Chapter 2
Chronic Complications of Diabetes

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Epidemiology and Overall Significance

The prevalence of diabetes and its complications is constantly increasing worldwide at an alarming rate. It has been estimated that over 415 million people were suffering from diabetes in 2015. Although diabetes is one of the world's oldest diseases, described in historical records of civilizations such as those found in ancient Egypt, Persia, and India, incidence of diabetes has increased by 50% over the past 10 years. The prevalence of diabetic complications is also increasing, and it is responsible for increased morbidity, disability, and mortality. Acute metabolic complications include diabetic ketoacidosis and hyperosmolar state from high blood concentration, and hypoglycemia and coma as the result of low blood glucose. However, the most devastating consequences of diabetes are associated with its long-term micro- and macrovascular complications as a result of chronic elevation of blood glucose. Microvascular complications include retinopathy, nephropathy, and neuropathy due to damage of small blood vessels. Macrovascular complications include cardiovascular disease resulting in myocardial infarction, and cerebrovascular disease manifesting as stroke. However, in addition to traditional chronic complications of diabetes, there are several other complications such as depression, dementia, and sexual and gastrointestinal dysfunction [1].

In addition to hyperglycemia, genetic and epigenetic modifications, nutritional factors, and sedentary lifestyle are underlying mechanisms in the pathogenesis of diabetic complications. Ageing, male gender, smoking, low level of physical activity, and high cholesterol are independent predictors of macrovascular complications,

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while smoking, hypertension, and duration of diabetes are predictive factors for microvascular complications [2, 3]. Diabetic nephropathy, neuropathy, and retinopathy are the main microvascular complications induced by chronic hyperglycemia. Diabetic nephropathy is the major cause of end-stage renal disease in Western countries. It is characterized by the development of albuminuria and proteinuria, with a subsequent decline in glomerular filtration rate over a long period of time. Nephropathy significantly increases the risk of development of cardiovascular diseases such as myocardial infarction and stroke [4]. Hypertension and hyperglycemia are the most important risk factors for development and progression of diabetic nephropathy. Hyperglycemia induces specific cellular effects affecting endothelial cells, smooth muscle cells, mesangial cells, podocytes, tubular and collecting duct system cells, and inflammatory cells. In addition, changes in hemodynamics occurring early in diabetes and associated with blood pressure, such as hyperfiltration, are one of the major contributors to damage of the glomerulus, the filtration component of the kidney, leading to albuminuria and proteinuria. In early stages of diabetic kidney disease, enlargement of the kidney is characteristic. Hypertrophy is seen within the glomeruli, causing mesangial expansion and thickening of the glomerular basement membrane, while growing of the proximal tubule is responsible for increases in glomerular filtration rate and consequently increases amounts of glucose, fatty and amino acids, growth factors, and cytokines, which are free to trigger a number of pathological pathways. Finally, deposition of extracellular matrix in the tubular component of the kidneys, known as tubulointerstitial fibrosis, is a major determinant of the progression of diabetic renal disease [5].

Diabetic retinopathy is the major cause of blindness in adults. Hyperglycemia is responsible for changes in vascular permeability, capillary microaneurysms, capillary degeneration, and formation of new blood vessels known as neovascularization [2]. Clinically, diabetic retinopathy is separated into nonproliferative and proliferative retinopathy. In nonproliferative retinopathy, hyperglycemia can lead to intramural pericyte death and thickening of the basement membrane, altering the vascular permeability and blood–retinal barrier, without visual impairment. In proliferative retinopathy, neovascularization and accumulation of fluid within the retina contribute to visual impairment and in more severe cases bleeding, with associated distorting of the retinal architecture, can lead to retinal detachment and transient or permanent blindness. In the majority of patients with duration of diabetes over 20 years some retinal lesions are present; in patients with type 1 diabetes, proliferative retinopathy is the major retinal disorder, while in patients with type 2 diabetes there is a higher incidence of macular edema [6].

Diabetic neuropathy is a chronic complication of diabetes that affects somatic and autonomic division of the peripheral nervous system. The majority of patients with diabetes will develop neuropathy, and neuropathy is a major factor in the development of diabetic foot, erectile dysfunction, and cardiovascular dysfunction. Diabetic neuropathy is characterized by the development of vascular abnormalities with capillary basement membrane thickening and endothelial hyperplasia, and by nerve fiber deterioration, with altered sensitivities to vibrations and loss of sensory perception. Clinically, hyperalgesia, allodynia, and paresthesias are present in half

of those with diabetic neuropathy, while some patients have painful diabetic neuropathy which can seriously impede quality of life. The size of neurons is also important, and hyperalgesia, allodynia, and paresthesias are often first observed in the feet because longer nerve fibers show an earlier loss of nerve conduction velocity [2, 7]. Loss of sensation in response to microtrauma and other common foot injury is responsible for a high risk of developing foot ulcers in patients with diabetes, which can result in amputation and disability. Some patients with progressive and heavily diabetic neuropathy can develop Charcot foot, characterized by bone destruction and deformity, ulceration, and finally amputation [8]. In addition to motor neuron dysfunction, the autonomic nervous system is also affected, characterized by orthostatic hypotension, gastroparesis, tachycardia, and erectile dysfunction. Gastrointestinal tract dysfunction characterized by nausea, bloating, diarrhea, and delayed gastric emptying can affect control of glycemia by delaying or accelerating digestion of food and absorption of glucose and key nutrients. The wide range of clinical manifestations in which diabetic neuropathy is the underlying condition is the reason why this chronic complication of diabetes can severely impede quality of life. On the other hand, the wide range of clinical manifestations in which diabetic neuropathy is the underlying conditions is the reason why diagnosis is often not determined at the beginning in uncommon forms of disease. In addition to optimization of glycemic control and management of neuropathic pain, there are still no specific therapies approved for the treatment of diabetic neuropathy. However, since diabetic neuropathy selectively targets sensory and autonomic neurons, with little vascular involvement, some investigators suggest that neuropathy is not a real microvascular complication [2, 7].

