypercalcaemia due to all-trans retinoic acid. Lancet 1992; 339 (8788): 308-9
221. Picolos MK, Lavis VR, Orlander PR. Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. Clin Endocrinol (Oxf) 2005; 63 (5): 566-76
222. Picolos MK, Orlander PR. Calcium carbonate toxicity: the updated milk-alkali syndrome; report of 3 cases and review of the literature. Endocr Pract 2005 Jul-Aug; 11 (4): 272-80
223. Spiegel AM, Rudorfer MV, Marx SJ, et al. The effect of short term lithium administration on suppressibility of parathyroid hormone secretion by calcium in vivo. J Clin Endocrinol Metab 1984; 59 (2): 354-7
224. Togari A. Adrenergic regulation of bone metabolism: possible involvement of sympathetic innervation of osteoblastic and osteoclastic cells. Microsc Res Tech 2002; 58 (2): 77-84
225. McPherson ML, Prince SR, Atamer ER, et al. Theophylline-induced hypercalcemia. Ann Intern Med 1986; 105 (1): 52-4
226. Bartalena L. Recent achievements in studies on thyroid hormone-binding proteins. Endocr Rev 1990 Feb; 11 (1): 47-64
227. Wolff J, Chaikoff I. Plasma inorganic iodide as homeostatic regulator of thyroid function. J Biol Chem 1948; 174: 555-64
228. Braverman LE, Ingbar SH. Changes in thyroidal function during adapation to large doses of iodide. J Clin Invest 1963; 42: 1216
229. Eng PH, Cardona GR, Fang SL, et al. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. Endocrinology 1999; 140 (8): 3404-10
230. Duncan L, Bateman DN. Sexual function in women: do antihypertensive drugs have an impact? Drug Saf 1993; 8 (3): 225-34
231. Cooper DS. Hyperthyroidism. Lancet 2003 Aug 9; 362 (9382): 459-68
232. Vorperian VR, Havighurst TC, Miller S, et al. Adverse effects of low dose amiodarone: a meta-analysis. J Am Coll Cardiol 1997; 30 (3): 791-8
233. Kennedy RL, Griffiths H, Gray TA. Amiodarone and the thyroid. Clin Chem 1989; 35 (9): 1882-7
234. Assessment of the iodine deficiency disorders and monitoring their elimination. A guide for programme managers. 2nd ed. Geneva: World Health Organization, 2001 (WHO/NHD/01.1)
235. Trifanescu R, Fica S, Barbu C, et al. Amiodarone-induced thyroid dysfunction in cardiac patients from areas with iodine deficiency. Rom J Intern Med 2004; 42 (3): 595-605
236. Basaria S, Cooper DS. Amiodarone and the thyroid. Am J Med 2005; 118 (7): 706-14
237. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med 1996; 335 (2): 99-107
238. Rao RH, McCready VR, Spathis GS. Iodine kinetic studies during amiodarone treatment. J Clin Endocrinol Metab 1986; 62 (3): 563-8
239. Temple R, Berman M, Robbins J, et al. The use of lithium in the treatment of thyrotoxicosis. J Clin Invest 1972; 51 (10): 2746-56
240. Brownlie BE, Chambers ST, Sadler WA, et al. Lithium associated thyroid disease: a report of 14 cases of hypothyroidism and 4 cases of thyrotoxicosis. Aust N Z J Med 1976; 6 (3): 223-9
241. Spaulding SW, Burrow GN, Bermudez F, et al. The inhibitory effect of lithium on thyroid hormone release in both euthyroid and thyrotoxic patients. J Clin Endocrinol Metab 1972; 35 (6): 905-11
242. Lazarus JH. The effects of lithium therapy on thyroid and thyrotropin-releasing hormone. Thyroid 1998; 8 (10): 909-13
243. Bagchi N, Brown TR, Mack RE. Studies on the mechanism of inhibition of thyroid function by lithium. Biochim Biophys Acta 1978; 542 (1): 163-9
244. Chan WB, Chow CC, Cockram CS. A patient with low free T4 and low thyroid-stimulating hormone without hypopituitarism. Int J Clin Pract 2004; 58 (10): 983-4
245. Krotkiewski M. Thyroid hormones and treatment of obesity. Int J Obes Relat Metab Disord 2000; 24 Suppl. 2: S116-9

246. Chen WL. [Controversy in medical practice: the pros and cons of treating hyperthyroidism with iodine-containing Chinese traditional herb medicine (author's transl)]. Zhonghua Nei Ke Za Zhi 1980; 19 (5): 377-8

247. Preziati D, La Rosa L, Covini G, et al. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. Eur J Endocrinol 1995; 132 (5): 587-93

248. Braga-Basaria M, Basaria S. Interferon-alpha-induced transient severe hypothyroidism in a patient with Graves' disease. J Endocrinol Invest 2003; 26 (3): 261-4

