CHAPTER 11

HORMONAL DISORDERS

HYPOTHYROIDISM

Hypothyroidism could be primary; common causes are autoimmune, and iatrogenic due to I^{131}, antithyroid or lithium treatment and thyroidectomy, or secondary to pituitary or hypothalamic disease.

SALIENT FEATURES

- Coarse dry skin, hoarse voice, facial puffiness, weight gain, cardiac enlargement and/or pericardial effusion, goiter with or without prolonged relaxation phase of deep tendon reflexes.
- Myxoedema coma is a rare complication of severe hypothyroidism with hypothermia, hypoventilation, hyponatraemia, hypoxia, hypercapnia and hypotension.
- Diagnosis is confirmed by low serum free thyroxine (FT_3 and FT_4), serum TSH raised in thyroid types and low in suprathyroid types. Thyroperoxidase (TPO) antibodies are present in 90-95% patients with autoimmune hypothyroidism.

Treatment

Pharmacological

Tab. L-thyroxine 50-100 mcg/day. Dose to be adjusted based on TSH levels. Goal is normal TSH (lower half of reference range). Measure TSH levels after about 2 months of instituting therapy. Adjust by 12.5 or 25 mcg increments, if TSH is high; decrement of same, if TSH is suppressed.

Full replacement achieved then follow up measurement at annual intervals and later at 2-3 years interval. Ensure ongoing compliance.

Special treatment considerations

- Hypothyroid woman should be euthyroid prior to conception and during early pregnancy (affect on foetal neuronal development).

- Elderly require less thyroxine (less by up to 20%), especially those with coronary artery disease. Starting dose 12.5 mcg/day with similar increments every 2 to 3 months until TSH is normalized.
- In hypothyroidism cases with low TSH (suprathyroid), cause is suspected, requires detailed investigations. Patient should be referred to a tertiary care level. Assess the response clinically and by serum TSH (serum T_3 in suprathyroid type) at 8 weekly intervals; once euthyroid state restored, follow-up at 6-12 months intervals.

Myxoedema coma

1. Warm blankets, mechanical ventilation for respiratory failure.
2. Correction of metabolic disturbances and treat precipitating factors.
3. L-thyroxine 500 mcg IV bolus, then 50-100 mcg IV daily; if IV preparation not available, same dose via Ryle's tube. Once acute phase is over, maintain L-thyroxine as above.
4. Inj. Hydrocortisone 100 mg IV stat, 25-50 mg 8 hourly.

   (**Caution**: Avoid sedatives)

Patient education

- L-thyroxine to be taken as single daily dose, ideally on awakening, at least 30 minutes before eating.
- Fibre and bran products (e.g. Isapghula husk) may impair absorption, as also cholestyramine, colestipol, iron sulphate, sucralfate, aluminium hydroxide. Metabolism of L-thyroxine is increased by phenytoin, rifampicin, carbamazepine.
- Explain to the patient that the treatment is life long. Do not modify dose or stop treatment without consultation.
- Over treatment may lead to decreased bone mineral density and adverse cardiac consequences.

(For treatment of hypothyroidism in children, see in Chapter-19).

References

1. An Update on the Management of Hyperthyroidism and Hypothyroidism. Arch Intern Med 2000; 160: 1067-1071.
2. Disorders of the Thyroid Gland. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp. 2911-2939.

HYPERTHYROIDISM

Classically occurs in Graves' disease, which is characterized by diffuse goiter, ophthalmopathy and dermopathy in varying combinations. Other important causes are toxic multinodular goiter (TMN) and toxic adenomas.

SALIENT FEATURES

- Sweating, tremors, wide pulse pressure, sinus tachycardia and atrial arrhythmias; worsening of angina or cardiac failure may predominate in older patients.
- Graves' disease—goiter, ophthalmopathy and dermopathy.
- Diagnosis is confirmed by low to undetectable serum TSH and increased serum free thyroxine (FT_3) and free (FT_4).

Treatment

Pharmacological

1. Adjunctive treatment—for adrenergic symptoms like sweating, tremor and tachycardia.
   Tab. Propranolol 40-120 mg a day.
   Or
   Tab. Atenolol 50-200 mg a day to be continued until patient becomes euthyroid.
2. Tab. Propylthiouracil 100-150 mg every 6-8 hours.
   Or
   Tab. Carbimazole 10-20 mg every 8-12 hours; after euthyroid state achieved in 6-8 weeks once daily dose possible.

Review with serum TSH and FT_3 after 3-4 weeks treatment has been initiated. Once controlled reduce to smallest effective dose or continue initial dose combined with L-thyroxine. Drugs are given for average of 2 years.

Definitive treatment is surgery/ablation of thyroid tissue (for details see thyroid swelling in surgery section Chapter 18).

Surgery. Subtotal thyroidectomy in younger patients (<30 years) in whom antithyroid therapy has been unsuccessful and in very large goiters.