Patients with diabetes have an increased risk of cardiovascular disease, and the risk of myocardial infarction is equivalent to that of nondiabetic subjects with history of previously myocardial infarction. In addition, the majority of patients with diabetes will die from cardiovascular disease [3]. Atherosclerosis is accelerated in diabetes, involving numerous cell types and cell-to-cell interactions, leading to formation of atherosclerotic plaques and manifesting as myocardial infarction and stroke. Dysfunction within the endothelium, which is crucial for maintenance of vascular homeostasis, is the most important early process involved in atherogenesis. Diabetes interrupts the balance between vasoactive factors, particularly nitric oxide, controlling permeability, integrity, and adhesiveness of endothelium; and consequently, proatherogenic cells bind to the vessel wall, leading to the proliferation of smooth muscle cells and matrix deposition and formation of atherosclerotic plaque. Atherosclerotic plaque may occlude coronary, carotid, or leg blood vessel, the condition which is common in diabetic patients with uncontrolled glycemia, hypertension, and hyperlipidemia [2, 3]. In addition to strict glycemic control, in order to reduce risk of cardiovascular disease, patients with diabetes, particularly type 2 diabetes, must be treated with blood pressure-lowering agents, lipid-lowering therapy, and antiplatelet agents. In contrast, diabetic cardiomyopathy occurs in patients with diabetes in the absence of hypertension and coronary artery disease. It is characterized by diastolic dysfunction; this is usually subclinical at the beginning but may progress and result in heart failure in the presence of preserved systolic function.

A number of pathological processes are included in the pathogenesis of diabetic cardiomyopathy, such as stiffening of the myocardium due to extracellular matrix deposition, hypertrophy, and neuronal abnormalities [1, 2].

Several mechanisms have been included in the development and progression of diabetic microvascular complications, such as production of advanced glycation end products (AGEs), proinflammatory microenvironment, and the induction of oxidative stress. AGEs are a heterogeneous group of molecules formed by the non-enzymatic glycation of plasma proteins, causing a disruption in their molecular formation and normal functioning, and also disrupting enzyme activity and interfering with receptor functioning. AGEs accumulate in different types of cells and organs, and affect their structure and function by cross-linking with proteins and lipids and nucleic acids, leading to development of diabetic complications. The crosslinking of AGEs with receptors localized in plasma membrane leads to up-regulation of a variety of transcription factors such as nuclear factor-KB and release of pro-inflammatory molecules and free radicals. AGEs also activate monocytes, increase endothelial permeability, and block nitric oxide activity in the endothelium. AGEs, significantly increased in patients with diabetes and coronary heart disease, modify LDL particles and accelerate atherosclerosis together with vascular damage [2, 9].

Overproduction of reactive oxygen species (ROS) under chronic hyperglycemia leads to oxidative stress, which plays an important role in the development of diabetic complications. Oxidative stress elevates polyol pathway activity, nonenzymatic glycation, and protein kinase C (PKC) levels, and inactivates endothelial nitric oxide synthase and prostacyclin synthase, two anti-atherosclerotic enzymes, leading to the development of diabetic complications. Overproduction of ROS under chronic hyperglycemia interacts with mitochondrial DNA, causing cellular damage. It has been suggested that ROS-mediated cellular damage may be responsible for pathologic “metabolic memory”, where microvasculature damage persists even after normalization of glycemia. In subjects with type 2 diabetes, insulin resistance induces mitochondrial ROS production from free fatty acids and inhibits anti-atherosclerotic enzymes, leading to atherosclerosis. Even in subjects without diabetes but with insulin resistance, cardiovascular risk is increased compared to subjects without insulin resistance. Some other pathways implicated in the development of diabetic complications, such as increased polyol flux and hexosamine formation, are linked to oxidative stress. Inflammation is also involved in the development of diabetic complications and atherosclerosis through increased levels of several inflammatory markers such as C-reactive protein, fibrinogen, plasminogen activator inhibitor 1, tumor necrosis factor alpha, interleukine-6, and others [2, 9].

Many cellular processes such as inflammation, plaque development, and perfusion are linked to proliferation of vasa vasorum; and initial angiogenic response in the adventitial vasa vasorum is stimulated by increased hypoxia-inducible factor and vascular endothelial growth factor (VEGF). VEGF contributes to the development and progression of microvascular complications, particularly diabetic retinopathy. VEGF treatment has been shown to restore microcirculation in vasa vasorum and limit progression of microvascular complications [6].

Rates of incidence of a broad spectrum of diabetes-related complications have declined substantially in the past 2 decades. The magnitude of reduction is greatest for cardiovascular disease, particularly acute myocardial infarction with over 60% risk reduction, and over 50% risk reduction in incidence of stroke and lower-extremity amputation. Reductions in rates were smallest for end-stage renal disease, because the rate of that complication increased in older adults. These reductions in incidence of diabetes-related complications probably reflects a combination of advances in acute clinical care, improvements in the health care system, and health promotions directed at patients with diabetes. Changes in management of care for patients with diabetes occurred in the years after major clinical effectiveness trials, paralleled by enhanced management of risk factors such as blood pressure, serum lipids, and smoking cessation, have influenced rates of a broad spectrum of diabetes-related complications. Nowadays, advances in interventional medical procedures, such as cardiac and lower extremities procedures with implantations of stents and revascularization, probably played a major role in reduction of rates of myocardial infarction and amputation. Social changes that decreased smoking rates and consumption of cholesterol and trans fat may also have an influence on risk of diabetes complications. In addition, increased detection of disease at earlier stages has resulted in reduction in the ratio of undiagnosed to diagnosed cases of diabetes. However, overall annual numbers of amputations, and cases of end-renal disease and stroke, continue to increase because the incidence of diabetes has doubled and prevalence has tripled in the past 15 years, suggesting that the absolute number of cases of diabetic chronic complications will probably continue to increase [10].