249. MacDonald PC, Madden JD, Brenner PF, et al. Origin of estrogen in normal men and in women with testicular feminization. J Clin Endocrinol Metab 1979; 49 (6): 905-16

250. Rampin O, Giuliano F. Central control of the cardiovascular and erection systems: possible mechanisms and interactions. Am J Cardiol 2000; 86 (2A): 19F-22F

251. Burnett AL, Musicki B. The nitric oxide signaling pathway in the penis. Curr Pharm Des 2005; 11 (31): 3987-94

252. Plosker GL, Brogden RN. Leuprorelin. A review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders. Drugs 1994; 48 (6): 930-67

253. MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med 1986; 104 (5): 648-51

254. Barradell LB, Faulds D. Cyproterone. A review of its pharmacology and therapeutic efficacy in prostate cancer. Drugs Aging 1994; 5 (1): 59-80

255. Barton C, Waxman J. Effects of chemotherapy on fertility. Blood Rev 1990; 4 (3): 187-95

256. Howell SJ, Shalet SM. Testicular function following chemotherapy. Hum Reprod Update 2001; 7 (4): 363-9

257. Molina JR, Barton DL, Loprinzi CL. Chemotherapy-induced ovarian failure: manifestations and management. Drug Saf 2005; 28 (5): 401-16

258. Whitten PL, Naftolin F. Reproductive actions of phytoestrogens. Baillieres Clin Endocrinol Metab 1998; 12 (4): 667-90

259. Solomon GM, Schettler T. Environment and health: 6. Endocrine disruption and potential human health implications. CMAJ 2000; 163 (11): 1471-6

260. Eertmans F, Dhooge W, Stuyvaert S, et al. Endocrine disruptors: effects on male fertility and screening tools for their assessment. Toxicol In Vitro 2003; 17 (5-6): 515-24

261. Turner KJ, Sharpe RM. Environmental oestrogens: present understanding. Rev Reprod 1997; 2 (2): 69-73

262. Landrigan P, Garg A, Droller DB. Assessing the effects of endocrine disruptors in the National Children's Study. Environ Health Perspect 2003; 111 (13): 1678-82

263. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet 2005 Jun 18-24; 365 (9477): 2125-36

264. Lamb DR. Anabolic steroids in athletics: how well do they work and how dangerous are they? Am J Sports Med 1984; 12 (1): 31-8

265. Maravellas C, Dona A, Stefanidou M, et al. Adverse effects of anabolic steroids in athletes: a constant threat. Toxicol Lett 2005 Sep 15; 158 (3): 167-75

266. Church JA. Oxandrolone treatment of childhood hereditary angioedema. Ann Allergy Asthma Immunol 2004; 92 (3): 377-8

267. Kaltsas GA, Isidori AM, Besser GM, et al. Secondary forms of polycystic ovary syndrome. Trends Endocrinol Metab 2004; 15 (5): 204-10

268. Meo R, Bilo L. Polycystic ovary syndrome and epilepsy: a review of the evidence. Drugs 2003; 63 (12): 1185-227

269. Emiliano AB, Fudge JL. From galactorrhea to osteopenia: rethinking serotonin-prolactin interactions. Neuropsychopharmacology 2004 May; 29 (5): 833-46

270. Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. J Clin Psychiatry 1994; 55 (9): 406-13

271. Baldwin DS. Sexual dysfunction associated with antidepressant drugs. Expert Opin Drug Saf 2004; 3 (5): 457-70

272. Dusing R. Sexual dysfunction in male patients with hypertension: influence of antihypertensive drugs. Drugs 2005; 65 (6): 773-86

273. Maggi M, Filippi S, Ledda F, et al. Erectile dysfunction: from biochemical pharmacology to advances in medical therapy. Eur J Endocrinol 2000; 143 (2): 143-54

274. Briganti A, Salonia A, Gallina A, et al. Emerging oral drugs for erectile dysfunction. Expert Opin Emerg Drugs 2004; 9 (1): 179-89

275. Nieman LK, Ilias I. Evaluation and treatment of Cushing's syndrome. Am J Med 2005 Dec; 118 (12): 1340-6

276. Turpeinen U, Markkanen H, Valimaki M, et al. Determination of urinary free cortisol by HPLC. Clin Chem 1997; 43 (8 Pt 1): 1386-91

277. Kudva YC, Sawka AM, Young WF, et al. Clinical review 164. The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. J Clin Endocrinol Metab 2003; 88 (10): 4533-9

278. Wassell J, Reed P, Kane J, et al. Freedom from drug interference in new immunoassays for urinary catecholamines and metanephrines. Clin Chem 1999; 45 (12): 2216-23

279. Ma RC, Chan WB, So WY, et al. Carbamazepine and false positive dexamethasone suppression tests for Cushing's syndrome. BMJ 2005; 330 (7486): 299-300

Correspondence: Dr *Ronald C.W. Ma*, Department of Medicine and Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China.
E-mail: rcwma@cuhk.edu.hk