Radioactive iodine (I^{131}). Method of choice in the elderly, younger patients (completed family) with recurrent thyrotoxicosis following surgery or when surgery is refused/ contraindicated.

(Caution: Radioiodine should never be given in pregnancy. In women of child bearing age, if radioiodine treatment is planned, a pregnancy test must always be carried out).

Pregnancy

In pregnant women, surgery should not be performed in the 1st and 3rd trimesters. Antithyroid drugs are less risky but may induce hypothyroidism in the foetus and should be used in the smallest necessary dose to keep serum TSH and FT_4 in normal range.

Propylthiouracil is preferred—usual maintenance dose is 200 mg/day. If >300 mg/ day required during 1st trimester, subtotal thyroidectomy indicated in the 2nd trimester. Propranolol should be avoided as it can cause foetal growth retardation and neonatal respiratory depression.

Ophthalmopathy

Refer to an ophthalmologist.

Initiate therapy in mild cases with elevation of the head at night, diuretics to decrease oedema, use of tinted sunglasses and 1% methylcellulose eyedrops to prevent drying and refer patients with severe and progressive exophthalmous to an ophthalmologist.

Toxic multinodular goiter

Radioactive iodine is the treatment of choice. Large doses are usually required. Treatment with antithyroid drugs given till patient is euthyroid.

Propranolol may be useful before and after radioactive iodine administration.

Thyrotoxic crisis or thyroid storm

Refer to a tertiary care.

Life-threatening exacerbation of hyperthyroidism with fever, vomiting, diarrhoea, jaundice, delirium and coma; usually precipitated by acute illness like stroke, infection, trauma, diabetic ketoacidosis, patients undergoing surgery or radioiodine treatment in a poorly prepared patient:

1. Tab. Propylthiouracil 600 mg loading dose, then 200-300 mg every 6 hours orally or through Ryle's tube.
   Or
   Tab. Carbimazole 15-25 mg 6 hourly.
2. One hour after 1st dose of antithyroid drug, saturated solution of Potassium iodide (SSKI) 5 drops every 6 hours.
   Or
   Lugol's iodine 10 drops 3 times a day.
   Or
   Sodium iodide 1 g IV slowly.
3. Tab. Propranolol 40-60 mg 4 hourly or 0.5-2 mg IV every 4 hours.
4. Inj. Dexamethasone 2 mg IV 6 hourly.
   Continue iodides and dexamethasone until normal metabolic stage achieved and supportive treatment like cooling, antipyretics, antibiotics for infection, IV fluids, etc.
   Once euthyroid status is achieved, manage as already outlined.

Patient education

- If fever or sore throat develops on antithyroid drugs, complete blood count should be done; discontinue, if PMN count 1500/mm^3.
- If allergic rash or drug sensitivity develops, give antihistamines and preferably change to another drug. If agranulocytosis, hepatitis, drug fever, arthralgias develop, preferably stop antithyroid treatment.
- Iodide—useful in impending thyrotoxic crisis and patients with severe cardiac disease; must be used only after following antithyroid drugs.

References

1. An Update on the Management of Hyperthyroidism and Hypothyroidism. Arch Intern Med 2000; 160: 1067-1071.
2. Disorders of the Thyroid Gland. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp. 2911-2939.

HYPOCALCAEMIA

Hypocalcaemia may be caused by hypoparathyroidism, pseudohypoparathyroidism, vitamin D deficiency states, chronic renal failure, malabsorption syndrome and hypomagnesaemia.

SALIENT FEATURES

- Circumoral paraesthesias, muscle cramps, confusion, tetany, convulsions. Positive Chvostek's and Trousseau's signs.
- ECG may reveal prolongation of the QT interval.
- Total serum calcium <8.5 mg/dl (ionized calcium <4 mg/dl). In hypoalbuminaemia, add 1 mg/dl of calcium to the estimated level for every one gram fall of albumin below 4 g/dl (corrected serum calcium).

Treatment (severe symptomatic hypocalcaemia)

Calcium gluconate solution 20 ml of 10% over 10-15 min followed by 60-80 ml of 10% solution in 1 L 5% dextrose (0.5-2.0 mg/kg/hour elemental Calcium).

(**Caution**: Should not be mixed with bicarbonate solution as it may result in precipitation of calcium carbonate).

Measure serum calcium every 4-6 h. Aim is to maintain the total serum calcium concentration at 7-9 mg/dl. Note that untreated hypomagnesaemia will often make hypocalcaemia refractory to therapy.

If associated with hypomagnesaemia, Inj. Magnesium sulphate 1-2 g IV on day 1 followed by oral Magnesium oxide 600-1200 mg 3 times a day to replenish stores.

Asymptomatic hypocalcaemia/Maintenance treatment

Treat the underlying cause, if possible. Usually long-term treatment required in conditions like hypoparathyroidism, pseudohypoparathyroidism, and chronic vitamin D deficiency states.

Tab. Calcium carbonate (40% elemental calcium by weight) 1-2 g elemental calcium orally 3 times a day initially and subsequently maintenance dose of 0.5-1 g 3 times a day.

