Chapter 1

Understanding Celiac Disease

The word celiac (ce·li·ac also coe·li·ac) is derived from the Latin word *coeliacus*, from the Greek word *koiliakos* (from *koilia*, abdomen, from *koilos*, hollow) meaning of or relating to the abdomen or abdominal cavity.

DEFINITION

Celiac disease, pronounced *se-le-ak*, is a condition in which the mucosa (lining) of the small intestine is damaged by ingestion of gluten in genetically susceptible individuals. Gluten is a protein found in certain grains including wheat, rye and barley. This not only causes a variety of symptoms for the patient but can also lead to several nutritional deficiencies due the body's inability to digest and absorb food properly. Removal of gluten from the diet leads to healing of the intestine with resolution of the symptoms and nutritional deficiencies.

PATHOGENESIS

Celiac disease results from an abnormal interaction between gluten, the immune system and the gut in genetically susceptible individuals. When the skin becomes affected in this process, the disorder is called dermatitis herpetiformis. This will be discussed in detail later.

In order to understand what happens in celiac disease, one needs to know what gluten is, what the role of genes is and

how our intestinal and immune systems normally work. The processes involved are complex and only a simplified description will be presented.

What is Gluten?

Gluten (from Latin *gluten* meaning "glue") is a protein found in wheat, rye and barley and their crossbred grains. Gluten is an umbrella term used to describe the various storage proteins in these grains. Wheat is about 10 to 15% protein and contains several types of glutens. The most common gluten fractions in wheat are *gliadins* and *glutenins*. The gliadins and glutenins are primarily responsible for the wheat dough's properties of thickness/stretching and stickiness/strength respectively. These properties are what makes a good bread from wheat flour.

The proteins (glutens) present in rye that chemically resemble gliadin are called *secalins* and in barley *hordeins.* All of these proteins are toxic to individuals with celiac disease. Grains like rice, corn and millet are from different families of proteins that are not harmful.

Gluten is a complex protein and discussion of its chemistry is beyond the scope of this book. Furthermore, details are of little benefit to the patients or primary care physicians. The bottom line to keep in mind is that wheat, rye and barley contain gluten. This will be discussed further in the chapter on Living with the Gluten-Free Diet.

The Gastrointestinal Tract (Gut)

The human gastrointestinal tract consists of the mouth, esophagus (food-pipe), stomach, small intestine, and the large intestine (*colon*). The small intestine is a long coiled tube extending from the stomach to the large intestine. The pancreas and liver are two other important organs in the abdomen that are involved in the digestive process.

Structure of the Gut

The length of the small intestine varies depending on the age and weight of the individual. The small intestine in an adult human measures on average 20 feet (6 meters), with a normal range of 3 to 7 meters. It is approximately 1 inch (2.5-3cm) in diameter. The large intestine is only about 5 feet (1.5 meters) long. It is called "large" because it is more than two times wider in diameter compared to the small intestine.

The small intestine is further divided into three structural parts. The first part that follows the stomach is called the duodenum and is about 10 inches (2cm) long. The second part called the jejunum is about 8 feet (2.5m) long and it passes imperceptibly into the last part called the ileum, which is about 12 feet (4m) long. The ileum connects to the large intestine (colon).

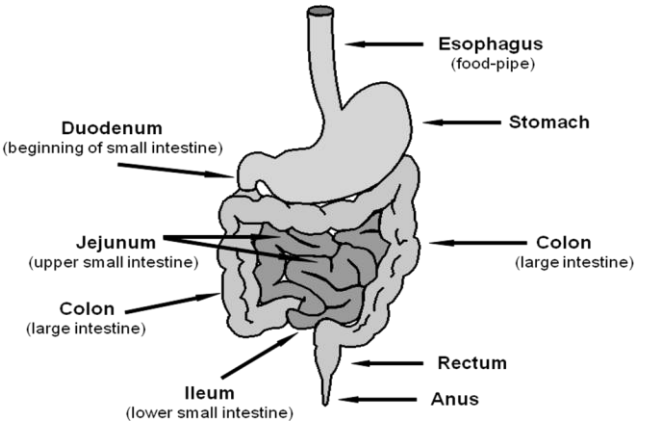


FIGURE 1: Parts of the Gastrointestinal Tract

Digestion and Absorption of Food

Food that is eaten cannot be absorbed intact. Digestion is the process of breaking the ingested carbohydrates, proteins and fat from food into smaller components, so that they can be absorbed into the body. There are 13 different vitamins that are

essential in human nutrition. These include the water-soluble C and B vitamins (e.g. folate, vitamin B12) and the fat-soluble vitamins (A, D, E and K). In addition, there are 16 minerals and trace elements that are also essential in our diet. These include iron, calcium, magnesium, copper, zinc and others. All these substances perform vital functions in our body and must be present in adequate quantity in our diet and absorbed from the intestine. For example, iron, folate and vitamin B12 are essential for adequate formation of red blood cells. Calcium and vitamin D are important for bone development.

All of the digestion and absorption of nutrients occurs in the small intestine. After the food is chewed and swallowed, the stomach churns it further into smaller bits with strong contractions. It then passes into the duodenum where a variety of enzymes secreted by the pancreas and the intestinal lining (mucosa) start the process of digestion. A fluid called bile is produced by the liver and stored in the gall bladder from where it is transported to the duodenum through a tube (bile duct) when required. Bile is essential for the digestion of fats. Digestion and absorption of fat is also important for adequate absorption of fat-soluble vitamins (A, D, E, K). The cells in the duodenum also produce several important hormones that are released into the circulation and stimulate the production of pancreatic enzymes and bile.

Contraction of the intestine (*peristalsis*) helps to mix the food and digestive enzymes and in moving this mixture (*chyme*) downwards. As the digested food travels down the intestines, absorption of carbohydrates, proteins and fats, minerals and vitamins occurs. The absorbed nutrients move across the wall of the intestines and into the blood vessels from where they are transported throughout the body for use. Most digestion and absorption occurs in the duodenum and jejunum, some in the ileum. The last part of the ileum called the terminal ileum absorbs vitamin B12 and bile that is recycled in the

body. Whatever remains enters the large intestine (colon) from where it is eventually passed out of the body as stool (feces).

What are Villi?

The inside of the small intestine is not a flat surface. If it were such, there would not be enough time for the nutrients to be absorbed from the small intestine given its limited length. To increase the surface area for the nutrients to be absorbed in the body, the lining of the small intestine is thrown into circular wrinkles or folds (mucosal folds). These mucosal folds are further covered with millions of tiny finger-like projections called villi, thereby further increasing the surface area available for absorption (Figure 2). On the villi are cells (*enterocytes*) that specialize in absorbing the nutrients. These cells are studded with very tiny projections on their surface called microvilli (also called brush border). All these structures increase the surface area of the intestine by several thousand fold, thus making the process of nutrient absorption extremely effective. As a simple tube, the small intestine would have a surface area of only about half a square meter. With the mucosal folds and villi, the surface area increases to approximately 250 square meters, about the size of a tennis court! The villi are longest and most abundant in the duodenum and jejunum, and become fewer and smaller in the ileum.

As will be seen later, understanding the structure and function of the villi is central to understanding what happens in celiac disease. All nutrients including carbohydrates, proteins, fat, vitamins and minerals are absorbed by the enterocytes lining the villi. Damage to the villi can potentially lead to deficiency of any or all of these nutrients.

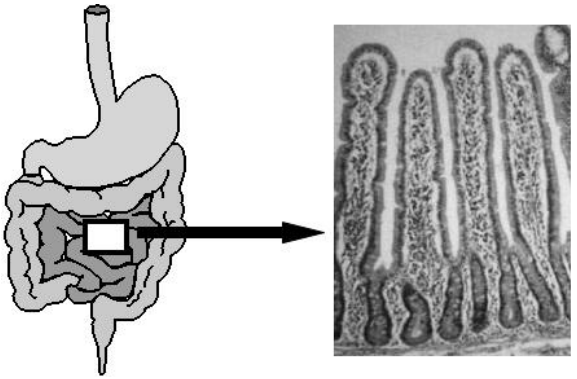


FIGURE 2: Normal Villi of Small Intestine

The Immune System

The immune system is a complex system consisting of a set of various cells and organs in the body that perform a variety of very important functions. The major function of the immune system is to fight off infections. The cells of the immune system also deal with any allergens that may get into the body. In addition, they remove any dead or cancerous cells. A defect in the immune system can lead to problems in any of these functions.

Structure of the immune system

The immune system has different types of white blood cells, each specialized to perform a specific function. These cells are present in the blood and most other organs of the body including the intestines.

The first line of defense against any harmful bacteria is a type of cell called *neutrophil*. These cells help kill the organisms by releasing certain toxic chemicals. Another major type of cell of the immune system is the *lymphocyte*. These are of two main types. The T lymphocytes are responsible for recognizing diseased cells like those infected with germs such as bacteria or viruses. The B lymphocytes produce proteins

called *antibodies* that latch on to the tiny substances called *antigens* present on the surface of bacteria and viruses, thereby destroying them. Macrophages are cells that literally ingest germs and other sick or dead cells. There are different types of macrophages in the body. One type is responsible for taking up various antigens that enter the body and presenting them to the T lymphocytes for eventual disposal. These are referred to as *antigen presenting cells*. There are also other types of cells in the immune system that are involved in an allergic response.

This may all seem fairly complicated but its relevance will become clear when the mechanisms causing celiac disease are discussed.

What is an Autoimmune Disease?

When a harmful organism like a virus or bacteria enters the body, the immune system recognizes it as a foreign agent. The cells of the immune system become activated and fight the invading agents. During this process a number of substances are released that create an inflammatory response in the body. These substances are called *cytokines*. These cytokines are responsible for causing symptoms of fever, loss of appetite and aches and pains that one experiences during an infection. The cytokines play a key role in getting rid of the pathogens.