Gastrointestinal Complications of Diabetes: Epidemiology and Pathogenesis

Gastrointestinal complications of diabetes have become increasingly prevalent as the rate of diabetes has increased, and include gastroparesis, small bowel enteropathy and nonalcoholic fatty liver disease. It is assumed that up to 75% of patients with diabetes may experience symptoms of gastrointestinal complications, leading to an increase in health care costs but also decrement deterioration in patient quality of life. Although gastrointestinal complications of diabetes are common, these complications are not commonly recognized in clinical practice. The pathogenesis of gastrointestinal complications is complex, primarily related to autonomic dysfunction of the gastrointestinal tract and also associated with hyperglycemia and duration of diabetes (Table 2.1). Although it is assumed that gastrointestinal complications of diabetes are common, particularly in longstanding diabetes and with development of autonomic neuropathy, such gastrointestinal complications and symptoms may precede or not correlate with the presence of autonomic neuropathy, duration of diabetes, or degree of glycemic control. The metabolic and anatomic changes cause abnormalities in vascular flow, peristalsis, reflective relaxation, and interstitial segmentation, manifesting clinically as dysphagia, gastroparesis, diarrhea,

Table 2.1 Gastrointestinal complications of diabetes

Organ	Causes	Functional defects	Symptoms
Esophagus	Autonomic neuropathy, hyperglycemia, metabolic syndrome, and obesity	Reduced esophageal musculature tone, reduced rate of smooth muscle contraction, delayed transit, gastroesophageal reflux due to altered motility of lower esophageal sphincter	Regurgitation, heartburn, dysphagia, odynophagia
Stomach	Autonomic neuropathy, hyperglycemia, long duration of diabetes, obesity, deficiency of apolipoprotein E	Hypomotility-delayed gastric emptying, spasm of pylorus, blunted antral contractions, increased sensitivity to distention	Vomiting, nausea, postprandial fullness, early satiety, upper abdominal pain, distension, anorexia, bloating
Small intestine	Autonomic neuropathy, hyperglycemia	Increased secretion, delayed transit	Distension, abdominal pain, bloating
Colon and anorectum	Autonomic neuropathy, hyperglycemia, long duration of diabetes, insulin-growth factor 1 reduction, impaired synthesis of neuronal nitric oxide	Increased secretion, delayed transit, reduced motility, reduced anal tone and sensation	Constipation, diarrhea, distension
Pancreas	Autonomic neuropathy, hyperglycemia, long duration of diabetes, pancreatitis	Reduced pancreatic enzyme secretion	Steatorrhea, diarrhea, weight loss
Liver	Hyperglycemia, hyperlipoproteinemia, insulin resistance	Fatty infiltration, fibrosis	Discomfort, upper abdominal pain, jaundice

constipation, abdominal pain, interstitial pseudo-obstruction, and anal incontinence (Table 2.1). Since there are many other causes of symptoms of gastrointestinal complications of diabetes, patients suspected of having those symptoms require detailed evaluation. The management of patients with gastrointestinal complications is challenging and requires a multidisciplinary approach. Since pathophysiological conditions associated with development of gastrointestinal complications of diabetes may become irreversible, optimal glycemic control must be achieved early in the disease process [11–13].

In the esophagus, autonomic nerves of the lower esophageal sphincter can be affected by diabetic neuropathy in patients with longstanding diabetes, resulting in reduced esophageal musculature tone and spontaneous contractions. It has been suggested that up to 63% of patients with diabetes have esophageal dysmotility, with no difference between patients with type 1 and type 2 diabetes. Esophageal dysmotility is more common in patients with long duration of diabetes, but only a minority of patients refer classical symptoms of dysphagia, heartburn, or odynophagia (painful swallowing). Prevalence of gastroesophageal reflux symptoms is also high, with prevalence up to 66% in patients with neuropathy. Peripheral

neuropathy is an independent risk factor for erosive esophagitis, although some patients might have an asymptomatic form of the disease. Abnormal manometric findings include hypotensive lower esophageal sphincter pressure, prolonged esophageal transit time, reduced rate of smooth muscle contraction, and diminished amplitude of peristaltic waves. Presence of metabolic syndrome in patients with type 2 diabetes is a risk factor for gastroesophageal reflux. Improvement in esophageal dysmotility and reflux can be achieved with better glycemic control and medications such as prokinetic drugs [14–17].

Gastroparesis is the most common gastrointestinal complication of diabetes in patients with long duration of diabetes, with symptoms of gastric retention in the absence of physical obstruction. Incidence is greater in patients with type 1 diabetes because of longer duration of diabetes, and with incidence between 27 and 65% compared to patients with type 2 diabetes, where the incidence is about 30%. The incidence of gastroparesis is higher in women, and obesity appears to independently predict symptoms of gastroparesis in patients with type 2 diabetes. Symptoms of gastroparesis include vomiting, nausea, postprandial fullness, early satiety, upper abdominal pain, distension, anorexia, and bloating. More than half of patients present with acute onset of symptoms, while one third of patients have chronic symptoms with periodic exacerbations. Gastropathy can contribute to bezoar formation and intestinal obstruction, ulcer development, and acute gastric dilatation [18]. The pathogenesis of diabetic gastroparesis is multifactorial. Well-known risk factors are hyperglycemia, long duration of diabetes, and presence of micro- and macrovascular complications of diabetes, particularly neuropathy. Diabetic gastropathy is thought to be a manifestation of autonomic neuropathy. Hyperglycemia is an independent risk factor for development of diabetic gastroparesis, while delayed gastric emptying in gastroparesis contributes to hyperglycemia. On the other hand, mismatch between insulin action and carbohydrate absorption can result in hypoglycemia in patients treated with insulin. Lost control of glucose management for no apparent reason in patients previously well controlled may indicate a digestive or absorption problem, even in asymptomatic patients. Up to 53% of patients may experience weight loss, while as many as 24% of patients may actually gain weight [19]. Hypomotility, manifested as delayed emptying, may interfere with the absorption of oral medications, and can lead to further hyperglycemia and greater autonomic nerve damage. Hyperglycemia is also associated with spasm of pylorus and small intestine, loss of normal migrating motor complexes, and blunted antral contractions. Impaired inhibitory nitric oxide containing nerves, absent or dysmorphic interstitial cells of Cajal, abnormal macrophage-containing immune infiltrates, and smooth muscle fibrosis are also implicated in the pathogenesis of diabetic gastroparesis. Abnormal mucosal nerve density and morphology is found on endoscopic biopsies from patients with diabetic gastroparesis [15]. In an animal model, deficiency of apolipoprotein E is a risk factor for diabetic gastroparesis. In physical examination, diagnosis of peripheral and autonomic neuropathy followed by endoscopy is most important. The diagnosis of gastroparesis is typically one of exclusion when postprandial gastric stasis is confirmed and other potential causes of presenting symptoms have been evaluated. The diagnosis of gastroparesis is made by

