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API *Manual of* Medicine



Sandhya A Kamath

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86 Disorders of Lipid and Lipoprotein Metabolism

Lipids are essential molecules in the human body, performing various biological functions such as energy storage, signaling molecules, precursors of steroid hormones, and structural components of cell membranes, liposomes, and vesicles. The link between animal fat consumption and cardiovascular disease (CVD) has been established through the seven countries study by Dr Ancel Keys. Lipids are organic hydrophobic compounds derived from fatty acids, with fatty acids and cholesterol being simple lipids and TGs and phospholipids being complex lipids. Lipoproteins are spherical particles that circulate in the blood carrying lipid molecules by making them soluble in plasma. They are an amalgamation of lipids and proteins, with apoproteins directing the lipoproteins toward their respective sites of metabolism

Dyslipidemia is a disorder of lipid metabolism characterized by excess or deficient lipoproteins, linked to increased risk of cardiovascular (CV) heart disease, increased mortality from CV, peripheral vascular disease (PVD), and cerebrovascular disease. The differential diagnosis of hyperlipidemia and dyslipidemia is shown in **Tables 86.1 and 86.2**.

Evidence for the benefits of treatment of dyslipidemia is limited, with low HDL-C and hypertriglyceridemia (termed as atherogenic dyslipidemia) associated with increased levels of small-dense LDL particles and insulin resistance. Atherogenic dyslipidemia has a strong association with type 2 diabetes mellitus (T2DM) and CHD.

Lipid levels alone do not account for the CHD risk. Other factors such as cigarette smoking, hypertension, diabetes, abdominal obesity, lack of physical activity, low daily fruit and vegetable consumption, alcohol overconsumption, and stressful lifestyle also play an important part in the development of atherosclerosis.

In India, limited data is available on the prevalence and patterns of dyslipidemia in urban and rural populations. The pattern of dyslipidemia seen is high TGs, borderline elevated LDL-C, and low HDL-C. No long-term studies have demonstrated association of various cholesterol fractions with CHD outcomes. Dyslipidemia is

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Table 86.1: Differential diagnoses contributing to lipids derangements.

Primary disorders	Secondary disorders
• Fasting hyperchylomicronemia • Familial hypercholesterolemia • Familial combined hyperlipidemia • Familial hypoalphalipoproteinemia • ApoCII deficiency • Familial defective ApoB100 • Dysbetalipoproteinemia • Polygenic hypercholesterolemia • LCAT deficiency • Sitosterolemia ABCA1 deficiency	• Diabetes mellitus • Hypothyroidism • Cushing syndrome • Obesity/Insulin resistance • Alcohol • Obstructive liver disease • High-carbohydrate diet • Nephrotic syndrome • Glucocorticoids • HIV infection • Renal failure • Hepatitis C infection, CLD • *Drug induced*: Protease inhibitors, estrogens, ethanol, beta-blockers, thiazides, antipsychotics, and anabolic steroids

(CLD: chronic liver disease; HIV: human immunodeficiency virus; LCAT: lecithin-cholesterol acyltransferase)

a condition characterized by elevated cholesterol, high LDL, and reduced HDL levels. It can be diagnosed through anthropometric measurements, biochemical evaluation, and fundus evaluation. Plasma lipids should be measured at least twice under fasting conditions to rule out alimentary lipemia. The Friedewald formula for calculating LDL-C is calculated as total cholesterol–HDL–VLDL. Non-HDL-C (total cholesterol minus HDL-C) is a measure of atherogenic lipoproteins.

Treatment approaches for dyslipidemia include lipid goals, such as total cholesterol <200 mg/dL, LDL-C <116 (reduced from previous value of 130 in 2019 ESC/ESA guidelines), <100 (moderate risk), <70 (very high risk), and a reduction in LDL by >50%, <55 (extreme risk). For CVD patients with a repeat vascular event <2 years from the first one, a reduced LDL goal of >40 mg/dL may be considered.