In chronic renal failure, calcium alone gives an inadequate response.

However, correct concomitant hyperphosphataemia before instituting following therapy:

Vitamin D 50000 IU/day for 1-2 weeks, then weekly or bimonthly.

Or

Calcitriol 1,25$(OH)_2D_3$ 0.25 mcg orally daily—more expensive but less toxic than vitamin D for hyperphosphataemia—advise low phosphate (low cereal) diet and phosphate binding agents, e.g. aluminium hydroxide.

Patient education

- Side effects of oral calcium carbonate are dyspepsia and constipation.
- Absorption requires gastric acid and is impaired in achlorhydria or when acid suppressive therapy is being given.
- Serum calcium should be monitored frequently (daily in severe hypocalcaemia, weekly with moderate hypocalcaemia for first month) and maintained at 8.0-8.6 mg/dl, and PTH and 24 h urinary calcium within 2-4 weeks of starting treatment.
- Once serum and urinary calcium is normal and PTH falls, maintenance treatment as described with reassessment at 3 monthly intervals.

References

1. Diseases of the Parathyroid Gland and Calcium Homeostasis. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp 3096-3120.
2. Calcium. In: The Washington Manual of Medical Therapeutics, Ahya SN, Flood K, Paranjothi S (eds)., 30th Edition, Williams and Wilkins, Lippincott, Philadelphia. 2001; pp-60-66.
3. Life-threatening Electrolyte Abnormalities. Circulation 2005; 112: IV-121-IV-125.

HYPERCALCAEMIA

The common causes are hyperparathyroidism and malignancy; others include excessive vitamin D action, high bone turnover or renal failure. Hypercalcaemia is defined as 10.5 mEq/L (or an elevation in ionized calcium > 4.8 mg/dL)

SALIENT FEATURES

- Generally symptoms appear when serum Ca >11.5-12.0 mg/dl; severe hypercalcaemia (>15-18 mg/dl) can result in death.
- Fatigue, depression, confusion, anorexia, nausea, vomiting, constipation, polyuria, short QT interval on ECG and occasionally cardiac arrhythmias.

Treatment

Treatment varies with severity; mild hypercalcaemia can be treated with rehydration only, while severe hypercalcaemia is treated as a medical emergency.

1. Rehydration infusion of 0.9% saline at 300-500 ml/hour (saline diuresis) until fluid deficit is replaced and diuresis occurs (urine output ≥ 200 to 300 ml/h). Once adequate rehydration has occurred, the saline infusion rate is reduced to 100 to 200 ml/h.

2. Monitor electrolytes especially potassium and magnesium and replace accordingly.
3. Haemodialysis is the treatment of choice to rapidly discrease rerum calcium in patients with heart failure or renal failure. For extreme conditions, chelating agent (e.g. 50 mmol PO_4 over 8 to 12 hours or EDTA 10 to 15 mg/kg over 4 hours).
4. Tab. Phosphorus (sodium and potassium phosphate) 1-1.5 g per day in 4 divided doses for several days, when hypophosphataemia is present.

Definitive treatment, wherever possible, is parathyroidectomy in hyperparathyroidism.

Patient education

- In patients with mild asymptomatic hypercalcaemia due to hyperparathyroidism, advise to keep active, avoid immobilization, drink adequate fluids and avoid thiazide diuretics, large doses of vitamin D or A and calcium supplements and calcium containing antacids.
- Check serum calcium and albumin twice a year, renal function and urine calcium once a year and bone density of distal radius once every 2 years.

References

1. Diseases of the Parathyroid Gland and Calcium Homeostasis In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp 3096-3120.
2. Calcium. In: The Washington Manual of Medical Therapeutics. Ahya SN, Flood K, Paranjothi S (eds)., 30th Edition, Williams and Wilkins, Lippincott, Philadelphia. 2001; pp-60-66.
3. Life-threatening Electrolyte Abnormalities Circulation 2005: 112; IV-121– IV-125.

DIABETES MELLITUS

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by hyperglycaemia. DM is divided into 2 broad categories: Type 1 DM characterized by insulin deficiency, and type 2 DM characterized by variable degree of insulin resistance, impaired insulin secretion and increased glucose production.

SALIENT FEATURES

- Polyuria, polydipsia, polyphagia and unexplained weight loss with a *random or casual plasma glucose ≥200 mg/dl or **fasting plasma glucose ≥126 mg/dl or 2 h plasma glucose ≥200 mg/dl after a 75 g glucose load. In the absence of unequivocal hyperglycaemia, the result should be confirmed by repeat testing.
- Impaired fasting glucose (IFG) 100-125 mg/dl and impaired glucose tolerance (IGT)-2 h plasma glucose 140-199 mg/dl are considered "pre-diabetes" and are risk factors for future diabetes and cardiovascular disease (CVD).