Sometimes, things will go wrong. The immune system develops a problem and recognizes a part of the body as a foreign agent. It will then attack that part of the body eventually destroying it much like killing a virus or bacteria. This is referred to as an autoimmune response. A common example of an autoimmune disease is type 1 diabetes. In this disorder, the immune system attacks and destroys the cells in the pancreas that make insulin. Insulin is an important hormone that controls glucose level in the blood. Once those cells are destroyed, insulin cannot be produced in the body and must be

given by injections. Type 1 diabetes is a serious disease and the deficiency of insulin production by the pancreas is permanent.

Celiac disease is also an autoimmune disease. In this case, the immune system attacks the intestines. However, celiac disease is unique amongst all other autoimmune diseases in that the trigger that initiates this process is known. That trigger is gluten. Therefore, one has the opportunity to effectively reverse the process of autoimmunity and the resultant intestinal damage by removing gluten from the diet. This is the basis for the effectiveness of the treatment of celiac disease with a gluten-free diet.

Role of Genes

Celiac disease is a genetic disorder. Our *genes* determine essentially everything about us; our physical characteristics, susceptibility to illnesses, etc. We have several thousand genes, each performing a specific function in the body. Celiac disease is strongly associated with certain *human leukocyte associated* (HLA) genes. These genes are expressed on *leukocytes*, a type of white blood cell which is part of our immune system. There are many different types of HLA genes performing various functions.

The two HLA genes that are important in celiac disease are HLA DQ2 and DQ8. Virtually all patients with celiac disease have either the DQ2 or DQ8 genes. However, these genes are also commonly present in the general population. In some areas, as many as 30 percent of the population carries these genes but only a tiny fraction will ever develop celiac disease. Therefore, the presence of these genes does not necessarily imply that an individual will develop celiac disease. However, the absence of these genes means that the person is very unlikely to develop celiac disease.

Several other genes are being investigated that may also be involved in celiac disease but HLA DQ2 and DQ8 are the best studied to date. Laboratory testing for these genes is available but is currently quite expensive. It will likely become available as a routine test in the near future and will play an important role in assessing the susceptibility for developing celiac disease.

O KEY POINT

The absence of HLA DQ2 and DQ8 genes indicate that the individual almost certainly does not have celiac disease.

What Happens in Celiac Disease?

Our understanding of the mechanisms involved in the development of celiac disease has greatly improved over the last decade. These processes are complex and only a schematic summary is shown in Figure 3. Understanding these processes is also key to developing any strategies to cure celiac disease.

The cells lining the intestine are called the *epithelium* and are normally bound together tightly, thus preventing any toxic substances or germs from entering the blood stream through the intestine. A protein in the epithelium called *zonulin* is believed to play a role in regulating this process. Patients with celiac disease seem to have an abnormality in the action of zonulin, which leads to increased permeability ("leaky gut"). Gluten is a large protein and normally is not able cross the epithelium. When there is increased permeability, gluten (gliadin) is able to make its way through the epithelium.

In the intestinal mucosa, an enzyme called *tissue transglutaminase* (TTG) modifies the structure of gliadin through a process called *deamidation*. The TTG is an important enzyme that is present in all tissues. It is responsible for joining and modifying proteins, a process that is essential for wound

healing and growth of bones, etc. In celiac disease, the TTG converts the gliadin into a form that interacts with and activates the immune cells. This deamidated gliadin is taken up by the *antigen presenting cells*. If the right genetic marker is present (i.e. HLA DQ2 or DQ8), this deamidated gliadin binds strongly to the HLA on these cells, much like a key fitting into a lock. This is now presented to the T lymphocytes which get stimulated and in turn activate other types of lymphocytes causing a release of a variety of substances (*cytokine*s). These cytokines initiate an inflammatory response causing damage to the epithelium and thus leading to villous *atrophy* (flattening).

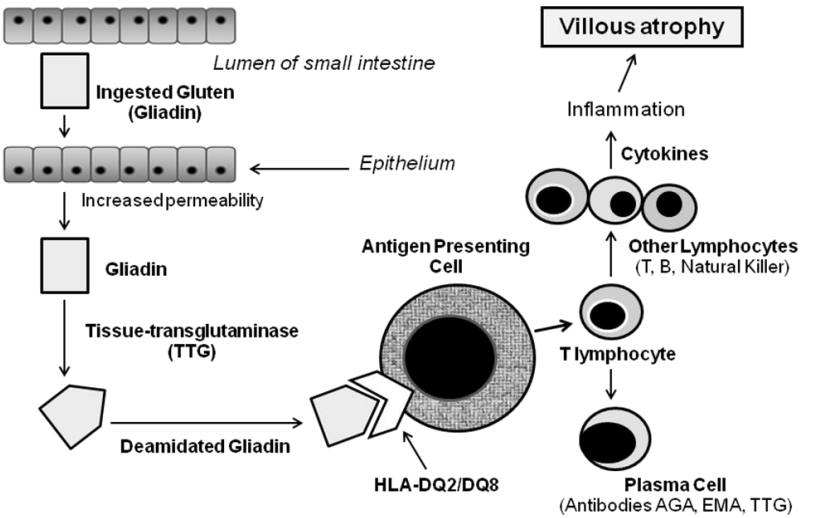


FIGURE 3: Mechanism of Gluten-Induced Villous Atrophy

The TTG, along with gliadin, gets incorporated into the lymphocytes that are making various antibodies to fight off the inflammatory process. These cells start to produce antibodies to TTG which are released into the circulation. These TTG antibodies in the blood are very good markers for the presence of celiac disease, as will be discussed in the section on Diagnosis.

What Triggers Celiac Disease?

Although our understanding of celiac disease has improved significantly, one mystery remains. Why, with the same genetic susceptibility, does the disease develop at six months of age in some and at sixty years in others? Clearly, there are other undefined genetic and environmental factors at play.

Physical stress on the body seems to act as a trigger in some patients. This commonly occurs after a gastrointestinal infection. Repeated intestinal infections in infancy and childhood seem to increase the risk of developing celiac disease. Such infections increase the permeability of the intestine ("leaky gut') and may initiate the process of gluten uptake. Other situations that are sometimes identified by patients as triggering celiac disease include pregnancy, surgery and trauma. Even emotional stress is sometimes blamed. These factors do not cause the disease but may trigger it in individuals who are susceptible to getting it. However, in most cases, no specific trigger can be identified.

Spectrum of Villous Atrophy: The Marsh Classification

The pathological changes of celiac disease in the small intestine are categorized by the Marsh classification (named after Dr. Michael Marsh). For patients and most physicians, the details may be of little relevance. It is, however, important for the pathologists and gastroenterologists. This is the main reason for discussing it briefly. Also, the Marsh classification is frequently mentioned in the celiac literature and some curious readers might wonder what it is all about.

The Marsh classification helps us understand that the lesion in celiac disease is progressive. As mentioned in an earlier section, lymphocytes are normally dispersed between the epithelial cells of the small intestine (*enterocytes*). These are

referred to as intra-epithelial lymphocytes. There are valleys between the villi called *crypts* that secrete fluid into the lumen and replace the aging cells that line the villi. In Marsh stage 1, these lymphocytes start to infiltrate the epithelium in increasing numbers. As the disease progresses, in addition to this increase in lymphocytes, the crypts become long due to an increase in their size (*hyperplasia*), as the cells regenerate trying to repair the damaged villi (Marsh stage 2).

MARSH CLASSIFICATION

- **Marsh stage (or type) 0** (pre-infiltrative): Normal mucosa
- **Marsh stage 1 (infiltrative):** Increased intraepithelial lymphocytes, greater than 30 lymphocytes per 100 enterocytes
- **Marsh stage 2 (hyperplastic):** Hyperplasia of crypts
- **Marsh stage 3 (destructive):** Variable degree of villous atrophy
- **Marsh stage 4 (hypoplastic):** Villous atrophy and hypoplasia of crypts

Stage 3 has been classified to include **Type 3a (partial villous atrophy)**, **Type 3b (subtotal villous atrophy)** and **Type 3c (total villous atrophy)**.

In the next phase (Marsh stage 3), there is now actual destruction and flattening (*atrophy*) of the villi. Marsh stage 3 is classical for celiac disease. Marsh stage 4 is rare; the disease is now so severe that the crypts are not able to regenerate.

Over the years, there have been several modifications to the Marsh classification. However, the basic principle remains that the lesion in celiac disease is progressive, moving from one stage to the next. The diagnosis of celiac disease does not necessarily require the presence of total villous atrophy as was the case in the past. Some patients have milder changes and the diagnosis can be missed if the pathologist interpreting the

biopsies is not aware of this phenomenon. These changes classically improve and eventually reverse after removal of gluten from the diet.

PREVALENCE

Celiac disease is one of the most common chronic gastrointestinal disorders in the world estimated to affect 0.5% to 1% of the population. The vast majority of individuals with celiac disease have not yet been diagnosed.

Celiac disease is truly a global disorder. It has been reported from North and South America, Europe, Australia, Africa, the Middle East, Iran and India. It is relatively uncommon in China, Japan and other Far East countries. Several studies from the United States and Europe show that about 1 in 100 children are affected by this disorder.

How has celiac disease become one of the most common intestinal diseases in humans? A brief look at the history of agriculture may shed some light. Thousands of years ago, the human diet consisted mainly of fruits, nuts and meats. Life was nomadic as people roamed from one place to another in search of food. When it was discovered that new plants arose from seeds falling to the ground from other plants, agriculture was born first in the Middle East region. Humans learned to domesticate crops and thus started the cultivation of grains like wheat, rye and barley. This provided great benefits, as the grains not only had nutritional value but could also be stored for consumption later. The human gut thus became exposed to wheat and related grains (gluten) and celiac disease began to surface.