gastric emptying scintigraphy using ^{99m}Tc sulfur colloid bound to solid food, which is the gold standard test for diagnosing gastroparesis. In patients with confirmed gastroparesis, patients should discontinue medications for hyperglycemia that exacerbate gastric dysmotility, particularly glucagon-like peptide-1 (GLP-1) receptor agonists, metformin, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Since some other drugs such as narcotics, tricyclic antidepressants, and anticholinergics can slow gastric motility; careful medical history must be done in subjects with symptoms of gastroparesis. In addition to better glucose control, quantitative dietary changes should be made by reducing the intake of foods high in fat, intake of insoluble dietary fiber, and alcohol [18].

Small-intestine and colorectal dysfunctions are also common in patients with long duration of diabetes, especially in those with diabetic gastroparesis. The pathophysiological mechanisms of development of enteropathy are similar of those of upper gastrointestinal disorders, and include advanced glycation end products that cause damage to cellular DNA and tissue. Up-regulated expression of advanced glycation end-products and their receptor in the small intestine and colon of diabetic rats have been found. In addition, patients with enteropathy have peripheral and autonomic neuropathy, and damage of the myenteric nerve plexus and fibrosis of the intestinal muscular layers result in stasis of the intestinal contents. Autonomic neuropathy is associated with altering sympathetic function in the gut by reducing input form alpha-2 adrenergic receptors. In patients with diabetes, insulin-growth factor 1 (IGF-1) is reduced which may result in smooth muscle atrophy, contributing to enteropathy [15]. Glucoregulation and diabetes duration are factors related to reduced IGF-1 expression in diabetes. Impaired synthesis of neuronal nitric oxide, an important neurotransmitter within the bowel, is also a mechanism involved in the pathogenesis of diabetic enteropathy. Potential contributory factors are enhanced oxidative stress and imbalance between inhibitory and excitatory enteric neuropeptide ratios. Intestinal stasis and reduced bowel motility results in constipation but also in small intestinal bacterial overgrowth, leading to diarrhea. Constipation is a common presentation of diabetic enteropathy, affecting up to 60% of patients with long duration of diabetes. Although constipation is more common than diarrhea in patients with diabetes, up to 20% of subjects with diabetes suffer from diarrhea. Diarrhea is most common in patients with type 1 diabetes and in men; it is typically painless but often associated with fecal incontinence and occurs nocturnally. Hyperglycemia and in particular acute hyperglycemia inhibits external anal sphincter function and decreases rectal compliance, leading to fecal incontinence [20]. Since pancreatitis occurs two to four times more commonly in patients with diabetes compared to nondiabetic populations, pancreatic exocrine insufficiency must also be excluded, and measurement of fecal elastase should be done in all patients with potential diabetic enteropathy. Although pancreatic exocrine dysfunction occurs in up to 80% of patients with type 1 diabetes, it is rarely significant enough to lead to clinical presentation such as diarrhea [21]. In addition, depression is prevalent in patients with diabetes and may also be linked to development of diabetic enteropathy, suggesting that emotional status is an important factor. On the other hand, patients with severe symptoms of enteropathy may become depressed and

require psychological support. Characteristically, constipation alternating with diarrhea is one of the most common symptoms of diabetic enteropathy. Many commonly used drugs in diabetes such as metformin, alpha-glucosidase inhibitors, and incretin-based therapies are associated with a variety of gastrointestinal side-effects, with altered bowel function. In such cases, reducing dose or discontinuing therapy are potential considerations. In patients with diabetes and diarrhea, celiac disease needs to be excluded, since celiac disease occurs more common in patients with diabetes. To exclude other causes of diarrhea or constipation, patients should undergo endoscopic examination, ultrasound, or computed tomography, and also laboratory exam. Treatment of diabetic enteropathy includes glycemic control, corrections of fluid and electrolyte deficits, and anti-diarrheal agents [11].