***** *Random/casual is defined as any time of day without regard to last meal*

******** *Fasting is defined as no caloric intake for at least 8 hours.*

Treatment of DM Type I

This type of DM will always require insulin in addition to dietary management.

Nonpharmacological

Principles of dietary therapy

1. Caloric requirement for normal weight individual: According to nature of work:

	Sedentary	Moderate	Heavy
Male (Kcal/d)	1800-2000	1800-2200	2200-3200
Female (Kcal/d)	1200-1500	1400-1600	1600-2400

2. Caloric distribution
   Carbohydrate 45-65% of total calories; Protein—10-35% of total Kcal/day (10% for those with nephropathy); 20-35% from fat; Saturated fat <7% of total Kcal/day
   Polyunsaturated fat 10% of Kcal/day. Intake of *trans*-fats should be minimized.
   Low carbohydrate diets (<130 g/day) not recommended in the treatment of overweight/obesity. Routine supplementation with antioxidants (vitamin E, C and carotene) not advised.
   Use of caloric sweetners including sucrose is safe when consumed within the intake levels recommended by FDA.
   Fibre (20-35 g/day) and sodium—3000 mg/day.
   Cholesterol—300 mg/day.

Pharmacological

Insulin therapy.

1. Therapy should be started with insulin (human) in a dose of 0.5 units/kg/day to 1.0 unit/kg/day.
2. Combination of regular + lente/semilente insulin should be used (now available as Premix preparation as well).
3. One-third of the total insulin requirement is given as regular and two-thirds as lente/semilente.
4. One-third of the total dose is used before dinner and two-thirds before breakfast.
5. Insulin is given SC 30-45 min before meals.
6. Medial aspect of thigh and abdominal wall are generally used for injection. Rotate injection site frequently. There is no need to use spirit swab, if the skin is clean.
7. Dose, type and timing of insulin is adjusted according to pre-prandial blood sugar levels (80-150 mg%). Level of blood glucose estimated depends on dose of plain insulin taken 3-4 hours before or intermediate/long-acting insulin taken 8-12 hours before the test.
8. Increment of dose should not be more than 10% of existing dose and dose readjustment should not be made earlier than 3 days.
9. Use of insulin analogs in select cases when it is justified on clinical grounds, preferably under guidance of a specialist. Patients must be properly trained for administration of SC injections.

10. Meals must be ensured after injection.
11. Explain features of hypoglycaemia to the patient (see section on Hypoglycaemia).
12. Diabetes self-management and adjustment of Insulin dose based on self-monitoring of glucose and carbohydrate count.

Treatment of DM Type 2

It is possible to control mild DM type 2 with nonpharmacological therapy (dietary control and exercise), however, moderate and severe forms will require, in addition, one or more oral hypoglycaemics and occasionally insulin therapy.

Nonpharmacological

Diet. Basic principles of the diet are same as in DM Type 1. Most of the patients in DM type 2 are, however, obese and should be put on dietary restrictions for weight reduction as above.

Exercise. Regular physical exercise for 1/2 to 1 hour (for sedentary workers) is recommended to have a better control of diabetes. Lifestyle modification of increasing physical activity in day-to-day work is also recommended. At least 150 min/week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (>70% of maximum heart rate). The physical activity should be distributed over at least 3 days/week and with no more than two consecutive days without physical activity. In the absence of contraindications resistance, exercise three times a week should be encouraged.

Pharmacological

If nonpharmacological measures not sufficient, oral agents may be used alone and in combination. Level of hyperglycaemia influences the initial choice of oral hypoglycaemic agents. Therapy usually started with metformin unless contraindicated. Metformin has the advantage of promoting mild weight loss in obese patients. Patient with fasting plasma glucose 200-250 mg/dl respond well. Treatment may be started with any of the following drugs and dose individualized and dose can be increased every 2-3 weeks as determined by blood glucose response:

Tab. Metformin 500 mg once or twice a day in obese patients and increase the dose to 1000 mg 2 times a day with meals.

Or

Tab. Glimipride 1-8 mg/day once daily to be taken at the same time every day with breakfast or Tab. Glipizide 2.5-40 mg/day before breakfast or Tab. Glipizide ER 5-10 mg/day with breakfast or Tab. Gliclazide MR 30 mg-120 mg/day as single dose at breakfast time.

(**Caution**: MR and ER tablets should be swallowed whole and not broken, chewed or crushed, as this would damage the modified release action)

Or

Tab. Glyburide (Glibenclamide) 1.25-20 mg/day administered with breakfast or with the first main meal.

Or

Tab Pioglitazone initially 15-30 mg, up to 45 mg usually once daily without regard to meals.