Diet and lifestyle are the first and foremost measures to be taken. Patients should be advised to take a diet high in vegetables, fruits, whole grains, poultry, fish, low-fat dairy products, legumes, vegetable oils, and nuts. Red meat, sweets, and sugar-sweetened beverages should be avoided. Carbohydrate intake should be 45–55%, added sugar <10% of daily intake, and reduced alcohol intake to <10 g/day.

Saturated fat should be limited to <10% of total calories and transfats should be avoided completely. Complex carbohydrates, polyunsaturated fats, and monounsaturated fats should be used as replacements.

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Table 86.2: Primary disorders of lipid metabolism.

Lipid abnormality	Metabolic defect	Biochemical abnormality	Age of onset	Presentation	Signs	Treatment
Fasting hyperchylomicronemia (Frederickson's type 1)	• LPL deficiency • ApoC II defect	• TG >500 mg/dL (usually >2,000) • Reduced post heparin • LPL activity	Childhood	Poor feeding, pancreatitis	Eruptive xanthomas, *lipemia retinalis*	Dietary fat <10% of total calories, omega fatty acids
Genetic familial hypercholesterolemia (type 2)	*LDL receptor* gene mutation	• LDL • Heterozygous >300 • Homozygous >600–1,000	Childhood in homozygous, early 40's in heterozygous	• CHD • Aortic valve disease	Tendon xanthomas, xanthelasma	Statins, fibrates, MTP inhibitors LDL apheresis
Familial combined hyperlipidemia (type III–IV)	Increased VLDL, IDL production	Increased VLDL, LDL	Adulthood	CHD	Xanthelasma	Statins (fibrates may worsen)
Familial dysbetalipoproteinemia (type III)	Defective binding of ApoE to LDL receptor	Increased VLDL and CM remnants and cholesterol, low LDL	>20 years obese	Premature PVD and CHD	Palmer xanthoma, tuberous	Dietary measures, fibrates, niacin
Familial defective ApoB100	Defective binding of ApoB100 to LDL receptor	Increased LDL, VLDL high normal	Adults	Premature CHD	Tendon xanthomas	Statins, ezetimibe

(CE: cholesteryl ester; CHD: coronary heart disease; CM: chylomicron; HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; LPL: lipoprotein lipase; PVD: peripheral vascular disease; TG: triglyceride; VLDL: very low-density lipoprotein)

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Weight management is recommended for obese or overweight patients with additional risk factors for cardiovascular disease (CVD). Inducing a calorie deficit of around 300–500 kcal/day can help in weight reduction.

Medications for dyslipidemia include agents that interrupt bile acid absorption from the gut (BAS), inhibit cholesterol synthesis in cells (HMG-CoA reductase inhibitors), or block cholesterol absorption from the gut (ezetimibe). Statins are the first line recommended drugs for managing ASCVD and hypertriglyceridemia. They have shown reductions in CVD by 20–33% and mortality reduction by up to 10% in meta-analyses of randomized controlled trials. Fibric acid derivatives, ezetimibe, and bile acid sequestrants are medications used to lower LDL-C and improve lipid metabolism. Fibrates are commonly used for severe hypertriglyceridemia and combined hyperlipidemia, but their CV benefits are not proven. Ezetimibe inhibits cholesterol absorption and is used in combination with statins to further lower LDL. Bile acid sequestrants (BAS) work by binding intraluminal bile acids and bile salts in the small intestine, increasing cholesterol conversion and promoting VLDL metabolism. Niacin is the most effective drug to raise HDL-C, but its mechanism of action is unclear. Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are lower VLDL concentrations but may increase LDL-C as VLDL is converted to LDL.

Newer drugs like mipomersen, a monoclonal antibody to PCSK9, have been approved for treating homozygous familial hypercholesterolemia (FH). These drugs inhibit ApoB formation and lower LDL-C levels in patients with homozygous and heterozygous FH. Monoclonal antibodies targeting PCSK9 target the protein involved in controlling LDL-R, leading to increased expression of LDL-Rs at the cell surface and reducing circulating LDL-C levels.