Non-alcoholic fatty liver disease (NAFLD), previously named also as a diabetes hepatitis, is characterized by accumulation of fat in the liver and refers to a spectrum of disorders ranging from simple hepatic steatosis to more severe manifestations, including non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and liver failure, in the absence of substantial alcohol consumption or other causes of liver disease such as viral hepatitis. NAFLD is usually clinically silent, and most patients seek care because of an incidental finding of elevated aminotransferase levels or radiographic studies suggesting the liver is fat. NAFLD is now considered as hepatic expression of insulin resistance and metabolic syndrome, responsible for the risk of advanced liver disease observed in these patients. NAFLD is associated with metabolic syndrome components such as obesity, diabetes mellitus, dyslipidemia, and hypertension [22]. Insulin resistance is the central pathophysiological phenomenon of metabolic syndrome, and with development of type 2 diabetes. The liver plays an important role in maintaining normal glucose concentrations, and it is also a major site of insulin clearance. NAFLD is strongly associated with reduced whole-body insulin sensitivity and adipose tissue insulin resistance. Hepatic insulin resistance, associated with obesity and dyslipidemia, is the underlying metabolic condition favoring the occurrence of NAFLD. Universal finding in NAFLD is the ectopic accumulation of fat in the liver, which is strongly associated with insulin resistance. Insulin resistance is associated with free fatty acid flux to the liver by decreasing inhibition of lipolysis and also by increasing de-novo lipogenesis. Whether insulin resistance causes hepatic steatosis or whether the accumulation of fat in the liver is the primary event leading to hepatic and then later peripheral insulin resistance is not clear. Several other factors including tumor necrosis factor alpha, oxidative stress, adiponectin, and leptin are also believed to have a role in the pathogenesis of NAFLD. NAFLD is diagnosed in clinical settings using imaging or liver biopsy if there is no significant alcohol overconsumption or other co-existing causes for chronic liver disease. The NAFLD fibrosis score is a clinically useful tool for identifying patients with higher likelihood of having fibrosis and cirrhosis, because the NAFLD fibrosis score has 67% sensitivity and 97% specificity in identifying the presence of advanced fibrosis. However, those techniques are not applicable in large epidemiological studies. Subjects with NAFLD typically have elevated circulating concentrations of markers of liver injury. Normal or mildly to moderate elevated serum levels of aspartate aminotransferase (AST),

alanine aminotransferase (ALT), or both (usually < 250 U/l) are the most common and often the only laboratory abnormality found in patients with NAFLD. In contrast to those with alcoholic hepatitis, the ratio of AST-to-ALT is usually less than 1. Since insulin resistance plays a key role in the pathogenesis of NAFLD, insulin-sensitizing drugs such as metformin and pioglitazone are used in the treatment of NAFLD in subjects with type 2 diabetes. Incretins, group of gastrointestinal hormones, are a new class of antidiabetic drugs used in the treatment of type 2 diabetes. However, glucagon-like peptide-1 (GLP-1) receptors are present on hepatocytes, and GLP-1 action shares key downstream components of the insulin signaling pathway in hepatocytes. GLP-1 or homologues intersect the insulin signaling pathway in hepatocytes, since this and inter-related pathways in hepatocytes have emerged as critical for the molecular basis of the emergence of hepatocyte insulin resistance. Finally, up to 80% of subjects with cirrhosis have abnormal glucose metabolism, and the term "hepatogenous diabetes" is used to describe diabetes developing in patients with cirrhosis [9, 22].

Type 1 vs Type 2 Diabetes Mellitus

Type 1 diabetes, previously called insulin-dependent diabetes or juvenile-onset diabetes, is an autoimmune disease caused by cellular-mediated autoimmune destruction of the pancreatic beta cells. It accounts for 5–10% of all diabetes, and the incidence and prevalence is increasing at a rate of about 3% per year globally. Type 1 diabetes affects males and females equally and decreases life expectancy by an estimated 13 years. Incidence of type 1 diabetes is positively related to geographic distance north of the equator. It is defined by the presence of one or more of autoimmune markers [autoantibodies to glutamate decarboxylase — GAD (GAD65), islet cell cytoplasmic autoantibodies (ICA), insulin autoantibodies (IAA), insulinoma-associated-2 autoantibodies (IA-2A), and zinc transporter 8 autoantibodies (ZnT8)]. The rate of progression depends on the age of antibody onset, the number of antibodies, antibody specificity and titer [23]. Type 1 diabetes also has strong human leukocyte antigen (HLA) associations, with linkage to the DQA and DQB genes, which can be either protective or predisposing. The higher prevalence of type 1 diabetes in relatives implies a genetic risk. Gene variants in HLA confer 50–60% of the genetic risk, while about 50 additional genes individually contribute smaller effects. Some of these gene variants modulate immune regulation and tolerance, modify viral responses, and responses to environmental signals and endocrine function [24, 25]. Type 1 diabetes and autoimmune destruction of beta cells has multiple genetic predispositions and also is connected with poorly understood environmental factors. Moreover, environmental factors interact with genetic factors in both the triggering of autoimmunity and the subsequent progression of type 1 diabetes, which may explain why most individuals with the highest-risk HLA haplotypes do not develop type 1 diabetes. In addition to interactions between environmental and genetic factors, the environmental factor exposures in the first few years of life are

the most powerful in the development of type 1 diabetes. In addition, enteroviral infections and altered intestinal microbiome composition are also environmental factors associated with type 1 diabetes. Exposure to foods including cereal and gluten early in life may influence beta cell destruction. Measuring autoimmune markers in relatives of those with type 1 diabetes may identify individuals who are at risk for developing type 1 diabetes and may enable earlier identification, but onset of disease cannot be prevented or delayed [26, 27]. In children, the rate of beta cell destruction is rapid. In younger patients with rapid beta cell destruction, patients present with acute symptoms of diabetes and over one-third with life-threating ketoacidosis. In adults, destruction of beta cells and onset of diabetes are slow, and this form of disease in individuals over 30–35 years and predominantly high GAD autoantibodies is usually named latent autoimmune diabetes in adults (LADA). LADA can be diagnosed in any age, even in the 8th and thth decades of life. An estimated 5–15% of adults diagnosed with type 2 diabetes actually have type 1 diabetes or LADA. Among US youth, Europoid Caucasians have the highest prevalence of type 1 diabetes. Patients with type 1 diabetes also have higher risk for other autoimmune diseases such as Hashimoto thyroiditis, celiac disease, vitiligo, autoimmune hepatitis, Graves' disease, Addison's disease, myasthenia gravis, and others [23, 24].