Celiac disease is on the increase. Some elegant studies from the United States show that the incidence of celiac disease is doubling every 15 to 20 years over the last half century. This

seems to be a true increase in the incidence and not simply due to better awareness and screening. The cause of this increase remains unclear. Wheat consumption is on the rise globally and the strains currently grown are very high in gluten content. Other environmental factors may also be responsible. In general, like celiac disease, other autoimmune and allergic disorders are on the rise.

The true prevalence of celiac disease in Pakistan is not known. However, it is believed to be a common problem in all four provinces.

CLINICAL FEATURES

From Paediatrics to Geriatrics, celiac disease knows no age limits. It can occur at any age once solid foods are introduced into the diet. Celiac disease can occur in infancy, childhood, adolescence, adulthood or old age. I once met a gentleman who was diagnosed at 89 years of age! Most patients with celiac disease are now diagnosed as adults in their forties. Celiac disease occurs in both sexes. Like other autoimmune disorders, it is more common in females.

> **KEY POINT**
> Celiac disease can present at any age once gluten is present in the diet.

The symptoms of celiac disease are highly variable. An individual may have one or more symptoms and symptoms may change over time. In some individuals the symptoms may be mild. They do not feel very ill and may not seek medical help. In such cases, the diagnosis can get delayed or missed altogether.

The symptoms of celiac disease can also be non-gastrointestinal in nature. Therefore, before ending up at a gastroenterology clinic, many patients shuttle between a variety of physicians including family doctors, internists, hematologists, rheumatologists, neurologists and surgeons. This is not only because celiac disease can present in unusual ways but also due to a general lack of awareness of this disorder amongst the health professionals.

> O **KEY POINT**
> Celiac disease is called "the great pretender" because it can mimic almost any other disorder.

Symptoms of Celiac Disease

The symptoms of celiac disease are listed in the Table 1. Some of these symptoms will be discussed in further detail.

Abdominal pain

Abdominal pain is the most common symptom of celiac disease. The pain is due to the inflammation of the intestine. The pain is usually chronic and can vary in intensity and frequency. It can be the only symptom or occur in combination with other symptoms discussed below. A patient with chronic abdominal pain should be screened for celiac disease.

Diarrhoea

Diarrhoea is defined as an excessive amount of fluid in the stools (feces). In celiac disease, diarrhoea occurs because the villi of the small intestine are damaged and unable to digest and absorb the nutrients. The unabsorbed food pulls water into the cavity of the intestine by a process called osmosis thus causing diarrhoea. The stools can appear greasy due to fat mal-

absorption (*steatorrhea*) and can be particularly foul smelling. They do not contain any blood.

TABLE 1:
SYMPTOMS OF CELIAC DISEASE

Common Symptoms

- Abdominal pain
- Diarrhoea
- Indigestion and gas
- Constipation
- Nausea and vomiting
- Abdominal distension/bloating
- Weight loss
- Anemia
- Weakness and Fatigue
- Weak bones (osteoporosis)

Others

- Neurological symptoms (neuropathy, ataxia, epilepsy, migraine, etc.)
- Depression
- Oral ulcers
- Menstrual irregularities
- Infertility
- Increased liver enzymes

Additional Symptoms in Children

- Irritability
- Growth failure/delayed puberty
- Short stature
- Dental enamel defects

Indigestion and Gas

These are non-specific symptoms and relatively common in the general population. With chronic indigestion, celiac disease

should be included in the list of possible diagnoses. Some patients with celiac disease can have lactose intolerance which can cause these symptoms. Lactose intolerance will be discussed in more detail later.

Constipation

Normally with malabsorption one thinks of diarrhoea. Interestingly, some patients with celiac disease can present with constipation. The cause of constipation in celiac disease is not fully known but is believed to be due to a problem with the normal motility (contractions) of the intestine. Celiac disease should be explored as a possibility in patients with chronic constipation, especially when the problem is intractable and not responding well to treatment with diet and laxatives.

Nausea and Vomiting

Some patients with celiac disease can present with nausea and vomiting. The symptoms can resemble those of gastro-esophageal reflux disease including heartburn. Vomiting is the result of inflammation in the duodenum. Sometimes the stomach can also develop inflammation in celiac disease. If a patient with acid reflux is not improving despite adequate therapy, one should consider celiac disease as the underlying problem.

Abdominal Distention and Bloating

A distended and protuberant abdomen is a common feature of celiac disease, especially in young children.

Weight loss

The inability to absorb nutrients will lead to loss of weight. Diarrhoea is often also present in these cases. Abdominal pain may further limit intake of food and aggravate the weight loss.

Infants and toddlers may present with failure to thrive. Children will stop growing if their nutritional needs are not met.

Anemia

Iron deficiency anemia has become one of the most common presentations of celiac disease in adults. The awareness of celiac disease being a cause of anemia remains poor and many individuals who have anemia are not diagnosed with celiac disease in time.

The term anemia refers to lack of blood in the body. Several nutrients are required for the adequate production of red blood cells including iron, folate and vitamin B12. The red blood cells are made in the bone marrow from where they move into the circulation. The red blood cells contain a substance called *hemoglobin* which has the ability to carry oxygen. Once in the blood, these cells transport oxygen from the lungs to various parts of the body, a process that is essential for life. Anemia can occur from decreased production or increased destruction of red blood cells or loss of blood from the body.

Anemia in celiac disease can occur from lack of iron, folate or vitamin B12. Vitamin E deficiency can also cause anemia. There can also be a combination of these nutritional deficiencies. Iron deficiency is the most common type of anemia found in celiac disease. There are good reasons for this phenomenon. Iron is primarily absorbed by the duodenum, which is the most proximal part of the small intestine. This is also the site of the greatest damage in celiac disease as this part of the intestine takes the brunt of the ingested gluten. (That is why the duodenum is the preferred site to biopsy during endoscopy to confirm the diagnosis of celiac disease). The damage to the mucosa of the small intestine can impair the

absorption of iron from the diet. In some cases of celiac disease, there is also occult blood loss in the stools due to chronic inflammation of the intestinal mucosa. As the iron stores in the body gradually get depleted, anemia develops. The individual may then develop a variety of symptoms including fatigue, exercise intolerance and shortness of breath. Administering iron supplements orally will not be of much help in this case as iron cannot be adequately absorbed from the intestines. Iron given by injections will improve the anemia but it will recur once the injections are discontinued. With a strict gluten-free diet the intestinal mucosa will heal, iron absorption will resume and anemia will be corrected. Iron supplements may be required in some cases to build up the iron stores in the body.

The stories of missed diagnosis of celiac disease in those with iron deficiency anemia are all too common. This is particularly common in females in whom the iron deficiency is often blamed on menstrual blood losses. There are cases of women having undergone hysterectomy (removal of uterus) to treat persistent iron deficiency. Others have had examination of their bone marrow done but to no avail. Individuals have been subjected to iron injections for years before someone thought of celiac disease. The diagnosis of celiac disease has been missed even in those who underwent upper gastrointestinal endoscopy for investigation of anemia because intestinal biopsies were not performed during the procedure. It is hoped that with better awareness of anemia in celiac disease, these types of stories will not occur.

O KEY POINT

Celiac disease should be considered as a diagnostic possibility in any individual with unexplained iron deficiency anemia, especially if there has been a poor response to oral iron supplementation.

Weakness and Fatigue

Weakness and fatigue are common symptoms in celiac disease. Occasionally, they are the only symptom. There could be several mechanisms responsible for excessive fatigue in celiac disease. Poor nutrition and weight loss can lead to tiredness. The patient may have anemia or low thyroid function (*hypothyroidism*). Commonly, no cause for fatigue is apparent but it improves rapidly once treatment with a gluten-free diet is started. Substances that mediate inflammation (*cytokines*) are released when there is active inflammation anywhere in the body including the intestine. This may cause tiredness and malaise in a way similar to what happens with a flu or a cold.

Bone Disease (Osteoporosis)

Lack of adequate calcium and vitamin D can lead to weak bones (osteoporosis). The patients may develop bone pain and, in advanced cases, fractures. Bone densitometry is a type of X-ray that assesses bone health. Osteoporosis may be the presenting symptom of celiac disease. Fortunately, treatment with a gluten-free diet and adequate supplementation with calcium and vitamin D improve the bones in most cases. The recovery is much more rapid and complete in children.

Neurological Problems

Celiac disease can be associated with a variety of neurological manifestations. The best described problems include peripheral neuropathy, ataxia, epilepsy and migraines. It is not fully understood whether these conditions are just associations or have a cause and effect relationship with celiac disease. Brain and nerve problems can occur from inflammation or as an autoimmune phenomenon. Nutritional deficiencies of folate, vitamin B12 and vitamin E can also cause damage to the nerves. The exact mechanism remains unclear.

Peripheral Neuropathy

Peripheral neuropathy is one of the most common neurological manifestations of celiac disease. The term is used to describe abnormal function of the nerves to the extremities (periphery) of the body. The patient complains of numbness and tingling sensations in the hands, feet and face. The treatment consists of a strict gluten-free diet. Medications may also be required.

Ataxia

Ataxia is a condition in which the balance of the body is disturbed. This may cause difficulty with coordination of muscle function and an unsteady gait. The patient may fall easily. The problem is generally due to disease of the *cerebellum*, the lower part of the brain in the back of the head. Peripheral neuropathy can also aggravate ataxia. Ataxia is one of the most common neurological conditions associated with celiac disease. About 10 to 15 percent of patients with ataxia of unknown cause have celiac disease.

Epilepsy

Epilepsy occurs due to a sudden increase in the electrical activity of the brain causing a variety of convulsions. There can be loss of consciousness and uncontrolled jerking of the limbs. Epilepsy, like celiac disease, is a common disorder in the general population. The association between the two diseases may be just a coincidence. However, epilepsy occurs more commonly in patients with celiac disease.

In children, an interesting association that can occur with celiac disease and epilepsy are calcifications in the occipital (rear) part of the brain. The calcifications are deposits of calcium in injured areas. It is believed to be an autoimmune phenomenon. In children presenting with epilepsy and brain calcifications, a search for celiac disease should be made.