Surgical treatments for homozygous FH include partial ileal bypass surgery, liver transplantation, and portacaval shunting. LDL apheresis can be used to lower atherogenic lipids in patients who cannot achieve lipid lowering despite combination therapy.

87 Disorders of Adipose Tissue and Obesity

Obesity and lipodystrophy are two conditions with common features of insulin resistance (IR), which arises from genetic and environmental causes. Adipose tissue dysfunction in these con-

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ditions promotes inflammation and ectopic fat accumulation. The pathogenetic mechanisms of both conditions are different, but the pathophysiologic consequences are similar, leading to insulin resistance. Adipose tissue is composed of a heterogeneous group of cells, including adipocytes, preadipocytes, fibroblasts, endothelial cells, inflammatory cells, and multipotent stem cells. Adipose tissue is divided into white adipose tissue (WAT) and brown adipose tissue (BAT), with white adipocytes storing excess calories as triglycerides and brown and Brite adipocytes promoting energy expenditure.

White adipose tissue is characterized by its large, round, and single nucleus, while BAT is highly vascular and has a rich nerve supply. Brown and Brite adipocytes have an abundance of uncoupling protein-1 (UCP1) due to their high mitochondrial content, promoting energy expenditure through various mechanisms. Recent studies have identified "batokines" released by BAT, such as fibroblast growth factor 21, neuregulin 4, vascular endothelial growth factor A, and bone morphogenetic protein 8B.

Subcutaneous adipose tissue (SAT) is present in the subcutaneous space, while visceral adipose tissue (VAT) is present in visceral sites. BAT is scattered in specific areas of the body, while Brite adipocytes are scattered in WAT depots. Both SAT and BAT play crucial roles in energy expenditure and metabolic benefits. Adipose tissue plays a crucial role in maintaining energy homeostasis by storing excess free fatty acids as triglycerides, releasing them in negative calorie states, and through adipocytokines. In a positive energy balance, insulin stimulates lipoprotein lipase activity, which hydrolyzes triglycerides in lipoproteins like VLDL and chylomicrons to release FFA. This is taken up by the adipose tissue, where it is re-esterified with glycerol-3-phosphate to form triglyceride, which is then stored. Other lipids such as diacylglycerol and other phospholipids are also formed. In negative calorie states, hormone sensitive lipase (HSL) activity is increased under the influence of raised catecholamines and low insulin.

Hormones such as glucocorticoids, thyroid hormone, sex hormones, growth hormone, and glucagon modulate the receptor activity of catecholamines and insulin. HSL causes release of FFA from the adipose tissue, which is taken up by skeletal muscles for utilization as an energy source or as substrate for triglyceride synthesis in the liver.

In order for adipose tissue to perform its primary and physiological role of maintaining energy homeostasis, at least two factors are needed: An adequate quantity of adipose tissue (SAT) that stores FFA as triglycerides and a healthy adipose tissue that

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expands physiologically with limited inflammation in response to calorie excess. Ectopic adiposity and overwhelming inflammation are the pathophysiologic link between lipodystrophy and obesity. Both conditions lead to ectopic adiposity and unwarranted inflammation, resulting in IR.

The causes and effects of inflammation are an endless cycle of inflammation, with obesity induced IR characterized by elevated proinflammatory cytokines and chemoattractants. In lipodystrophy, the accelerated death of adipocytes recruits inflammatory cells, leading to the formation of "Crown-like structures" (CLSs) surrounded by macrophages. The phenotype of adipose tissue in both obesity and lipodystrophy is influenced by various factors, including the presence of adipose tissue, adipose tissue inflammation, and the presence of adipose tissue inflammation. The human gut microbiota, composed of around 100 trillion cells, is influenced by factors such as mode of delivery, weaning, nutrition, antibiotic use, gut inflammation, and genetics. Factors such as food additives, such as sweeteners and emulsifiers, can affect the gut microbiota's composition, leading to increased metabolic syndrome and chronic inflammatory diseases. Loss of diversity and abundance is associated with disturbances in body homeostasis. T cell phenotype differences between lean and obese mice are crucial in obesity-associated inflammation. CD8+ and TH1 are abundant in obese mice, while CD4+ regulatory T cells protect metabolism against inflammation.