Combination therapy. If monotherapy fails with oral hypoglycaemics at maximal tolerated doses as does not achieve or maintain A1C target over 3-6 months, add a second oral agent or GLP-1 receptor agonist or insulin. Following combination can be given, if inadequate glycaemic control with single oral hypoglycaemic agent:

Sulphonylurea + metformin

Sulphonylurea + pioglitazone

Sulphonylurea + alpha glucosidase inhibitor (Acarbose)

Insulin + metformin

Insulin may be required in patients with primary (markedly symptomatic and/or elevated blood glucose levels or A1C) or secondary failure to oral agents; often as single dose of intermediate acting insulin 0.3-0.4 units/kg/day either before breakfast or at bedtime in combination with Tab. Metformin. Insulin is also required in situations like pregnancy, surgery, infection, etc.

Consider insulin as initial therapy in patients with:

- Fasting plasma glucose >250-300 mg/dl since more rapid glycaemic control will reduce glucose toxicity to islet cells, improve insulin secretion and possibly make oral hypoglycaemic agents more effective.
- Lean patients or those with severe weight loss.
- Underlying renal or hepatic disease, or acutely ill or hospitalized patients.

Glucose monitoring

Self-monitoring of blood glucose (SMBG) should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy. For patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) alone, SMBG may be useful as a guide to management. When adding to or modifying therapy, type 1 and 2 should test SMBG more often than usual. To achieve postprandial glucose targets, postprandial SMBG may be appropriate. When prescribing SMBG, ensure that patients receive initial instruction in, and routine follow-up evaluation of, SMBG technique and their ability to use data to adjust therapy.

Continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (age ≥25 years) with type 1 diabetes. Although the evidence for A1C-lowering is less strong in children, teens, and younger adults.

Perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycaemic control). Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycaemic goals. Use of point-of-care testing for A1C provides the opportunity for more timely treatment changes.

Glycaemic goals

Glycaemic control is fundamental to the management of diabetes and glycaemic goals are shown in Table 11.1. Lowering A1C has been associated with a reduction of microvascular and neuropathic complications of diabetes and possibly microvascular disease.

Table 11.1. Summary of recommendations on glycaemic goals for adults with diabetes

Glycaemic control	
A1C	<7.0%.
Preprandial capillary plasma glucose	90-130 mg/dl (5.0-7.2 mmol/l)
Peak postprandial capillary plasma glucose	<180 mg/dl (10.0 mmol/l)
Blood pressure	< 130/80 mmHg
Lipids	
LDL	<100 mg/dl (<2.6 mmol/l)
Triglycerides	<150 mg/dl (<1.7 mmol/l)
HDL	>40 mg/dl (> 1.0 mmol/l)

Key concepts in setting glycaemic goals:
- A1C is the primary target for glycaemic control
- Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, etc.
- Certain populations (children, pregnant women, and elderly) require special considerations
- More stringent glycaemic goals (i.e. a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycaemia
- Less intensive glycaemic goals may be indicated in patients with severe or frequent hypoglycaemia
- Postprandial glucose may be targeted, if A1C goals are not met despite reaching preprandial glucose goals

PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

A. CVD

CVD is the major cause of mortality for individuals with diabetes. It is also a major contributor to morbidity and direct and indirect costs of diabetes. Emphasis should be placed on reducing cardiovascular risk factors, when possible, and clinicians should be alert for signs and symptoms of atherosclerosis.

1. Hypertension/blood pressure control

Screening and diagnosis

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg should have blood pressure confirmed on a separate day.

Goals

- Patients with diabetes should be treated to a systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg. (for details see section on Hypertension).

2. Dyslipidaemia/lipid management

Screening

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values (LDL <100 mg/dl, HDL >50 mg/dl, and triglycerides <150 mg/dl), lipid assessments may be repeated every 2 years.

Treatment recommendations and goals

- Lifestyle modification focusing on the reduction of saturated fat, *trans*-fat, and cholesterol intake; weight loss (if indicated); and increased physical activity has been shown to improve the lipid profile in patients with diabetes.
- In individuals without overt CVD
  - o The primary goal is an LDL < 100 mg/dl (2.6 mmol/l).
  - o For those over the age of 40 years, statin therapy to achieve an LDL reduction of 30-40% regardless of baseline LDL levels is recommended.
  - o For those under the age of 40 years but at increased risk due to other cardiovascular risk factors who do not achieve lipid goals with lifestyle modifications alone, the addition of pharmacological therapy is appropriate.
- In individuals with overt CVD
  - o All patients should be treated with a statin to achieve an LDL reduction of 30-40%.
- Lower triglycerides to <150 mg/dl (1.7 mmol/l) and raise HDL cholesterol to >40 mg/dl (1.0 mmol/l). In women, an HDL goal 10 mg/dl higher (>50 mg/dl) should be considered.
- Statin therapy is contraindicated in pregnancy.

3. Antiplatelet agents

- Use aspirin therapy (75-162 mg/day) as a secondary prevention strategy in those with diabetes with a history of CVD.
- Use aspirin therapy (75-162 mg/day) as a primary prevention strategy in those with:
  - o Type 1 and 2 diabetes at increased cardiovascular risk, including those who are >40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidaemia, or albuminuria).

4. Smoking cessation

- Advise all patients not to smoke.
- Include smoking cessation counselling and other forms of treatment as a routine component of diabetes care.