Migraines

Patients with celiac disease suffer from migraines more commonly than others. Migraines are severe headaches that occur suddenly and can be very disabling. Treatment with a gluten-free diet helps reduce the severity and frequency of migraines.

Oral Ulcers

Recurrent oral ulcers (aphthous) or canker sores can also occur in celiac disease and could provide another clue to the possible presence of this disorder. The exact cause of these ulcers in celiac disease is unknown but it is felt to be an autoimmune phenomenon. If a patient has frequent oral ulcers, celiac disease should be explored as a diagnostic possibility.

Reproductive Problems and Infertility

Celiac disease may increase the risk of infertility, both in females and males. The exact cause is not known but nutritional deficiencies and abnormal hormone production may play a role. Women may also suffer from menstrual irregularities and miscarriages. These problems occur in untreated celiac disease and tend to resolve with appropriate therapy.

Undiagnosed celiac disease in the mother at the time of delivery can lead to increased risk of preterm birth, increased risk of Cesarean section and babies born with low birth weight. In contrast, known maternal celiac disease diagnosed before birth does not seem to be associated with any adverse fetal outcomes.

O KEY POINT

Celiac disease should be a consideration in the diagnostic workup of infertility.

Liver Disease

Liver inflammation can sometimes occur from gluten injury. This is referred to as "celiac hepatitis" (*hepatitis* means inflammation of the liver). Isolated increase in liver enzymes (*transaminases*) is the commonest presentation. A liver biopsy may show nonspecific histological changes. Some patients may develop obvious signs of liver disease like *jaundice* (yellow eyes).

Just as individuals with celiac disease can develop liver problems, those with liver problems may be suffering from undiagnosed celiac disease. Celiac disease can coexist with other autoimmune liver disorders including autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis. There have been reports of patients undergoing a liver transplant after developing liver failure due to unrecognized celiac disease.

The precise mechanisms involved in celiac disease causing inflammation of the liver are not known. There could be several possible mechanisms. The liver may be affected by an autoimmune process (autoimmune hepatitis). Patients with one autoimmune disorder like celiac disease are at risk of developing another autoimmune disorder. Another proposed mechanism is that the cells of the immune system have receptors that can sense molecules present in bacterial pathogens. When the immune system senses these molecules, certain chemicals are released which set off an inflammatory response to help control the pathogen. As mentioned previously, intestinal permeability is increased in patients with celiac disease. This disruption of the intestinal barrier (leaky gut) permits products from the bacteria present normally in the gut to enter the blood stream and reach the liver. This can trigger a response from immune cells in the liver resulting in inflammation and damage. Finally, gluten itself could directly

trigger a liver immune response just as it does in the small intestine.

Celiac disease should be a diagnostic consideration in any individual with a chronic increase in liver transaminases for which no other cause is found ("cryptogenic" liver disease). Serological testing for celiac disease is recommended in such cases before more invasive diagnostic procedures like liver biopsy are undertaken. A gluten-free diet normalizes liver enzymes and histological changes in most patients.

Dental Enamel Defects

Dentists should be aware that celiac disease can sometimes affect the teeth. If the disease develops in children while the permanent teeth are developing i.e., before seven years of age, abnormalities in the structure of the dental enamel can occur. These defects most commonly occur in the permanent dentition, symmetrically and chronologically in all four sections of dentition. A variety of dental abnormalities can be seen including yellow or brown opacities, horizontal grooves, pits and structural defect of the teeth in severe cases. Immune-mediated damage to the teeth is suspected to be the primary cause. Calcium malabsorption may also play a role. Diagnosis of celiac disease can sometimes be made from a smile!!

Short Stature

Short stature (height) can be the only presenting feature of celiac disease in the absence of other symptoms. Celiac disease is far more common than growth hormone deficiency or any other hormonal cause of short stature. The cause of celiac disease-associated short stature is unclear. Proposed mechanisms include growth retardation due to generalized or selective malnutrition (e.g., zinc deficiency), alterations in the insulin-like growth factor-1 pathway and an impaired pituitary release

of growth hormone. The latter reverts to normal after treatment with the gluten-free diet. Celiac disease should be considered in any child with short stature.

> O **KEY POINT**
> Patients with celiac disease can present with extra-intestinal symptoms.

Familial Risk

Celiac disease is a hereditary disorder and tends to run in families. First degree relatives including siblings, parents and children of the patient with celiac disease have a 10 to 15 percent risk of developing this disorder. The second degree relatives are also at a high risk. If a relative has an autoimmune disorder, the risk almost doubles. Most authorities recommend screening both first and second degree relatives for celiac disease.

The incidence of celiac disease in twins further confirms its genetic nature. If an identical twin has the disease, the other has a 70 percent chance of developing it. In non-identical twins, the risk is about 30 percent. This implies that although genetics strongly affect the susceptibility for developing celiac disease, there are non-genetic factors at play as well.

> O **KEY POINT**
> Celiac disease is a familial disorder and the physician should inquire about symptoms in both first and second degree relatives.

Other High Risk Groups

Besides family relatives, there are others groups of patients who are at high risk of developing celiac disease. The two best described groups include those with an autoimmune disease and genetic disorders.

Autoimmune Diseases

- Type-1 diabetes (insulin dependent)
- Thyroid disease
- Sjogren's syndrome
- Addison's disease
- Primary biliary cirrhosis

Genetic Disorders

- Down syndrome
- Turner syndrome
- IgA deficiency

Sjogren's syndrome is a rare disorder in which there is a defect in the glands that produce mucous. The mucous is a fluid that provides moisture. The glands that produce saliva in the mouth and tears in the eyes are most commonly affected. The patient complains of dry mouth and eyes. Sometimes the pancreas can become affected leading to problems with digestion of food.

Addison's disease is atrophy (destruction) of the *adrenal* glands. The adrenals are two small glands located on top of each kidney. They produce several very important hormones that regulate the body's response to stress, metabolism of nutrients, cardiovascular and immune functions. The patient develops weakness, dehydration, low sodium and blood glucose. The disease is potentially fatal if not recognized and managed appropriately.

Down and Turner syndromes are abnormalities of the *chromosomes*. The chromosomes are tiny structures that comprise the genetic material and are present in almost all cells of the human body. Patients with chromosomal defects can have a variety of health problems. Those with Down syndrome commonly have mental retardation and may not be able to communicate their symptoms very well.

Individuals with IgA deficiency have a higher risk of developing celiac disease. Ig stands for *immunoglobulins* which are types of antibodies made by the cells of the immune system. There are five types of immunoglobulins: IgA, IgD, IgE, IgG and IgM, each performing a specific function. The IgA is primarily produced by the immune cells present in the gastrointestinal and respiratory tracts. Approximately 1 in 600-700 otherwise healthy individuals have IgA deficiency. Some of them are prone to getting infections of the digestive and respiratory systems, while in most there are no health problems. IgA deficiency is more common in patients with celiac disease. The importance of IgA deficiency will again be highlighted when the diagnostic tests for celiac disease are discussed later.

Some authorities recommend screening for celiac disease in all patients in the above-mentioned high risk groups. Others recommend screening only those who are symptomatic.

O **KEY POINT**

Celiac disease is a serious disorder that requires careful evaluation and treatment.

Celiac Disease in the Elderly

Traditionally, celiac disease has been considered to be a disorder of childhood. It is now well known that celiac disease is not age specific. The majority of individuals now being diagnosed with celiac disease are adults. Many of these are elderly individuals. Not realizing that celiac disease can affect the elderly can lead to delays in the diagnosis even when these individuals present to their family physicians with typical symptoms. How could the 70-year-old grandfather have celiac disease, the doctor wonders? Many older individuals have

other co-morbid conditions like high blood pressure, diabetes, heart problems and cancer and this can further cloud the physician's thinking about celiac disease as a possible diagnosis.

Improving awareness and better education of the primary-care physicians can help change this perception. How many of those senior citizens with irritable bowel syndrome, chronic fatigue and refractory iron deficiency anemia and could have celiac disease?

> O **KEY POINT**
> If you look for celiac disease in a patient, you will frequently find it.

The Celiac Iceberg

Celiac disease has traditionally been considered to be a disorder of the gut. However, it is now becoming evident that it is, in fact, a multi-system disorder in which other organs of the body are also affected, directly or indirectly.

Celiac disease has two clinical patterns; *symptomatic* and *asymptomatic*. The asymptomatic form is further classified into *silent* and *latent*. Patients in all these groups have the genetic susceptibility (HLA DQ2/DQ8) and a positive serology. The Celiac Iceberg provides a useful model to reinforce the concept that symptomatic celiac disease represents the tip of the iceberg, i.e. only a small number of all those with celiac disease (Figure 4). The vast majority of individuals have little or no symptoms.

Symptomatic Celiac Disease (classical, atypical)

The symptoms of celiac disease can be *classical* (typical) or *atypical*. Patients with classical celiac disease present with gastrointestinal symptoms of malabsorption i.e. diarrhoea, abdominal pain and weight loss. Atypical symptoms are non-

gastrointestinal in nature. For example, the patient may present with extreme fatigue, migraine headaches, short stature or infertility. Atypical presentations are now becoming more typical. Those classical cases of severely malnourished and wasted children with celiac disease seen in many textbooks are now rarely seen in clinical practice. Many patients with celiac disease are obese at diagnosis. Various symptoms of celiac disease have been discussed earlier in this chapter.

