The lacrimal and salivary glands, which are by definition involved in Sjögren's syndrome, are exocrine glands. Exocrine glands secrete their products to the outside of the body, in contrast with endocrine glands which deposit their secretions internally in the blood. In addition to the lacrimal and salivary glands, the exocrine glands also include glands in the stomach, intestines, airways (nose, sinuses and lungs), skin and vagina, and the pancreas and prostate. Impaired functioning of the exocrine glands can therefore have an impact on these organs too.

The gastrointestinal tract forms a relatively large part of a human being's insides (see figure 9.1). The most important function of the intestines is the absorption of food and liquid. Why should people with Sjögren's syndrome have gastrointestinal problems?

If we take a look at the medical literature, there is virtually nothing to be found about the combination of Sjögren's syndrome and gastrointestinal disorders. Occasionally you find something about a form of stomach inflammation associated with vitamin B12 deficiency (pernicious anaemia).\(^1,2\) The pancreas is sometimes mentioned, a gland that resembles the salivary glands in certain respects.\(^3-5\) Since little real information is to be found about gastrointestinal disorders associated with Sjögren’s syndrome, it is sometimes assumed that gastrointestinal problems do not occur with Sjögren’s syndrome. Nothing could be less true.

The process of digestion starts in the mouth when you chew your food. Since the quantity and quality of saliva is often poor in Sjögren’s syndrome patients, digestive problems probably begin right here.

Problems that may occur in association with Sjögren's syndrome

**Difficulty in swallowing**

Difficulty in swallowing food can have a variety of causes in Sjögren’s syndrome. One obvious cause is dryness of the mouth and throat. In addition, the function of the oesophagus may also be impaired, not only due to dry mucous membranes but also to disorders in the pattern of contractions in the oesophagus. The cause of this may lie in the muscles themselves or in the nerve fibres that “control” the muscles.

**Chronic atrophic gastritis**

Chronic atrophic gastritis is the medical term for chronic inflammation of the gastric mucosa (lining of the stomach), resulting in a gradual deterioration of the structure and function of the mucosa. This can lead for example to a reduction in the production of gastric acid. This form of inflammation of the gastric mucosa also exists as a separate medical condition, but occurs more commonly in Sjögren’s syndrome patients (maybe as many as 50%) than in the remainder of the
population. However, this generally concerns a mild form without detrimental consequences.\textsuperscript{2,6,7}

**Gastric ulcer**

A gastric ulcer, with or without bleeding, in Sjögren’s syndrome is mainly the consequence of using older types of NSAIDs. This occurs less frequently with the modern variant of NSAIDs, the selective COX-2 inhibitors (coxibs) or the combined use of NSAIDs with proton-pump inhibitors such as omeprazol. NSAIDs are discussed in chapter 5.

**Functional dyspepsia**

Functional dyspepsia (FD) is defined as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of organic, systemic, or metabolic disease that is likely to explain the symptoms.\textsuperscript{31}

Typical dyspeptic symptoms are epigastric pain, early satiety, postprandial fullness and epigastric burning. Bloating, belching, nausea, and vomiting may also occur but are less typical.

It is extremely important to realize that dyspeptic symptoms may be due to underlying peptic ulcer disease and gastroesophageal reflux disease (GERD). Malignancies of the upper gastrointestinal tract and celiac disease are less common but also important causes of dyspeptic symptoms.\textsuperscript{30}

In patients with Sjögren’s syndrome, the prevalence of FD was 65% as compared to 39% (!) in healthy controls.\textsuperscript{28}

**Impaired gastric emptying and gastroparesis**

Impaired gastric emptying (IGE) and gastroparesis are defined on the basis of the time from the ingestion of a bolus of food until 50% of the bolus has been cleared from the stomach and/or the bolus is beginning to be cleared from the stomach. Gastroparesis is the more severe variant of impaired gastric emptying.\textsuperscript{30}

IGE may be a symptom of an underlying disease such as diabetes mellitus or hypothyroidism. If no underlying cause is found, it is considered to be one of the many functional bowel disorders, in particular functional dyspepsia (see above). However, most studies failed to find a convincing relationship between delayed gastric emptying and symptom pattern.\textsuperscript{30}

Hammar et al.\textsuperscript{29} found that 43% of patients with Sjögren’s syndrome showed signs of IGE, while 29% fulfilled the criteria for gastroparesis. Objective signs of IGE in Sjögren’s syndrome were associated with increased ESR and IgG, and the presence of rheumatoid factor. Impaired gastric emptying was, however, poorly associated with autonomic dysfunction and gastrointestinal symptoms.