5. Coronary heart disease (CHD) screening and treatment

- In patients >55 years of age, with or without hypertension but with another cardiovascular risk factor (history of CVD, dyslipidaemia, microalbuminuria, or smoking), an ACE inhibitor (if not contraindicated) should be considered to reduce the risk of cardiovascular events.
- In patients with a prior myocardial infarction or in patients undergoing major surgery, β-blockers, in addition, should be considered to reduce mortality.
- In asymptomatic patients, consider a risk factor evaluation to stratify patients by 10 year risk and treat risk factors accordingly.

6. Nephropathy screening and treatment

- Goal is to reduce the risk and/or slow the progression of nephropathy, optimize glucose and blood pressure control.

Screening

- Perform an annual test for the presence of microalbuminuria in type 1 diabetic patients with diabetes duration of ≥ 5 years and in all type 2 diabetic patients, starting at diagnosis and during pregnancy.
- Serum creatinine should be measured at least annually for the estimation of glomerular filtration rate (GFR) in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine alone should not be used as a measure of kidney function but instead used to estimate GFR and stage the level of chronic kidney disease (CKD).
- Reduction of protein intake to 0.8-1.0 g/kg/d individuals with diabetes and the earlier stages of CKD and to 0.8 g/kg/d in the later stages of CKD may improve measures of renal function (urine albumin excretion rate and GRF) and is recommended.

7. Retinopathy screening and treatment

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes. The prevalence of retinopathy is strongly related to the duration of diabetes. Diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults aged 20-74 years. Glaucoma, cataracts, and other disorders of the eye may occur earlier in people with diabetes and should also be evaluated.

General recommendations

- Optimal glycaemic and blood pressure control can substantially reduce the risk and progression of diabetic retinopathy.

Screening

- Adults and adolescents with type 1 and 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 3-5 years after the onset of diabetes.

Treatment

- Laser therapy can reduce the risk of vision loss in patients with high-risk characteristics (HRCs).
- Promptly refer patients with any level of macular oedema, severe non-proliferative diabetic retinopathy (NPDR) or any PDR to an ophthalmologist.

Intensive diabetes management with the goal of achieving near normoglycaemia prevents and/or delays the onset of diabetic retinopathy. The presence of nephropathy is associated with retinopathy. High blood pressure is an established risk factor for the development of macular oedema and is associated with the presence of PDR. During pregnancy and 1 year postpartum, retinopathy may be transiently aggravated; laser photocoagulation surgery can minimize this risk.

8. Neuropathy screening and treatment

Recommendations

- All patients should be screened for distal symmetric polyneuropathy (DPN) at diagnosis and at least annually thereafter, using simple clinical tests.
- Electrophysiological testing is rarely ever needed, except in situations where the clinical features are atypical.
- Once the diagnosis of DPN is established, special foot care is appropriate for insensate feet to decrease the risk of amputation.
- Simple inspection of insensate feet should be performed at 3- to 6-month intervals. An abnormality should trigger referral for special footwear, preventive specialist, or podiatric care.
- Screening for autonomic neuropathy should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type-1 diabetes. Special electrophysiological testing for autonomic neuropathy is rarely needed and may not affect management and outcomes.

Diagnosis of neuropathy

Patients with diabetes should be screened annually for DPN using tests such as pin-prick sensation, temperature and vibration perception (using a 128-Hz tuning fork), and 10 g monofilament pressure sensation at the distal plantar aspect of both great toes and ankle reflexes. Combinations of more than one test have >87% sensitivity in detecting DPN. Loss of 10 g monofilament perception and reduced vibration perception predict foot ulcers. A minimum of one clinical test should be carried out annually, and the use of two tests will increase diagnostic ability.

Diabetic autonomic neuropathy

The symptoms of autonomic dysfunction should be elicited carefully during the history and review of systems, particularly since many of these symptoms are potentially treatable. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation,

gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycaemic autonomic failure.

Most patients will require pharmacological treatment for painful symptoms (Table 11.2).

Table 11.2 Drugs to treat symptomatic DPN

Class	Examples	Typical doses*
Tricyclic drugs	Amitriptyline	10-75 mg at bedtime
	Nortriptyline	25-75 mg at bedtime
	Imipramine	25-75 mg at bedtime
Anticonvulsants	Gabapentin	300-1,200 mg 3 times daily
	Carbamazepine	200-400 mg 3 times daily
	Pregabalin	100 mg 3 times daily
5-hydroxytryptamine and norepinephrine uptake inhibitor	Duloxitine	60-120 mg daily
Substance P inhibitor	Capsaicin cream	0.025-0.075% applied 3-4 times daily

*Dose response may vary; initial doses need to be low and titrated up.