Type 2 diabetes, previously called as noninsulin-dependent diabetes or adult-onset diabetes, accounts for 90–95% of all diabetes. Patients with type 2 diabetes have relative insulin deficiency and do not need insulin treatment in the beginning (Table 2.2). Compared to patients with type 1 diabetes, autoimmune destruction of beta cells does not occur, and the majority of subjects are overweight or obese, with body fat distribution predominantly in the abdominal region [23]. Although patients with type 2 diabetes have negative autoimmune markers of diabetes, genome-wide association studies have identified more than 130 genetic variants associated with type 2 diabetes. Obesity is considered to be the major risk factor for type 2 diabetes mellitus. Excess weight causes insulin resistance. Insulin resistance could be defined as the metabolic state in which the measured tissue response to insulin is less than that expected for the apparently available insulin. Insulin resistance is the central pathophysiological phenomenon of metabolic syndrome,

Table 2.2 Type 1 vs type 2 diabetes

Type 1	Type 2
– Autoimmune disease	– Obesity related disease
– High risk of ketoacidosis	– No risk of ketoacidosis
– Insulin therapy from the beginning	– Not need insulin treatment in the beginning
– Acute presentation of disease	– Long presymptomatic phase before the diagnosis
– Occurs in childhood and adolescence	– Occurs in adults
– Weight loss at diagnosis	– Without weight loss at diagnosis
– Strong human leukocyte antigen (HLA) associations	– Without HLA associations
– Presence of one or more of autoimmune markers	– Negative autoimmune markers
– Positive family history in ~5% of patients	– Positive family history in ~40% of patients

characterized by a clustering of independent cardiovascular risk factors including impaired glucose regulation, central obesity, dyslipidemia, and hypertension. In insulin resistance, carbohydrate intake increases blood glucose, but insulin-dependent glucose uptake in liver, muscle, and fat tissue is reduced. As a consequence of this, there is enhanced glucose synthesis from glycogen in the liver and enhanced fat degradation in fat tissue, and elevation of free fatty acids in the blood. Also, due to hyperglycemia, compensatory increases in secretion of insulin from the pancreas are produced, leading to hyperglycemia and hyperinsulinemia in the bloodstream. Increased secretion of insulin from the pancreas may ultimately result in pancreas exhaustion and diabetes development. As a consequence of hyperglycemia and hyperinsulinemia, increases in prothrombotic factors, serum viscosity, uric acid, homocysteine, white blood cell count, C-reactive protein (CRP), albuminuria, non-alcoholic fatty liver disease, and decreased circulating concentrations of adiponectin are also present (Fig. 2.1) [9, 28, 29]. In insulin resistance state, the sodium reabsorption in kidney is increased, as well as angiotensinogen, resistin, and leptin secretion from adipose tissue; and all those are implicated in pathophysiology of hypertension. Elevated levels of free fatty acids associated with insulin resistance cause endothelial dysfunction characterized by reduced production of nitric oxide, and resultant decrease in nitric oxide bioactivity is important in initiation and progression of atherosclerosis. Cross-talk between inflammatory-signaling pathways and insulin-signaling pathways causes both metabolic insulin

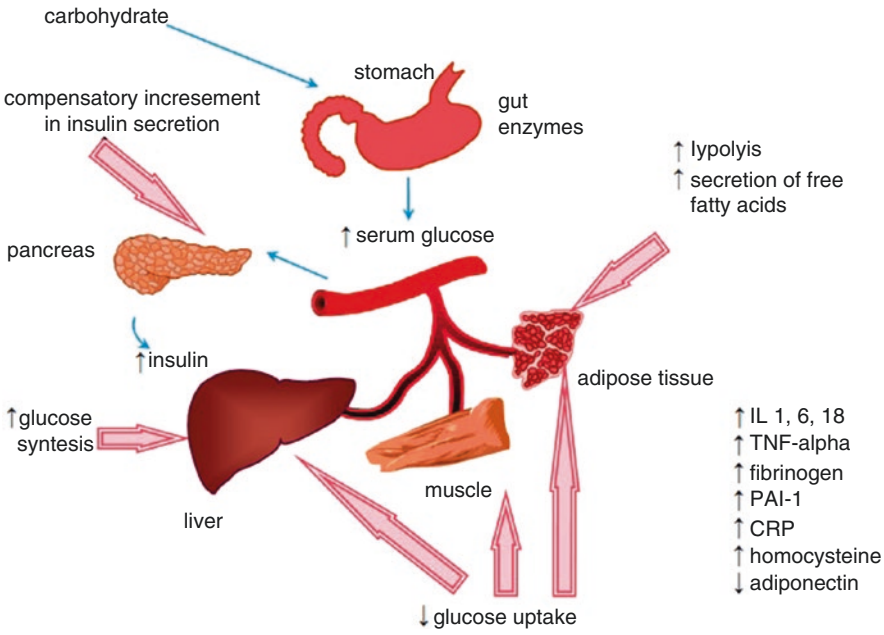

Fig. 2.1 Insulin resistance in development of hyperglycemia and hyperlipidemia. *IL 1, 6, 18* interleukin 1, 6, 18, *TNF-alpha* tumor necrosis factor alpha, *PAI-1* plasminogen activator inhibitor-1, *CRP* C-reactive protein

resistance and endothelial dysfunction, which synergize to predispose to cardiovascular disorders [30]. Insulin resistance is also an independent risk factor for the micro- (nephropathy, neuropathy and retinopathy) and macro- (coronary artery disease and peripheral vascular disease) vascular complications in patients with type 2 diabetes. Insulin resistance may improve with weight reduction but is seldom restored to normal [29]. Compared to type 1 diabetes, hyperglycemia develops gradually, and there is often a long presymptomatic phase before the diagnosis of type 2 diabetes. It is associated with stronger genetic predisposition compared to type 1 diabetes, although genetics of type 2 diabetes is poorly understood. In younger and not overweight patients, antibody testing (particularly GAD) for type 1 diabetes or LADA should be performed [31].