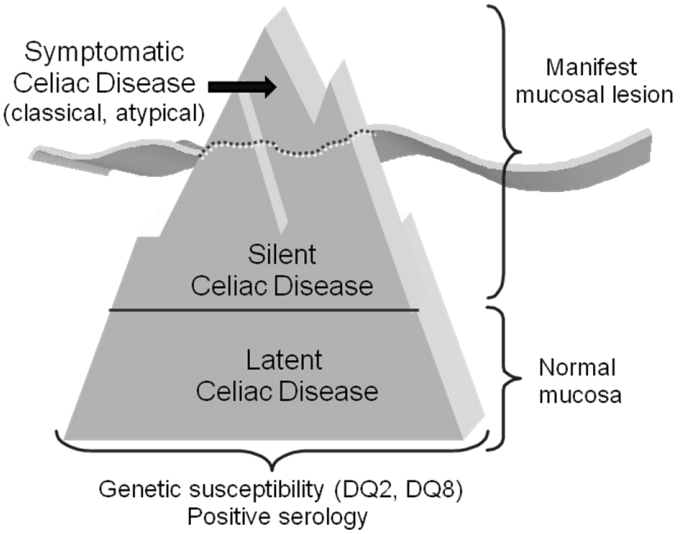


FIGURE 4: The Celiac Iceberg

In these symptomatic patients, the serology (antibody blood test) will be positive in the majority of cases and a small intestinal biopsy will also be abnormal. They are treated with a gluten-free diet.

O **KEY POINT**

Overweight individuals can also have celiac disease.

Asymptomatic Celiac Disease (silent, latent)

Some patients with celiac disease have no symptoms. However, their serology is positive and the small intestinal biopsy abnormal, thus confirming celiac disease. This is referred to as asymptomatic or "silent" celiac disease. The serological testing is often performed in these individuals because they belong to a high risk group such as family members of a patient with celiac disease.

There is controversy whether these asymptomatic patients with abnormal biopsy should be treated with a gluten-free diet. Most authorities recommend treatment as it may prevent the long-term complications of celiac disease. However, a gluten-free diet is lifelong, complex and restrictive and it is often difficult to convince a patient with no symptoms to go on any treatment.

The disease may not be "silent" after all. It is only after starting a gluten-free diet that those individuals realize that they used to feel unwell previously. If at any time these individuals become symptomatic, treatment with a gluten-free should be initiated.

Latent (or potential) celiac disease presents an interesting problem. Here the individual has no symptoms but a positive serologic test for celiac disease. However, the intestinal biopsy is completely normal. What does this mean? Since the intestine is normal, treatment with a gluten-free diet is not recommended by most authorities. However, these patients should be monitored closely as they do have a high risk of developing full blown celiac disease. In that case, a repeat intestinal biopsy should be considered.

How does the Celiac Iceberg model apply to the population in Pakistan? Given the lack of easy availability and the high cost involved in serological testing, it is unlikely that asymptomatic

celiac disease will be a major issue in our country, at least in the near future. Furthermore, the treatment of asymptomatic celiac disease remains controversial. Therefore, it may be more prudent and cost effective if the medical community focuses on recognizing and diagnosing symptomatic patients, both classical and atypical.

> O **KEY POINT**
> Not everyone with celiac disease has symptoms.

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH) is "celiac disease of the skin". It is a chronic condition that presents with a blistering skin rash associated with severe itching and burning sensations. Genetic factors, the immune system and sensitivity to gluten seem to play a role in causing this disease.

Dermatitis herpetiformis is characterized by a rash that is extremely itchy. It is one of the itchiest skin conditions described and, before the advent of effective therapy, DH was reported as a cause of suicide in some patients. It can occur anywhere on the body. The most common areas affected include the elbows, knees, scalp, back of the neck, the upper back, and the buttocks. The rash tends to have a symmetric distribution. Continuous scratching can cause the skin to break and bleed with secondary infections. Diagnosis is often delayed because nobody thinks of DH as the cause of the problem.

About 10% of patients with celiac disease have DH. It is more common in males. The onset of DH is usually in the late second to the fourth decades of life. This disorder is rare in children.

O KEY POINT

The characteristic feature of the skin rash in dermatitis herpetiformis is that it is chronic and intensely itchy.

Most patients with DH have few or no bowel complaints. Only a small number have abdominal pain, bloating and diarrhoea. Thyroid abnormalities and other autoimmune diseases occur more frequently in these patients. For unknown reasons, a sensitivity to iodine is also common.

Dermatitis herpetiformis can be effectively diagnosed with a carefully performed skin biopsy. The biopsy should be taken next to a blister and not of the lesion itself. Granular IgA antibody deposits on histology are unique to DH and confirm the diagnosis. The majority (80%) of individuals with DH have an abnormal mucosal lining of the small intestine similar to those in patients with celiac disease. The TTG antibody may or may not be positive as it correlates with the severity of the bowel lesion which may be absent in some patients. Some patients may require a small intestinal biopsy to reinforce the diagnosis and the need for a gluten-free diet

The treatment of DH includes topical and oral medications (Dapsone and others) and a strict gluten-free diet. The resolution of skin lesions can be slow in some patients. The medications only relieve the symptoms of DH and do not address the underlying cause which is gluten ingestion. The gluten-free diet is the key to long-term successful management of this disorder.

O KEY POINT

If the skin biopsy confirms dermatitis herpetiformis, the patient has celiac disease and should be managed as such.

DIAGNOSIS

The diagnosis of celiac disease requires a high index of suspicion. With lack of awareness, even classical cases can be missed. The diagnosis of celiac disease cannot be made on symptoms alone. Confirmation by laboratory tests is necessary. These include serological tests and an intestinal biopsy. Routine blood tests including hemoglobin, *ferritin* (iron stores), *albumin* (a protein) and calcium should be obtained. Depending on the clinical picture, testing various vitamins and mineral levels may be considered. This is helpful in cases of malabsorption.

Serological Tests

One of the major advancements in celiac disease over the last few decades has been the development of *serological* (blood) tests to screen for celiac disease. These are also called *antibody* tests. Antibodies are substances produced by the immune cells in response to a foreign protein (*antigen*).

A variety of serological tests are available to screen for celiac disease and include the following:

(1) Anti-gliadin Antibody (AGA)

These are antibodies to gliadin, the component of gluten which is the major trigger in celiac disease. These were the first antibody tests to be developed. However, they are neither very sensitive nor specific. This means that in some people with celiac disease these tests may be negative (false negative) while they may be positive in some of those who do not have celiac disease (false positive). Because of this limitation and the availability of more accurate tests, the AGA is not recommended for routine screening.

(2) Endomysial Antibody (EMA)

These are antibodies formed against the *endomysium*, a structure of the smooth muscle connective tissue. (Later it was discovered that the exact target antigen was tissue transglutaminase). This is a highly accurate test for celiac disease. If the result is positive, the person almost certainly has celiac disease. Although rare, the EMA can sometimes be negative in individuals who may have celiac disease (false negative). This test is expensive to perform and its accuracy is dependent on interpretation by laboratory personnel. It has largely been replaced by the TTG antibody test.

(3) Tissue-Transglutaminase Antibody (TTG)

The TTG is currently the recommended antibody test to screen for celiac disease and is the one most commonly employed around the world. Tissue transglutaminase is an enzyme (protein) found in almost all tissues of the body including the intestines. Two types of TTG antibodies are formed: IgA TTG and IgG TTG. The IgA TTG is the one that is measured by most laboratories. IgG TTG can be measured but is not commonly available. Like other screening tests, the TTG antibody can sometimes be negative in patients with celiac disease (false negative). Rarely, it can be positive in patients with diseases other than celiac disease.

The TTG antibody test is less reliable in children under two years of age. Also, the IgA TTG will be falsely negative in a patient with celiac disease who has selective IgA deficiency.

The TTG antibody test is now available in select laboratories in Pakistan. This test is still expensive but, if performed in timely manner, it can be cost-saving as other unnecessary investigations are avoided. Also, once the test becomes widely available, the price will likely decrease.

(4) Deamidated Gliadin Peptide Antibody (DGP)

These antibody tests are new and are not yet routinely available. DGP antibodies are formed against the gliadin that has been modified by the tissue transglutaminase in the intestine (explained in the section on Pathophysiology). They are available in both IgA and IgG classes. Their accuracy is similar to the TTG antibody test.

> O **KEY POINT**
>
> The antibody tests are for screening purposes and may be negative in some individuals with celiac disease.

Utility of Antibody Tests

It is not exactly clear how all these antibodies are formed and what role they play in celiac disease. They are not believed to be directly harmful to the intestine. However, they provide an important tool to investigate celiac disease.

It is important to note that when tested for these antibodies, the patient must be on a regular (gluten-containing) diet. A gluten-free diet will make the test negative over time, usually within six to twelve months.

The antibody tests can be useful in the following situations:

- ❖ Screening of symptomatic patients and/or high risk individuals
- ❖ When a biopsy is not feasible or shows equivocal findings
- ❖ Monitoring compliance with the gluten-free diet

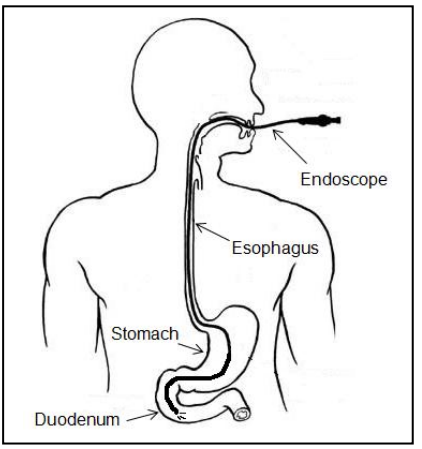
The antibody and HLA-DQ2/DQ8 tests, though still expensive, are increasingly become available for clinical use around the world. The presence of HLA-DQ2/DQ8 and two positive antibody tests in a patient may obviate the need for a small intestinal biopsy for diagnosis of celiac disease in the future.