M2 macrophages in lean adipose tissue release anti-inflammatory cytokines, but no satisfactory explanation exists for the differential T cell recruitment. MiRNAs, which regulate cellular expression and fate, play a key role in obesity, with miRNA223 playing a key role in macrophage polarization and anti-inflammatory stimulation. MiRNAs, which regulate cellular expression and fate, play a key role in obesity, with miRNA223 playing a key role in macrophage polarization and anti-inflammatory stimulation.

The gut microbiota affects metabolic processes in numerous ways, such as the central nervous system, adipose tissue, liver, pancreas, and skeletal muscle. Changes in diet and gut microbial composition promote a "leaky gut" membrane, increasing endotoxin absorption and resulting in metabolic endotoxemia. The endocannabinoid system plays an important role in gut-adipose tissue crosstalk, with cannabinoid receptors CB1 and CB2 being key members.

The endocannabinoid signaling system also regulates energy homeostasis by modulating food intake, gastric emptying, and gastrointestinal motility. The system affects adipose tissue

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function and homeostasis by facilitating adipogenesis and expansion through interactions with PPARα and γ and by regulating inflammation.

The cocktail of inflammatory molecules in adipose tissue dysfunction promotes a dysmetabolic and proatherogenic state. Lifestyle modification is the most important measure in preventing and managing obesity, and pharmacotherapy currently focuses on suppression of appetite, which has been satisfactory with significant adverse effects. There is a dire need to develop obesity pharmacotherapy that targets energy expenditure and allocation, gut microbiota and inflammation, and epigenetic mechanisms. Lifestyle modification is a crucial therapeutic option for obesity management, with the diabetes prevention program (DPP) showing its effectiveness in preventing diabetes in high-risk individuals. A calorie-restricted diet with energy intake below energy expenditure is crucial for weight loss. Behavioral therapy is essential for long-term changes in eating behavior, physical activity, and controlling environmental stimuli. Adipose tissue plays a crucial role in energy homeostasis, promoting ectopic adiposity and insulin resistance. Understanding the biology and pathology of adipose tissue in obesity and lipodystrophy can help develop targeted therapy for managing obesity and diabetes.

88 Disorders of Iron Metabolism and Iron Overload Syndromes

Iron overload occurs when iron accumulation in the body exceeds iron loss, characterized by elevated serum ferritin, excessive iron deposition in the liver/myocardium, and the need for phlebotomies to induce iron-limited erythropoiesis. Iron is distributed between red blood cell hemoglobin, the liver (hepatocytes), muscle, and macrophages of the reticuloendothelial system. Iron homeostasis is tightly regulated, with four major cell types determining body iron content and distribution: Duodenal enterocytes (site for dietary iron absorption), erythroid precursors (iron utilization), reticuloendothelial macrophages (iron storage and recycling), and hepatocytes (iron storage and endocrine regulation) **(Fig. 88.1)**.

Dietary iron is found in heme and ionic (nonheme) forms, and their absorption occurs at the apical surface of duodenal enterocytes. Dietary nonheme iron is primarily in an oxidized form, which is imported from the lumen by the apical divalent metal transporter 1 (DMT1) after reduction from ferric to ferrous iron by