Compared to type 1 diabetes, the onset of type 2 diabetes can be delayed or even prevented with effective interventions such as weight loss and physical activity. Intensive lifestyle interventions (minimum of 7% weight loss and 150 min of physical activity per week) could reduce the incidence of type 2 diabetes by 58% over 3 years because weight loss improves insulin sensitivity in liver and skeletal muscle. Moderate intensity physical activity, such as 150 min of brisk walking per week, has been shown to improve insulin sensitivity and reduce abdominal fat. Reducing caloric intake is of paramount importance for those at high risk for developing type 2 diabetes, particularly the quality of fats consumed in the diet. For example, the Mediterranean diet, which is relatively high in monounsaturated fats, may help to prevent type 2 diabetes. Whole grains may help to prevent type 2 diabetes, while red meats and sugar-sweetened beverages are associated with an increased risk of type 2 diabetes. Defects in insulin secretion are partially reversible with weight loss and food restriction in recent-onset type 2 diabetes, but not in those with long duration of diabetes. Pharmacologic agents including metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, and thiazolidinediones have been shown to decrease diabetes in those with prediabetes. Metformin has the strongest evidence base as pharmacologic therapy for diabetes prevention, and metformin together with intensive lifestyle modification can reduce risk of developing type 2 diabetes up to 50%. Metformin should be recommended as an option for high-risk individuals, especially in those with marked insulin resistance [32, 33].

Diabetes is historically classified as type 1, type 2, gestational, and a group of "other specific syndromes" called secondary diabetes. However, there are individuals with other subtypes of disease with a well-defined etiology that may be clinically characterized (e.g., maturity-onset diabetes of the young (MODY), LADA, or nowadays new onset diabetes after transplantation (NODAT). In clinical practice, patients with MODY are usually classified as a type 1 diabetes because of onset of diabetes in childhood, while 5–15% of adults diagnosed with type 2 diabetes actually have LADA or even type 1 diabetes [34]. Recently, the American Diabetes Association, the European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists convened a research symposium in order to define the phenotypes and genotypes of subtypes of diabetes, which will facilitate individualized treatment [35].

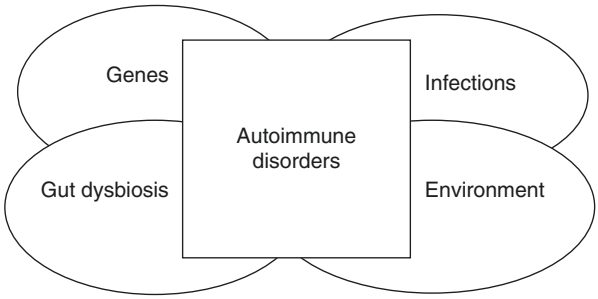

Fig. 2.2 Genetic, gut dysbiosis, infections, and environmental factors play major roles in the development of autoimmune diseases

Role of Genetic Predisposition

Autoimmune diseases have increased alarmingly worldwide in recent decades; they are far more commonly found in women and are one of the top ten leading causes of death in women and female children of all age groups. Those autoimmune disorders with increasing incidence and prevalence include type 1 diabetes, Crohn's disease, rheumatoid arthritis, and multiple sclerosis. Autoimmunity develops over time, and genetic predisposition, environmental factors such as infections and gut dysbiosis play an important role in the development of autoimmune diseases (Fig. 2.2). Multiple genes and genetic variants predispose humans to multiple autoimmune diseases. One of the most common genetic associations with autoimmune diseases is the protein tyrosine phosphatase gene PTPN22. PTPN22 is expressed in lymphocytes and found in patients with autoimmune disorders such as type 1 diabetes and autoimmune thyroiditis. Cytokines and cytokine receptors, such as interleukin 12 and 23, are found in patients with autoimmune disorders such as inflammatory bowel disease and psoriasis. Tumor necrosis factor (TNF) is also associated with autoimmune diseases, notably rheumatoid arthritis and psoriasis. The importance of clusters of differentiation (CD) in the maintenance of effector T cell populations in type 1 diabetes and systemic lupus erythematosus (SLE) has been described in recent studies. The traditional method used to estimate genetic and environmental contributions to disease are twin studies. Concordance rate of autoimmune diseases in monozygotic twins is only 10–40%, indicating that environmental factors play a major role in triggering autoimmune disorders [36].

A genetic component in the genesis of upper gastrointestinal tract disorders such as esophageal achalasia, functional dyspepsia, and hypertrophic pyloric stenosis have been established. Motility of the gastrointestinal tract is finely balanced between smooth muscle contractility and the related pacemaker activity evoked by the interstitial cells of Cajal, which are also regulated by sympathetic and parasympathetic nerves. Achalasia, characterized by incomplete relaxation of the lower esophageal sphincter and absence of peristalsis, results from loss of neurons in the lower part of esophagus. Although an achalasia phenotype is present in genetic syndromes such as Down, Allgrove, and familial visceral neuropathy, it seems that the etiology of achalasia is multifactorial, and that a combination of risk genes and environmental factors leads to the development of disease. Those environmental factors include immune-mediated inflammatory disorder induced by a virus such as herpes simplex virus (HSV). Several studies have found that polymorphism of

genes encoding for proteins involved in the immune response such as phosphatase 22, interleukin-10, and interleukin-23 is associated with achalasia. Polymorphism of inducible neuronal nitric oxide (iNOS) and vasoactive intestinal polypeptides (VIP), involved in both defense against infections and inhibitory neurotransmission, is also associated with risk of achalasia [37, 38].