Small Intestinal Biopsy

A small intestinal biopsy is the diagnostic test to confirm celiac disease. The biopsy is a tiny sample taken from the mucosa (lining) of the small intestine and examined for inflammation and damage to the villi. In the past this was done using an instrument called Crosby capsule. It will be described in the chapter History of Celiac Disease. These days, most commonly the biopsy is done through a procedure called endoscopy

Endoscopy

The small intestinal biopsy is taken during a procedure called an endoscopy. The patient is sedated. Children often require a general anesthesia. A flexible tube (endoscope) is then introduced through the mouth and advanced into the duodenum. A thin wire (forceps) is passed through a channel in one end of the instrument till it comes out at the other end in the lumen of the bowel. Tiny pinches are taken from the mucosa with the forceps. The biopsy specimen is sent to the pathology laboratory for special staining and microscopic examination.



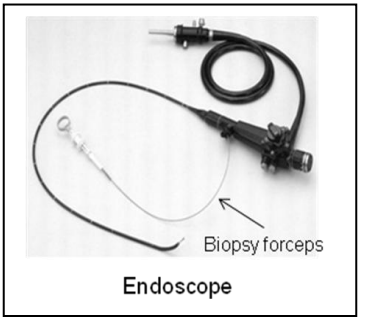


FIGURE 5: The Endoscope

Endoscopy is a safe procedure and generally takes less than thirty minutes to complete. It is performed by gastro-enterologists, who are physician specialists in diseases of the digestive system. A variety of changes can be seen affecting the mucosa in celiac disease. These changes include the following:

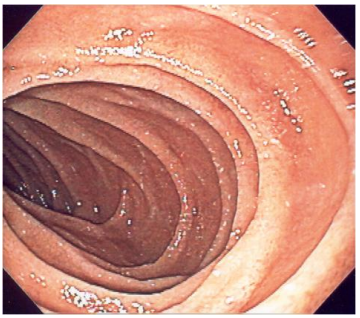
- ❖ Absence or flattening of mucosal folds
- ❖ Notching of mucosal folds (scalloping)
- ❖ Fissuring of the mucosa between the folds ("cracked mud" appearance)

Of note, the mucosa may appear grossly normal in some patients. Therefore, it is mandatory that biopsies be obtained irrespective of the appearance of the mucosa.

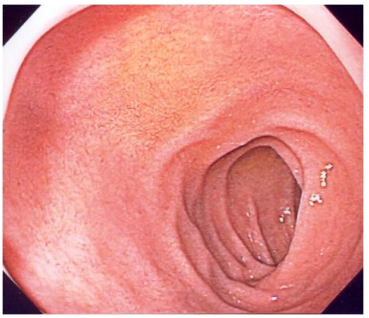
Performing a Biopsy

It is important to note that celiac disease may not affect the small intestine in a uniform fashion. Some areas may be involved while others may be spared and look relatively normal. This patchy nature of celiac disease is increasingly being recognized. For this reason, multiple biopsies should be obtained during endoscopy. A minimum of four biopsies from different parts of the duodenum is recommended. There is recent evidence that in some cases the lesion may be limited to the duodenal bulb. The bulb (or cap) is the very first part of the duodenum where it is connected to the stomach. One or two biopsies should be taken from the duodenal bulb in addition to the four biopsies.

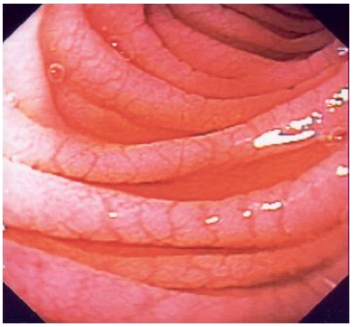
The biopsy samples are small and can get crushed during handling and processing. Multiple biopsies also help limit problems with orientation of the specimens and artifact during processing and staining.



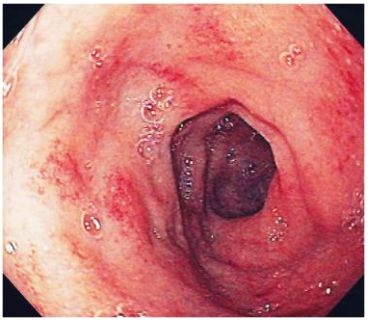
Normal duodenum
(Endoscopic view)



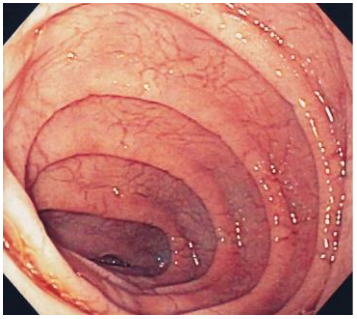
Normal duodenal bulb
(Endoscopic view)



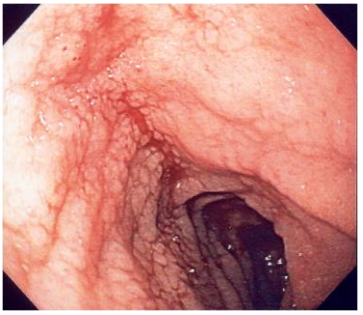
Duodenum in celiac disease
(Scalloping of mucosal folds)



Duodenal bulb in celiac disease
(Erythema, friability)

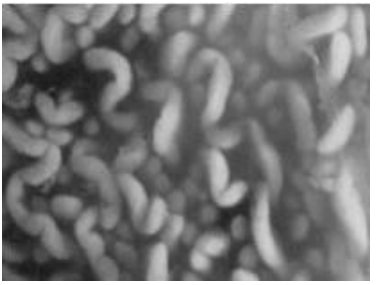


Duodenum in celiac disease
(Mosaic pattern of folds)

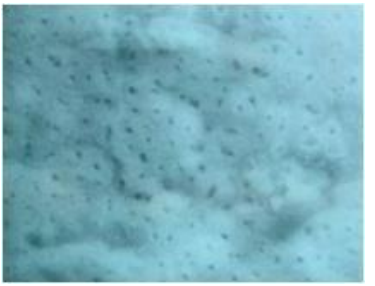


Duodenal bulb in celiac disease
(Nodularity, loss of folds)

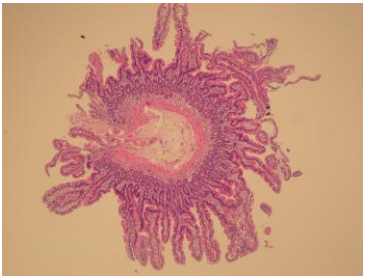
FIGURE 6: Endoscopic Images of the Duodenum



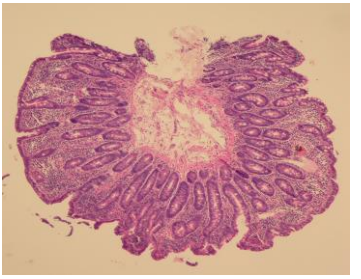
Normal intestinal villi
(Dissecting microscope view)



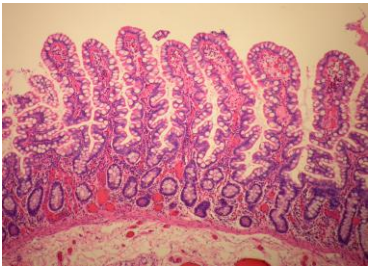
Celiac disease
(No villi present)



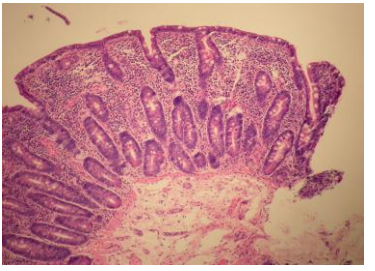
Normal intestinal villi
(Microscopic view; low power)



Celiac disease
(Total villous atrophy)



Normal intestinal villi
(Microscopic view; high power)



Celiac disease
(Total villous atrophy)

FIGURE 7: Microscopic Images of the Duodenal Biopsies

An Approach to Diagnosis

A simplified approach to evaluation in celiac disease is presented in Figure 8.

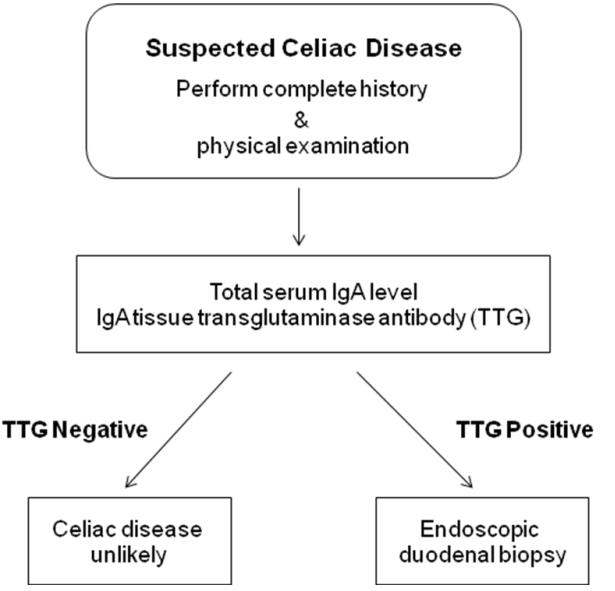


FIGURE 8: An Approach to Diagnosing Celiac Disease

If the patient has IgA deficiency, the IgA-TTG result will be meaningless. Other serological tests may then need to be considered. Furthermore, a negative TTG antibody does not completely rule out celiac disease but makes it very unlikely. If celiac disease is still suspected, the patient should have a biopsy.

Gluten Challenge

A common problem that is encountered by gastroenterologists is that a patient starts a gluten-free diet without having a biopsy. Patients do this on their own or are advised by their family physicians to try a gluten-free diet. The symptoms

improve but the patient is left with the uncertainty of whether he/she truly has celiac disease. In this situation, an oral gluten challenge is required to induce the intestinal inflammation and then an intestinal biopsy to confirm or refute the diagnosis.