Amputation and foot ulceration are the common consequences of diabetic neuropathy and major causes of morbidity and disability in people with diabetes. The presence of erythema, warmth, or callus formation may indicate areas of tissue damage with impending breakdown. Examine the patient's feet at every encounter and annual comprehensive foot examination to include inspection assessment of pulses, testing for loss of protective sensation (monofilament, pinprick, etc.) and adopt multidisciplinary approach at the first sign of foot ulcer and for those with high-risk feet. Bony deformities, limitation in joint mobility, and problems with gait and balance should be assessed.

Patient education

- Explain the nature of the disease and potential complications arising due to poorly controlled diabetes.
- Stress the importance of maintenance of normal weight, adhering to regular dietary and regular exercise schedule include counselling regarding the "better" choices from items available in the commissary. Encourage weight loss, if BMI >25 and education about diet portion control.
- Lifestyle modifications may have other beneficial effects (reduced cardiovascular complications).
- Exercise 150 minutes/week of moderate intensity aerobic activity.
- Patient should always carry identification card along with diagnosis, medication and contact numbers in emergency.
- Explain about the warning symptoms and signs of hypoglycaemia and need to take sweets/candies/drinks in such a situation.

- Regular follow-up to monitor BP (quarterly), HbA1c testing (2-4 times/year), eye examination (annual), foot examination (1-2 times/year by physician; daily by patient); screening for diabetic nephropathy (annual); lipid profile (annual).
- In patients with long-standing diabetes, give instructions for care of feet, choice of footwear and avoid walking barefoot.
- Advise all patients not to smoke and counsel on smoking cessation.
- Limit alcohol to one drink/day or less in adult women and two drinks/day or less in adult men.

(See also diabetes mellitus in Chapter 19)

DIABETIC KETOACIDOSIS

Ketoacidosis is acute complication of diabetes, usually occurs in type 1 but can occur in type 2 and characterized by hyperglycaemia, hyperketonaemia and acidosis. Important precipitating factors include poor compliance to treatment and infections/stress.

SALIENT FEATURES

- Nausea, vomiting, abdominal pain, dehydration and altered sensorium.
- Diagnosis is confirmed by demonstration of ketones in urine (or elevated levels in blood), hyperglycaemia, low arterial pH, low bicarbonate (>15 mmol/l) and high anion gap (>15 mmol/l).

Treatment

Treatment includes confirmation of diagnosis and continuous monitoring of the response to treatment as follows:

- Suspect and confirm diagnosis, assess fluid loss and degree of acidosis.
- Suspect and complete blood counts, glucose, renal functions, electrolytes and arterial blood gases.
- Evaluate for precipitating factor(s)/sepsis.

First hour

- If blood pressure is normal, infuse 1000 ml of normal saline.
- If shock and oligaemia, rapid infusion of normal saline until blood pressure rises to normal and subsequently continue with infusion, saline at the rate of 1 liter/hour.

1. Inj. Insulin (regular) 5-10 units/hour IV infusion.
   Or
   Inj. Insulin (regular) 20 units IM immediately followed by 5 units/hour.
2. Inj. Potassium chloride (KCl) 10-20 mmol (max 40 mmol), if serum K^+ not more than 5 mmol/l and urine output is adequate.
3. Inj. Sodium bicarbonate 50-100 mmol infused over 30-60 minutes, if arterial blood pH <7.00.
4. If infection/sepsis suspected, Inj. Cefixime 1-2 g IV 12 hourly to be started.

Second hour

- Continue IV normal saline 500 ml/hour (use 0.45% saline, if serum sodium >150 mmol/l).
- Continue insulin infusion as above (if blood glucose >250 mg/dl).
- Continue IV infusion of KCl (rate of infusion adjusted according to serum level).

Third and fourth hours

- Continue as for second hour.
- Observe for cognitive/neurological functions.

Fifth to eighth hours

- Normal saline infusion 250 ml/hour; change to dextrose saline, if blood glucose <250 mg/dl.
- Neutralizing insulin (1 unit per 2 g of glucose infused) infusion to continue until ketonuria disappears.

After eight hours

- Continue IV fluids and insulin.
- Change to subcutaneous insulin when ketones disappear.
- Stop KCl infusion when plasma levels are normal.
- Change antibiotic, if culture sensitivity report demands.

(For complications of diabetes mellitus see also Diabetic Retinopathy in Chapter-13).

Patient education

- Explain about the importance of regular intake of insulin and diet as per requirement.
- They should consult the physician soon, if there is any symptom suggestive of infection.

References

1. Executive Summary: Standards of Medical Care in Diabetes—2012. Diabetes Care 2012; 35 2001; (Suppl. 1).
2. American Diabetes Association: Clinical Practice Recommendations update 2011.
3. Diabetes Mellitus. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp. 2968-3003.

NON-KETOTIC HYPEROSMOLAR COMA

It is characterized by profound dehydration due to sustained hyperglycaemic dehydration and hyperosmolarity, usually seen in elderly patients with type 2 DM, associated with stroke or sepsis.