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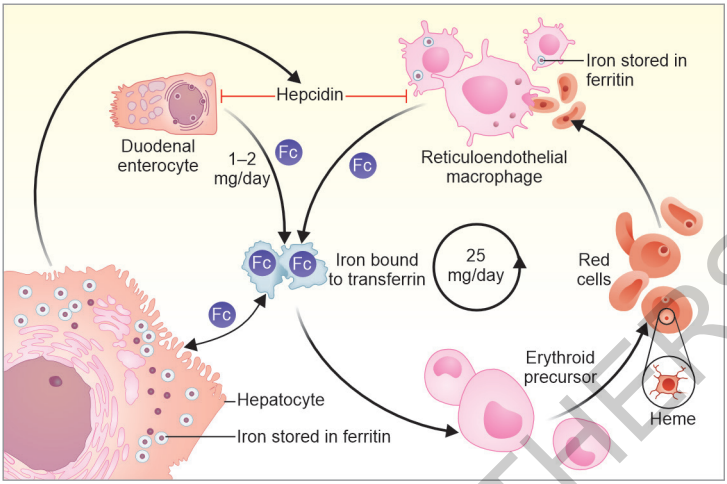


FIGURE 88.1: Iron cycle. Duodenal enterocytes absorb iron which circulates bound to transferrin and is used primarily by erythroid precursors in the synthesis of heme. Reticuloendothelial macrophages clear senescent erythrocytes and release the iron from heme to export it to the circulation or store it in ferritin. Hepatocytes are another site of iron storage as ferritin and the principal site of production of the peptide hormone hepcidin. Hepcidin blocks the release of iron from enterocytes and reticuloendothelial macrophages by degrading the iron exporter ferroportin.

Source: Adapted from Fleming RE, Ponka P. Iron Overload in Human Disease. N Engl J Med. 2012:366:348-59.

duodenal cytochrome B reductase (DCYTB) enzyme. Heme iron is absorbed through incompletely identified mechanisms, such as heme receptors.

Enterocyte oxygen tension regulates iron absorption via the transcription factor hypoxia-inducible factor 2α (HIF-2α) and subsequent changes in transcription of DMT1 and ferroportin. Enterocyte iron content regulates iron absorption via iron regulatory protein (IRP) types 1 and 2 and messenger RNAs encoding DMT1, ferroportin, ferritin, and HIF-2α. Systemic regulation of iron absorption is mediated by the hormone hepcidin, which binds to the iron exporter ferroportin and induces its degradation, decreasing the transfer of iron from enterocytes to the circulation.

Reticuloendothelial cells act as the major hepcidin-regulated iron repository, turning over about 10 times per day. Hepatocytes are an important site of iron storage in the form of ferritin, and iron overload states result in NTBI being the major contributor to iron loading in hepatocytes. Hepcidin, a 25 amino acid cysteine-rich peptide, plays a key role in iron homeostasis and is affected by inflammation, iron status, erythropoietic activity, and oxygen

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tension. Erythropoiesis affects hepcidin production, with increased erythropoiesis leading to decreased hepcidin expression. Decreased oxygen tension also increases hepcidin expression. Under hypoxic conditions, HIF transcription factors upregulate the expression of the membrane protease matriptase-2, which cleaves hemojuvelin from the hepatocellular surface and attenuates BMP-6-mediated signaling to hepcidin. There is considerable overlap in the regulation of hepcidin by hypoxia and iron.

Iron overload syndromes are classified according to the underlying pathophysiological defects, whether it is in the hepcidin-ferroportin axis, erythroid maturation, or iron transport. Hereditary hemochromatosis is the most common disorder of the hepcidin-ferroportin axis, characterized by "insufficient hepcidin production" or "hepcidin resistance." Type 1 hemochromatosis is the classical and most common of the primary hemochromatosis syndromes, with an autosomal recessive inheritance. Type 2 hemochromatosis is a rare autosomal recessive disorder in patients with two mutations of the *Hemojuvelin* gene, resulting in decreased hepcidin synthesis and uninhibited ferroportin-mediated transport of iron from enterocytes into plasma even in the presence of tissue iron overload.

Type 3 hemochromatosis is a rare autosomal recessive disorder in patients with two mutations of the *Hemojuvelin* gene located on chromosomes 1q21. This mutation results in decreased hepcidin synthesis and uninhibited ferroportin-mediated transport of iron from enterocytes into plasma even in the presence of tissue iron overload. Type 4 hemochromatosis is caused by a loss-of-function mutation in the *FPN1* gene leading to iron overload.