There is a considerable variation in how people with celiac disease react to gluten ingestion, both in terms of amount and the frequency of intake. For this reason, it is not clear how much gluten should be ingested daily for a challenge and each case should be considered individually. For a gluten challenge in adults, the British Society of Gastroenterology recommends an intake of 10 gram of gluten (i.e. equivalent to four slices of bread) per day for a minimum of two weeks. In children, it is suggested that the challenge last for at least six weeks. The recommended duration of the challenge may be too short in some cases. Individuals may not develop symptoms within two weeks in which case the duration should be extended to twelve weeks or until symptoms develop. The biopsy should be performed earlier if the patient experiences significant symptoms. However, the development of symptoms on a gluten challenge without evidence of an abnormal biopsy is insufficient to make the diagnosis of celiac disease. Some individuals may require several months (even up to two years) of gluten challenge to become symptomatic or develop the typical changes on biopsy.

The tissue-transglutaminase antibody (TTG) and the endomysial antibody (EMA) blood tests will not become positive with a gluten challenge of a few weeks. They may become positive if the gluten ingestion continues for several months. Whether these tests turn positive or not, an intestinal biopsy should be done to confirm the diagnosis.

Before embarking on a gluten challenge, patients should discuss this with their physician. Since a small intestinal biopsy will be required to confirm the diagnosis of celiac disease, arrangements should be in place for the timely endoscopy and

biopsy. Moreover, individuals can get quite ill while on a gluten-containing diet and should have close medical supervision when undergoing a gluten challenge.

A normal biopsy and serology after a properly conducted gluten challenge rules out celiac disease and indicates that the diagnosis of celiac disease in the past may have been incorrect.

> O **KEY POINT**
> A gluten-free diet should NOT be started before confirming the diagnosis of celiac disease with an intestinal biopsy.

Understanding Gluten-Related Terminology

(Intolerance vs Sensitivity vs Allergy)

Gluten-related terminology can be confusing. Terms like **intolerance, sensitivity and allergy** are often used interchangeably. However, these could mean different things to different people. In a broad sense, a food intolerance or sensitivity or allergy all imply that an individual gets symptoms when the offending food is consumed. Moreover, the underlying mechanisms are different. Simply put, Gluten Intolerance can be considered to be an umbrella term under which there is gluten/wheat allergy, gluten sensitivity (non-celiac) and celiac disease.

Food allergies are common and can occur at any age. In food allergy, there is an immunological reaction in which the patient forms immunoglobulins (most commonly IgE) in the blood against the offending antigen (food). When the antigen gets into the body it binds to the IgE antibody and in that process chemicals like histamine are released that can cause a variety of symptoms including skin rash, swelling, breathing difficulty, vomiting, diarrhea and shock. Symptoms often occur immediately after ingestion of the allergen but sometimes can take longer. One can apply this explanation to wheat/gluten

allergy. Patients do not have tissue-transglutaminase antibody (TTG) in the blood as is the case in celiac disease and there is no ongoing damage to the intestine. A person may outgrow this type of food allergy over time. This is not celiac disease.

Gluten sensitivity is another term that is applied interchangeably with intolerance. In a sense, any individual who has celiac disease is actually gluten "sensitive". However, the term is used to describe patients who can get a variety of symptoms when they eat gluten and feel better on a gluten-free diet but do not have celiac disease. It is sometimes referred to as "non-celiac gluten sensitivity". There is no mediation by IgE and other auto-antibodies like TTG are not present. The biopsy is normal and there is no damage to the intestine. It is a poorly defined phenomenon and there is no single test to make a diagnosis. It is not known how common this condition is as individuals often diagnose themselves. It is also not clear if this is a permanent problem or whether some may outgrow this over time.

In contrast to these two conditions, celiac disease is an autoimmune disorder in which ingestion of gluten causes damage to the small intestine in genetically susceptible individuals. There is a delayed type of immune reaction, different from an allergic response. Therefore, celiac disease is not considered a typical food allergy. To reinforce the point that there is actual damage to the bowel, celiac disease is also called "gluten-induced enteropathy" (the term *enteropathy* means damage to the small intestine). There is also production of TTG auto-antibody. Celiac disease is a permanent disorder and the patient will not outgrow it although symptoms in response to gluten exposure may become variable over time. The treatment is a strict lifelong adherence to a gluten-free diet.

If individuals have difficulty understanding the concept of gluten intolerance versus sensitivity versus allergy, they should

consult their physician. Self diagnosis and empiric treatment with a gluten-free diet is not recommended.

> O **KEY POINT**
> Celiac disease is an all or none phenomenon. Either the person has it or does not, although the severity of the disease may vary.

TREATMENT

At present, there is no cure for celiac disease. The only treatment for celiac disease is a gluten-free diet. The patient must abstain from ingesting foods and beverages that may contain wheat, rye or barley. This is discussed in detail in the chapter Living with a Gluten-Free Diet.

It is important to keep in mind that the intolerance to gluten in celiac disease is permanent and does not go away over time. Also, gluten should be avoided strictly and with no exceptions. Even small amounts of gluten in the diet can lead to problems. Since the dietary restriction is for life, it is important that a gluten-free diet not be started until the diagnosis is confirmed with an intestinal biopsy.

> O **KEY POINT**
> Adherence to a gluten-free diet must be STRICT and LIFELONG.

Response to a Gluten-Free Diet

Once gluten is removed from the diet, whatever symptoms were present before the diagnosis, begin to improve. The abdominal pain resolves, diarrhoea disappears, energy level improves and weight gain starts. The intestinal damage reverses and eventually normalizes. Most patients feel better in

a few weeks. In others, it may take longer. Children tend to improve rapidly, even within a few days.

If the initial damage to the intestine was severe, recovery can take a long time. In some cases it may take up to two years. The patients should not feel discouraged. Each day should be better than the previous one.

Vitamin and Mineral Supplements

If mineral and/or vitamin deficiencies are present at diagnosis, oral supplementation should be provided. Iron deficiency is the most common abnormality and is easily diagnosed by measuring hemoglobin and serum ferritin. Iron deficiency improves once the gluten-free diet is started. However, dietary lack of iron is also common in our country, especially in women. It would be beneficial to provide iron supplements in therapeutic doses. This should be continued for several months to replenish the iron stores in the body.

Laboratory confirmation of other minerals and vitamin deficiency can be expensive and it may be cost effective to recommend a multivitamin tablet taken daily for a few months. Calcium and vitamin D supplements should be provided if bone disease is present.

Lactose Intolerance

Lactose is a type of sugar (carbohydrate) present in milk and other dairy products. The epithelial cells lining the small intestine secretes an enzyme called *lactase* that digests lactose by breaking it into two smaller components glucose and galactose which are then absorbed in the body by the villi. Lactose intolerance occurs when lactase is absent in the intestines. The unabsorbed lactose enters the colon where the bacteria that are normally present there will break it down. This may result in abdominal pain, bloating, gas and diarrhoea.

Primary (permanent) lactose intolerance is a common genetic condition is which the lactase enzyme is not produced by the intestine. The individuals have to consume a lactose-free diet or take oral supplements of the lactase enzyme when taking dairy products. Secondary (temporary) lactose intolerance can occur in any condition in which the lining of the small intestine is damaged with loss of lactase enzyme production. This can happen in conditions like intestinal infections and celiac disease, to mention a few. In many cases, this is a transient problem and as the intestine heals, the ability to digest lactose recovers.

Some patients with celiac disease may develop secondary lactose intolerance with difficulty in digesting milk and other dairy products. They should avoid dairy products for a few weeks. Milk is one of the best sources of calcium and an oral calcium supplement should be taken if milk is not included in the diet.

Coping with the Diagnosis

The diagnosis of celiac disease can be overwhelming. Patients may feel depressed to learn that they can never eat wheat products again. Feelings of denial, anger and frustration may occur. Many patients feel relieved to eventually find out what is wrong with them after years of suffering. For them, the diagnosis is a blessing.

Coping with celiac disease can be challenging. The following tips may help patients who are newly diagnosed.

- Learn all about celiac disease that you can. Well-informed patients are better able to handle the issues related to their health.

- ❖ Try to be positive. There are few disorders that can be so effectively treated with a diet alone. There are no medications or surgery involved.

- ❖ Involve your family and friends. Educate them about your condition and your dietary needs.

The main issue in celiac disease involves diet and this will be discussed in detail in Chapter 2.

> O **KEY POINT**
> Patients with celiac disease can lead a full and healthy life on a gluten-free diet.

FOLLOW-UP

All patients with celiac disease should have careful follow-up with their physician and dietitian. Most patients feel very well after starting gluten-free diet and may neglect to return to their physician for follow-up.

Regular visits to review symptoms and a complete physical examination to look for any complications are important. Children's height and weight should be monitored regularly to ensure adequate growth. Body mass index (BMI) should be calculated in all patients. The TTG antibody test should be repeated 9 to 12 months after diagnosis at which time it should become negative. A continuously positive test implies ongoing gluten exposure.

Repeat Intestinal Biopsy

There is some controversy as to whether all patients with celiac disease should have a follow-up biopsy to document intestinal

healing. Some gastroenterologists routinely perform a follow-up biopsy in all adults after six to twelve months of starting a gluten-free diet. Others perform the biopsy selectively. In case of ongoing symptoms or if there is any doubt about the diagnosis of celiac disease, a repeat biopsy should be considered. Under the guidelines provided by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition, a routine follow-up biopsy is not recommended in children unless the above-mentioned problems are present.

KEY POINT

Celiac disease is a permanent problem. A person will not "outgrow" it.

Non-Responsive Celiac Disease

Removal of gluten from the diet should lead to improvement in symptoms and resolution of the intestinal damage. This is part of the definition of celiac disease. Although a prolonged period of treatment may be needed to see a response, notable improvement should occur within six months of starting a gluten-free diet. However, in practice this is not always the case. This phenomenon of failure to respond to treatment with a gluten-free diet or the recurrence of symptoms or laboratory abnormalities is called "Non-responsive celiac disease".

Non-responsive celiac disease is a common problem that can affect anywhere from 7 to 30 percent of patients. A limited number of etiologies account for the majority of cases. In non-responsive celiac disease, the following possibilities should be considered.