Functional dyspepsia is defined as a presence of persistent symptoms in the upper part of the abdomen in the absence of organic pathology. The toll-like receptor-2 (TLR-2) genotype modulating the degree of inflammatory response to Helicobacter pylori infection is associated with functional dyspepsia. Although serotonin 5-hydroxytryptamine (5-HT) is a key signaling molecule affecting upper gastrointestinal motor and sensory functions, the results from the studies suggest that the serotoninergic pathway play a minor role in the pathophysiology of dyspeptic symptoms. Polymorphism in the GNβ3 gene, involved in the release of 5-HT and several other neurotransmitters, has been associated with dyspepsia. Polymorphism of transient receptor potential vanilloid 1 (TRPV1) is a risk factor for functional dyspepsia, while polymorphism of sodium channel Na (V) 1.8 has been found to be protective [39, 40].

Five twin studies investigating risk of functional gastrointestinal disorders found genetic liability of irritable bowel syndrome and functional gastrointestinal disorders up to 20% based on concordance rates. It has been suggested that social learning or stability of the family environment may have greater influence on the irritable bowel syndrome than genetics alone. The majority of genes studied in irritable bowel syndrome encode serotonin-related proteins, proteins involved in noradrenergic signaling, and immune markers. Alterations in brain- and gut-related 5-HT signaling could explain altered motility and secretion associated with increased anxiety and stress responsiveness. A few other gene polymorphisms (interleukin-10, tumor necrosis factor α, serotonin) were correlated with irritable bowel disease, but in studies with small sample size and unreliability of the clinical phenotype [41, 42].

Celiac disease is an autoimmune condition that occurs in genetically predisposed people by exposure to gluten. The gliadin fraction in gluten-containing grains is the instigator leading to autoimmunity, and has toxic effects on intestinal cells in gluten-sensitive people. Chronic inflammation of the lamina propria, an increase in intraepithelial lymphocytes, and small bowel villous atrophy are responsible for impaired nutrient absorption and nutritional deficiencies in celiac disease. The development and anatomy of the pancreas and small intestine are close; and the pancreatic lymph nodes, which have been linked to insulitis and destruction of beta cells, share close connections with gut immune system. In diabetes-prone rats, mesenteric lymph nodes were seen to proliferate in response to wheat antigens prior to the development of pancreas islet autoimmunity, providing evidence for a direct role of gluten in the development of autoimmune diabetes [36]. The association between celiac disease and type 1 diabetes was first reported in late 1960s. The diagnosis of celiac disease involves a serological screening test for tissue transglutaminase, and anti-tissue transglutaminase antibodies are present in up to 16% of children and about 2% of adults with type 1 diabetes, more frequently than in the general population where the prevalence is about 1%. Parallel with increasing incidence of type 1 diabetes, an increasing incidence of celiac disease during recent decades has also been reported, and the majority of cases with celiac disease are

thought to be already present at the onset of diabetes. Two inflammatory disorders, type 1 diabetes and celiac disease, have a common genetic origin, and both diseases are associated with the HLA class II genes (HLA-DQB1) on chromosome 6p21. HLA genes are essential to the regulation of the immune response, and many of the HLA-DQ loci have been found in association with other autoimmune diseases such as rheumatoid arthritis and Hashimoto thyroiditis. HLA DQ2 and/or DQ8 are present in over 95% of patients with celiac disease and in 55% of patients with type 1 diabetes. From 21 non-HLA loci associated with type 1 diabetes, two have association with celiac disease, while from 11 non-HLA loci associated with celiac disease, three are associated with type 1 diabetes. Suffering from both diseases can have a severe impact on quality of life because of the increased risk of developing osteoporosis, lymphoma, or small bowel cancer, and higher prevalence of chronic complications of diabetes [43, 44].

Autoimmune hepatitis, particularly autoimmune hepatitis type 2, has been reported to occur in patients with type 1 diabetes. Islet cell antibodies (ICA) and insulin autoantibodies have been found in 60.7 and 18.5% of patients with autoimmune hepatitis. The co-occurrence of autoimmune hepatitis-related auto-antibodies, such as antinuclear antibody (ANA), anti-smooth muscle antibodies (SMA), and anti-liver/kidney microsomal (LKM-1) antibodies in patients with type 1 diabetes has also been found. Up to 27% of patients with type 1 diabetes have positive ANA [45].

Crohn's disease is a common form of chronic inflammatory bowel disease. The pathogenic mechanisms are poorly understood, but probably involve a dysregulated immune response to intestinal bacteria and possibly defects in mucosal barrier function or bacterial clearance. Genetic predisposition to Crohn's disease is suggested by twin studies that contrast monozygotic concordance rates of 50% with only 10% in dizygotic pairs. A major collaboration of UK scientists has provided an insight into the genetics underlying Crohn's disease, and also identified for the first time a gene linking type 1 diabetes and Crohn's disease. The study was part of the Wellcome Trust Case Control Consortium (WTCCC), the largest ever study of the genetics behind common diseases including diabetes, and included 17,000 people with type 1 diabetes and 1180 people with Crohn's disease. They confirmed the importance of a process known as autophagy, a process responsible for clearing unwanted bacteria from cells; and abnormalities in the autophagy pathway correlate with susceptibility to inflammatory bowel diseases such as Crohn's disease. The final novel common gene in the development of type 1 diabetes and Crohn's disease has been identified. The gene, PTPN2 (protein tyrosine phosphatase, nonreceptor type 2) on chromosome 18p11, which encodes the T cell protein tyrosine phosphatase TCPTP, a key negative regulator of inflammatory responses, was confirmed by both the subsequent disease-specific studies in Crohn's disease and in type 1 diabetes. In addition, a significant contribution of human leukocyte antigen (HLA) system class II region to Crohn's disease has also been found, though less marked than that seen in classical autoimmune conditions such as type 1 diabetes. Causes of Crohn's disease and type 1 diabetes are complex, and genes almost certainly interact with environmental factors such as diet and bacterial and viral infections; and molecular genetic studies of Crohn's disease have stressed the importance of defects in autophagy and the processing of phagocytosed bacteria [36, 38, 46].

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