Neonatal hemochromatosis is not inherited and usually presents in the second or third-trimester as fetal loss or acute liver failure. Hepcidin is inappropriately low in comparison with iron excess, correlated with the onset and severity of iron overload. Hepcidin deficiency correlates with the onset and severity of iron overload.

Treatment of hereditary hemochromatosis is managed with therapeutic phlebotomy. Porphyria cutanea tarda is the most common type of porphyria and is characterized by elevated iron stores. Disorders of iron transport are characterized by insufficient delivery of transferrin-bound iron for the synthesis of heme, resulting in iron-restrictive erythropoiesis, anemia, or both contributing to low hepcidin levels and iron overload.

Hypotransferrinemia is a rare autosomal recessive disorder characterized by reduced functional transferrin concentration, leading to anemia with loss of the ferritransferrin signal and low hepcidin levels. Erythroid maturation disorders represent secon-

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dary iron overload, characterized by ineffective erythropoiesis with secondary expansion of erythropoiesis. Thalassemias are broadly of two types: α-thalassemia and β-thalassemia, with iron overload being a major cause of illness. Chelation therapy is the most widely used therapeutic option in these patients.

Sideroblastic anemias are heterogeneous disorders of heme synthesis with both hereditary (congenital) and acquired forms. Hereditary sideroblastic anemia is due to mutations in genes required for the production of heme precursors, resulting in defective erythropoiesis and iron overload. Acquired sideroblastic anemia can be idiopathic or secondary to myelodysplastic syndromes, nutritional deficiencies, lead poisoning, zinc poisoning, alcohol, and certain drugs. Iron overload occurs due to excessive iron absorption, exogenous iron administration, and ineffective hematopoiesis.

Congenital dyserythropoietic anemias (CDAs) are a heterogenous group of genetic disorders that result in ineffective erythropoiesis and dyserythropoiesis that leads to iron overload. They are characterized by macrocytic or normocytic anemia and low reticulocyte count since birth. The diagnosis is made based on characteristic erythroblast morphology.

Anemia of chronic disease (ACD) is anemia that occurs in infections, inflammatory, or neoplastic diseases and persists for more than 1–2 months. ACD is characterized by IL-6-mediated elevation in hepcidin, leading to hypoferremia despite adequate reticuloendothelial iron store. Peripheral blood smear shows normocytic normochromic anemia, reduced serum iron, total iron-binding capacity (TIBC), and transferrin saturation.

Transfusion iron overload occurs in conditions requiring frequent blood transfusions, such as sickle cell anemia, thalassemia, aplastic anemia, hemolytic anemia, Blackfan–Diamond syndrome, myelodysplastic syndrome, and leukemias. The number of blood transfusions leading to iron overload depends on the underlying disease and duration between transfusions.

Clinical features depend on the degree of iron overload and affected organs. Cardiac involvement is the major determinant of the prognosis in iron overload, with cardiac manifestations such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and pedal edema. Endocrine dysfunction affects virtually all glands, with pituitary involvement occurring in over 50% of patients. Up to 14% may develop insulin-dependent diabetes mellitus (IDDM). Endocrine manifestations may include stunted growth, delayed puberty or decreased libido, bronze/gray skin coloration, easy bruising, and cachexia. Thyroid, parathyroid, and exocrine pancreas are also affected. Neutrophils from patients with secondary

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iron overload have an increased iron and ferritin content and a phagocytosis defect.

Serum ferritin is the most widely used serum marker for transfusion iron overload, with levels varying from 1,000 to 3,000 ng/mL. Inflammation, disseminated malignancy, and chronic diseases can also increase ferritin levels. Elevated serum iron and transferrin saturation with decreased TIBC are other findings.

Treatment for patients with transfusion iron overload is anemic, and they are treated with chelation therapy, such as deferoxamine (DFO), deferasirox, and deferiprone (DFP). The signs and symptoms of iron overload are nonspecific, and early diagnosis is essential for prevention of iron overload-related tissue damage.