SALIENT FEATURES

- Severe dehydration, altered sensorium and marked hyperglycaemia. There may be features of venous thrombosis due to hyperviscosity.
- Other features include focal neurological deficit and sepsis.
- Diagnosed by finding very high blood glucose (>500-1000 mg/dl), high plasma osmolality, acidosis and azotaemia.
- Features like nausea, vomiting, abdominal pain and Kussmaul's respiration are characteristically absent.

Treatment

1. Normal saline or half normal saline (0.45%) 2-3 liters rapidly infused over 2-3 hours. Administration of 0.45% normal saline is indicated, if serum sodium is >150 mEq/L.
2. Inj. Insulin (regular) 5 units/hour as IV infusion.
3. Potassium chloride and sodium bicarbonate infusion as per requirement and administered as in ketoacidosis.

HYPOGLYCAEMIA

Hypoglycaemia occurs due to increased utilization of glucose by the body (as during fasting, exercise or in alcoholics) or over dose of hypoglycaemic drug(s).

SALIENT FEATURES

- Symptoms due to sympathetic stimulation (like anxiety, sweating, palpitation, tremors); neuroglycopenia (light headedness, confusion/altered sensorium, convulsions, focal neurological deficits) or general (weakness, hunger or blurred vision). Prolonged hypoglycaemia may result in permanent neurological deficits.
- Diagnosis confirmed by estimation of blood glucose (< 70 mg/dl) by glucometer/ diastix, etc.

Treatment

Immediate

1. If patient presents early signs and is conscious, oral glucose (15-20 g) preferred or sweets/biscuits/sweet drink, etc.
2. If unconscious diabetic patient on treatment and glucometer is not available, give Inj. Glucose (25-50%) 50-100 ml infused rapidly IV.
   Or

Inj. Glucagon 1 mg IM or SC. If patient receiving long-acting insulin/oral hypoglycaemic agents, continue IV infusion of 5% glucose with regular monitoring of blood glucose hourly. Contraindicated in hypoglycaemia caused by sulphonylureas as glucagon stimulates insulin secretion.

Note: In case of doubt between hypoglycaemia and diabetic ketoacidosis, always choose to give 25% dextrose because hypoglycaemia can kill a patient whereas slight rise in glucose in diabetic ketoacidosis will not alter the prognosis of the patient.

After 15-20 minutes

Check blood glucose after 15-20 minutes and confirm recovery.

On recovery

Identify cause and re-educate patient to avoid future episodes.

If recovery is delayed or patient was on long-acting insulin or oral hypoglcaemic agents:

- Patient unconscious give infusion of 5-10% Dextrose
- Patient conscious give more oral glucose.

Note: Slow recovery form coma may be due to cerebral oedema, but may respond to IV mannitol and forced ventilation with high inspired oxygen concentration.

Patient education

- Explain about the symptoms of hypoglycaemia. Stress upon regular intake of meals along with hypoglycaemic agents and advise them to keep some sweet candies with them all the time. They should use these or any other sugar/glucose containing snacks/drinks at the earliest, if symptoms of hypoglycaemia are experienced.

References

1. Executive Summary: Standards of Medical Care in Diabetes—2012. Diabetes Care 2012; 35 2001; (Suppl.
2. American Diabetes Association: Clinical Practice Recommendations update 2011.
3. Diabetes Mellitus. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp 2968-3003.

ERECTILE DYSFUNCTION

Psychogenic factors are very important. Other important aetiological factors are diabetes mellitus, atherosclerosis and many drugs especially antihypertensives. Besides a complete history, examination and routine investigations like complete blood picture, plasma glucose and lipid profile, special investigations like serum prolactin, serum testosterone and plasma gonadotrophins and at times vascular testing or psychological tests may be helpful.

Treatment

Vacuum constriction devices

Surgery, e.g. surgical implant of semirigid or inflatable penile prosthesis.

Pharmacological

Tab. Sildenafil 25-100 mg; the onset of action is within 60-90 minutes.

Lower initial doses in the elderly, in renal insufficiency, or patients on drugs like erythromycin, cimetidine and ketoconazole which may increase the serum concentration.

(**Caution**: Contraindicated with concomitant nitrate therapy, congestive heart failure and cardiomyopathy; cautious use in coronary artery disease, borderline hypotension, hypovolaemia and patients on complex antihypertensive treatment).

Or

Inj. Testosterone enanthate 100-200 mg IM every 1-2 weeks in low testosterone states.

Or

Intraurethral Alprostodil (Prostaglandin E_1) semisolid pellets of 125-1000 mcg.

Or

Intracavernosal Alprostodil self-injection 1-40 mcg.

Patient education

- Counselling of both partners.
- Explain the side effects of sildenafil and other drugs. Sildenafil can cause headache, facial flushing, dyspepsia, nasal congestion and transient altered colour vision.

Reference

1. Sexual Dysfunction. In: Harrison's Principles of Internal Medicine. Fauci, Braunwald, Kasper et al (eds), 18th Edition, McGraw Hill Company Inc., New York, 2012; pp 374-380.