**Coeliac disease**

Coeliac disease is a disease of the small bowel characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to dietary gluten and which demonstrate improvement after withdrawal of gluten from the diet.

**Forms of coeliac disease**

The availability of serologic testing (see below) for coeliac disease and the common use of upper endoscopy has complicated the definition, since these tests have identified patients who appear to have the disease but have variable degrees of histopathologic changes and/or symptoms. Thus, several categories of coeliac disease have emerged. Whether these phenotypes are clinically useful remains to be determined.\textsuperscript{32}

- the **classical form**: fully developed villous atrophy and features of intestinal malabsorption
- the **atypical form**: fully developed villous atrophy in the setting of milder clinical features such as iron deficiency, osteoporosis, short stature, and/or infertility. Despite the historical title of “atypical”, this form is the most common.

- the **silent form** in which villous atrophy is found after testing asymptomatic patients (e.g., because of a family history of celiac disease or during an upper endoscopy performed for another reason).
- a **potential form** in those who have never had a biopsy consistent with coeliac disease, but show serologic and/or immunologic abnormalities characteristic for the disorder. This is most often detected in patients with a family history of coeliac disease.
- a **latent form** in patients who had a previous diagnosis of coeliac disease that responded to gluten withdrawal but retained normal villous architecture after gluten reintroduction. The latent form also refers to patients with elevated IgA tTG serology but normal intestinal mucosa who may subsequently develop coeliac disease.

The natural history of these various forms of coeliac disease is incompletely understood. In particular, the long-term risk of complications in patients who are asymptomatic is unclear. Such patients may also be least likely to comply with a gluten free diet.
Gluten and gliadin
Gluten in food plays an important role in causing the abnormalities seen in coeliac disease. Gluten is the protein content of wheat, barley and rye. Gliadin is the alcohol soluble fraction of gluten. Gliadin consists of large peptides that cannot be degraded by gastric and pancreatic proteases. The enzyme tissue transglutaminase deaminates the gliadin peptides thereby increasing the immunogenic properties.

Prevalence
Coeliac disease affects about 1% of the population, but only 10-15% of them have been diagnosed. Only people with particular HLA-antigens (HLA-DQ2 or HLA-DQ8) can acquire coeliac disease but the manifestation of the disease also depends on many other variables. Children who have had breast feeding have a lower risk, whereas the introduction of gluten in the food before the age of 4 months or after the age of 7 months increases the risk. Intestinal infections such as with rotavirus also increase the risk of developing coeliac disease.

Symptoms
Classical symptoms are diarrhoea, weight loss, or symptoms that suggest malabsorption or anaemia. Patients with atypical form of disease may present with nonspecific abdominal pain, oesophageal reflux, osteoporosis, elevated serum transaminases levels, insulin dependent diabetes mellitus, or neurological symptoms.

Diagnosis and serology
Almost all patients with atypical presentation have serum antibodies to tissue transglutaminase (tTG) but of people with antibodies to tTG, only a minority has coeliac disease. Therefore, a definite diagnosis of coeliac disease requires a biopsy of the small intestine in this situation. On the other hand, a negative test for anti-tTG in a patient with atypical symptoms is sufficient to exclude coeliac disease.

In a patient with classical symptoms (see above), a small intestine biopsy is always necessary to diagnose or exclude coeliac disease as anti-tTG can be positive or negative.