Serum ferritin, transferrin saturation, NTBI, LPI, and hepcidin are noninvasive methods for assessing iron overload and monitoring chelation therapy. Liver biopsy is the gold standard method for measuring LIC, which accurately reflects total body iron stores. Computed tomography scans have less sensitivity for hepatic iron overload, but a normal hepatic CT density does not exclude iron overload.

Magnetic resonance imaging is a rapid, noninvasive, and cost-effective imaging method for assessing iron deposition in the liver, heart, joints, and pituitary. It can be used to detect hemochromatosis in the joints of thalassemia patients receiving multiple transfusions.

Iron chelation therapy aims to maintain a safe iron level and remove excess stored iron and reverse-related complications. The therapy is generally started after 2–3 years of transfusion or when ferritin exceeds 1,000 ng/mL, LIC is >3 mg Fe/g dry weight, and/or when cardiac MRI shows severe cardiac iron accumulation. Intensification of iron disorders can involve escalation to maximal allowed doses, switching to another chelator, or using combined chelating agents like DFP, DFO, and deferasirox. Deferoxamine is the first available chelator effective in reducing serum ferritin levels and hepatic iron, preventing endocrine complications. It is a parenteral drug that requires subcutaneous or intravenous infusions due to its short half-life and poor oral bioavailability. Common side effects include redness and induration at the infusion site. Deferiprone is approved for treating iron overload due to blood transfusions in patients with thalassemia, as it decreases serum ferritin levels.

Deferiprone is a bidentate chelating agent with high affinity for iron and low affinity for copper and zinc. It is recommended to take 25 mg/kg three times per day, with a maximum daily dose of 100 mg/kg/day. Deferasirox is preferred due to its convenient once-daily oral dosing and cost-effectiveness. Calcium channel

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blockers as adjuvant agents may help prevent tissue iron accumulation under iron overload conditions, but this approach is still investigational. Experimental approaches for correcting iron disorders include increasing hepcidin levels/decreasing ferroportin activity, decreasing hepcidin levels/increasing ferroportin function, and based on the hypoxia-responsive pathway.

89 The Porphyrias

Porphyrias are rare inherited metabolic disorders caused by the deficiency of a specific enzyme in the heme biosynthetic pathway. There are eight enzymatic steps in the conversion of glycine and succinyl-coenzyme A (Co) to heme. Porphyrias can be classified as either hepatic or erythropoietic. Acute porphyrias can be classified as acute porphyrias, presenting with acute neurovisceral attacks, and cutaneous porphyrias, characterized by photosensitive skin lesions.

Acute intermittent porphyria (AIP) is a rare inherited disease in India, mainly concentrated in the Maheshwari and Kumhar communities of North West Rajasthan in and around Bikaner. The prevalence in India is 1 in 4.4 million, with high prevalence in Bikaner district and specific communities. AIP has a female predilection and has been described in recent years.

Acute porphyric attacks can be triggered by severe fasting or dieting, alcohol, certain drugs, and other intercurrent illnesses or stress. Most drugs exacerbate the attack of porphyria are closely associated with the induction of cytochrome P450 enzymes. Currently, the prognosis of patients with AIP is good even with severe attacks, but clinicians should be aware of a potentially fatal outcome of the disease.

Clinical manifestations and pathogenesis of AIP include abdominal pain, mild mental symptoms, neurological, and autonomic dysfunction. Both acute peripheral neuropathy and severe encephalopathy may develop if an acute attack is not diagnosed in time. Acute attacks can be iatrogenic, mainly due to administration of porphyrinogenic drugs when the diagnosis is delayed.

Paralysis is usually reversible with appropriate supportive treatment but requires many months of rehabilitation. Patients may have generalized convulsion, sensory disturbance, postural hypotension, severe tachycardia, and/or hypertension due to autonomic neuropathy. Rare complications of attacks include

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ISBN 978-93-5696-946-9