Wrong Diagnosis!

If an individual with celiac disease does not improve on a strict gluten-free diet, the diagnosis of celiac disease may be incorrect. The changes seen on the intestinal biopsy in celiac

disease are not unique to this disorder. Similar changes can also be seen in other conditions like intestinal infections, inflammatory bowel disease, etc. Therefore, it is important that the diagnosis of celiac disease be firmly established in all cases.

Ongoing Gluten Exposure

Contamination of the diet with gluten is the leading cause of non-responsive celiac disease accounting for a third to half of all cases. There could be several possible reasons for this. There may be hidden gluten in the diet of which the patient is unaware. The patient may be knowingly consuming gluten-containing foods and, for whatever reason, does not tell the physician. (Some patients feel guilty or embarrassed to admit their dietary indiscretions!). Furthermore, patients may think that occasional use or taking small quantities of gluten-containing foods is acceptable.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is the second most common cause of non-responsive celiac disease. This is sometimes referred to as post-inflammatory IBS. Although the intestine heals from the gluten-induced injury, the nerves and muscles of the intestine become “sensitized” (irritable). The patient feels discomfort in response to even normal intestinal contractions. A variety of symptoms including abdominal pain, diarrhoea and constipation can occur. This type of IBS may improve over time.

Lactose Intolerance

As discussed previously under the section Treatment, some individuals with celiac disease develop lactose intolerance. In many cases, this is a temporary problem and as the intestine

heals, the ability to digest lactose recovers. Symptoms include abdominal pain, gas, bloating and diarrhoea. A trial of a lactose-free diet should be considered to see if it helps the symptoms.

Microscopic Colitis

Some individuals with celiac disease develop an autoimmune microscopic inflammation in their colon (colitis). There are two types of microscopic colitis namely *lymphocytic colitis* and *collagenous colitis*. The main symptom in these conditions is severe, watery diarrhoea. An endoscopic examination of the colon (colonoscopy) and biopsies are needed to make this diagnosis. Treatment includes a strict gluten-free diet and in some cases medications.

Pancreatic Insufficiency

Occasionally, a patient with celiac disease develops pancreatic insufficiency, i.e. the digestive function of the pancreas becomes impaired. As mentioned earlier, the pancreas is an organ in the abdomen that produces a variety of enzymes that play a key role in the digestion of food. Hormones released from the upper small intestine stimulate the pancreas to produce these enzymes. With intestinal inflammation induced by gluten, this hormone secretion may become impaired. If the food cannot be digested, it cannot be absorbed. The undigested food leads to diarrhea and subsequent weight loss. In some cases, this pancreatic problem is temporary and improves over time. Pancreatic insufficiency can be effectively treated by taking oral pancreatic enzyme supplements.

Small Bowel Bacterial Overgrowth

The large intestine normally contains many types of bacteria of which the exact function in human health is still being

investigated. However, there are relatively few bacteria in the small intestine. Inflammation and damage can provide an environment for growth of these bacteria, a phenomenon called small bowel bacterial overgrowth. This can lead to diarrhoea and weight loss from malabsorption of fat and other nutrients. Deficiency of iron and vitamin B12 can also occur. Once identified, bacterial overgrowth can be successfully treated by administrating oral antibiotics.

Development of another Autoimmune Disease

Celiac disease is an autoimmune disease and patients are at risk of developing other autoimmune diseases. A common disorder is inflammation of the thyroid gland by an autoimmune mechanism. This problem is called *autoimmune thyroiditis* or *Hashimoto's thyroiditis*. The thyroid a small gland located in the neck and produces hormones which regulate metabolism of our body. They also influence growth and development and affect the function of the heart. When the function of the thyroid gland deteriorates (becomes low or *hypothyroid*), the patient may develop symptoms that resemble those of celiac disease. The most common symptom is excessive fatigue. Constipation and extra weight gain can also occur. Therefore, if a patient on a gluten-free diet continues to have or develops new-onset fatigue without any obvious cause, thyroid disease should be excluded. This can be investigated easily by doing blood tests to assess thyroid function and can be effectively treated with oral thyroid hormone supplementations.

Co-existing Conditions

Celiac disease is common. So are other disorders like acid reflux and functional gastrointestinal diseases like irritable bowel syndrome and dyspepsia (indigestion). It is, therefore, possible that a person with celiac disease may have two

diseases independent of each other. The symptoms of these diseases resemble those of celiac disease.

Management of Non-Responsive Celiac Disease

Careful evaluation of the diet is the first thing that should be done. Often foods that are contaminated with gluten are inadvertently being consumed. Any foods or beverages that cannot be confirmed to be gluten-free should be excluded from the diet. A review with a dietitian is essential. If symptoms still persist, the patient should contact his/her physician to address the above-mentioned causes and also to exclude Refractory Celiac Disease.

Refractory Celiac Disease

Sometimes the terms refractory celiac disease (also called refractory sprue) and non-responsive celiac disease are used interchangeably. However, the diagnosis of refractory celiac disease requires repeat small intestinal biopsy showing persisting abnormalities of celiac disease (*enteropathy*) despite being on a strict gluten-free diet for at least one year with all other causes of ongoing gastrointestinal symptoms excluded. Refractory celiac disease can be present at the time of initial diagnosis, i.e. the patient never improves on a gluten-free diet or it can develop later after the patient has been well for a period of time. Main symptoms are weight loss and diarrhoea.

Refractory celiac disease is rare. The elderly, those with very severe disease and those who do not follow a gluten-free diet seem to be at higher risk. It can be a serious problem that may require medications to suppress the overactive immune system. Some patients develop ulcers in the jejunum (upper part of small intestine) and a small number develop a cancer of the immune system called *lymphoma* in the intestines. Treatment of refractory celiac disease is complicated and these

patients must be managed and followed closely by their gastroenterologist.

Long-Term Complications of Celiac Disease

Celiac disease can be effectively treated with a gluten-free diet and long-term complications are rare. These complications are more commonly seen in patients with unrecognized or poorly treated disease. The two complications of most importance are the development of malignancy and other autoimmune disorders. Regular follow-up is recommended to monitor for these problems.

There is evidence that strict adherence to a gluten-free diet will significantly reduce the risk of long-term complications. Patients should be informed of this as it will provide them with an incentive to remain strictly on the gluten-free diet.

Malignancy

Malignancy (cancer) is one of the most important and serious complications of celiac disease. The risk of developing cancer is significantly higher in patients with celiac disease than the general population. A variety of cancers have been described in celiac disease. The most common type is *non-Hodgkin's lymphoma*. Lymphoma is a malignancy of the cells and organs of the immune system and can involve the T or B lymphocytes. This can involve the intestines, lymph glands or other organs of the body. The best described lymphoma is the *enteropathy-associated T-cell lymphoma* (EATL). Other types of malignancies in celiac disease include those of the thyroid, esophagus and *adenocarcinoma* of the small intestine. Malignancy can occur in children but is extremely rare.

The good news is that the risk of developing a malignancy decreases significantly after being on a strict gluten-free diet for five years.

Autoimmune Disorders

As discussed previously, patients with celiac disease also have a higher risk of developing other autoimmune disorders, most commonly thyroid disease. Other autoimmune disorders like type 1 diabetes may also occur and require careful monitoring.

It is not fully known if a strict gluten-free diet will eliminate the risk of developing another autoimmune disease. There is some evidence that the risk is reduced but more research is needed in this area.

> O **KEY POINT**
>
> Staying on a strict gluten-free diet will reduce the risk of developing any long-term complications of celiac disease.

Curing Celiac Disease

Traditionally, a very simplistic approach has been taken to the management of celiac disease. "You have celiac disease, go home, start a gluten-free diet and you'll be fine", tells the doctor. For many patients this new life is complicated and for them the gluten-free diet is no less than a drug therapy with all its costs and complexities. It must be remembered that celiac disease is a permanent disorder. Although patients feel better on a gluten-free diet, it does not mean that the disease is gone.

Since a highly effective treatment for celiac disease has been available in the form of a gluten-free diet, not much emphasis has been placed on finding a permanent cure for celiac disease. Patients also find the gluten-free diet restrictive and some continue to have symptoms while on the diet likely from unrecognized cross contamination. There would not be a patient who has not wished at one time to go back on a regular diet. This has led researchers to focus on finding a cure for celiac disease.

This chapter will end with a few comments on “curing” celiac disease. Curing celiac disease would imply that a person could eat a regular diet. It is quite unlikely that any of the current research endeavors will be able to find a “cure” in which an unrestricted diet can be consumed forever. What is more likely to happen is that patients may be able to enjoy gluten-containing foods occasionally, on special occasions or during everyday situations when gluten-free products are unavailable.

There are several strategies currently being developed in this regard. The research in this area is difficult to undertake as it requires repeated biopsies of the small intestine of patients to examine the effects of gluten exposure. Some of the highlights of current research in this area include the following:

- Reducing intestinal exposure to gluten by digesting gluten in the food with enzymes before it is ingested or immediately after ingestion.
- Preventing uptake of gluten by the intestines by combining gluten with another compound making it so large that it cannot go across the intestinal epithelium.
- Preventing uptake of gluten by the intestines by blocking the action of *zonulin*, i.e. reducing intestinal permeability.
- Blocking the action of tissue transglutaminase (TTG) enzyme in the intestine.
- Blocking the HLA DQ2/DQ8 receptor in the intestine.
- Modifying the T cell response to gluten or blocking its action in the intestine.
- Developing a vaccine against gluten.
- Engineering strains of wheat that are very low in gluten content.
- Reducing the risk of developing celiac disease by continuing breast feeding and introducing gluten gradually in the baby’s diet.

This all sounds very exciting and promising. It will not be surprising if one day in the future patients with celiac disease will be able to eat a piece of cake or a *samosa*. Until that time, they should remain strictly gluten-free.