Diseases associated with coeliac disease
Dermatitis herpetiformis is a skin disease with pruritic papulovesicles over the external surface of the extremities and on the trunk. The diagnosis is confirmed histologically by the demonstration of granular IgA deposits along the nonaffected subepidermal basement membrane. The majority of patients have anti-tTG antibodies. Dermatitis herpetiformis occurs in up to a quarter of patients with coeliac disease. Both diseases are associated with the same HLA-antigens (see before). Coeliac disease in patients with dermatitis herpetiformis is often asymptomatic, but the skin lesions in most patients respond to gluten withdrawal.

Coeliac disease is closely associated with diabetes mellitus type 1. About 5 percent of adults with type 1 diabetes have biopsy proven coeliac disease but many have no overt clinical manifestations. The age of onset and the severity of diabetes do not appear to be influenced by the presence of coeliac disease. Whether a gluten-free diet improves diabetes in diabetic patients with celiac disease is unclear.

Coeliac disease has been detected in up to 8 percent of patients with selective IgA deficiency. Selective IgA deficiency occurs in 1-2 percent of patients with coeliac disease.

The prevalence of biopsy proven coeliac disease in Down syndrome has been reported to be as high as 16 percent.

Coeliac disease may be associated with nonspecific mild chronic elevation in ASAT and ALAT levels. Biopsy proven coeliac disease may account for 4 percent of abnormal liver function tests of unexplained etiology.

There is an increased incidence of autoimmune thyroid disease among patients with coeliac disease. Hypothyroidism is more frequent than hyperthyroidism.

Women with untreated coeliac disease may have an increased frequency of menstrual abnormalities (later menarche, earlier menopause) and infertility. Treatment of celiac disease appears to prevent these problems.

Coeliac disease, which is often clinically unsuspected, may account for as many as 5 percent of patients with autoimmune myocarditis or idiopathic dilated cardiomyopathy. Cardiac function improved following a gluten-free diet.

Oral lesions (erythema or atrophy) and a soreness or burning sensation of the tongue have been described in association with coeliac disease and respond to a gluten-free diet.

Sjögren’s syndrome and coeliac disease
A Finnish study found that coeliac disease could be diagnosed in 5 of 34 (14.7%) Sjögren’s syndrome patients. In a recent Canadian study, this was the case in 5 of 50 (10%) Sjögren’s syndrome patients.

Prognosis
Untreated coeliac disease is associated with high morbidity and increased mortality.
**Hypersensitivity and intolerance to food**

Hypersensitivity and intolerance to food are subjects about which little is known and which is difficult to manage from both the doctor and patient’s point of view. Problem centre round the fact that certain foods are not tolerated. This means that consumption of the food in question can cause symptoms such as nausea, diarrhoea, pain, dizziness or skin reactions (itching, hives). Since scarcely any tests exist that prove the association between a specific food and symptoms, many patients simply exclude the suspect food from their diet and then wait and see whether the symptoms subside. If it is at matter of just one food, this method can be successful, but it is frequently a question of a large number of food items.

The exact ingredients of food products are by no means always known and the symptoms do not always occur every time the food in question is consumed. This often leads to doubt by doctors concerning the association between the food and the symptoms. It would seem that intolerance to certain foods, for whatever reason, occurs more commonly than normal in patients with Sjögren’s syndrome.

Although nothing is certain, there is a possible explanation. Mucous membranes play a protective role. Since Sjögren’s syndrome causes problems with mucous membranes in general, it is not unreasonable to assume that there could also be problems with the intestinal mucosa. This would result in the intestinal wall having closer contact with substances in the intestines than is normally the case. This may also play a role in the more common occurrence of hypersensitivity to medicines in Sjögren’s syndrome patients.

**Colitis**

Colitis (inflammation of the large intestine) can be the result of infection with *e.g.* salmonella or shigella) bacteria. There are also forms of colitis where the cause is unknown such as colitis ulcerosa and colitis in Crohn’s disease. The term "spastic colitis" was formerly used to describe the condition which is now known as irritable bowel syndrome (see below). The name spastic colitis is misleading, however, since IBS is not an inflammatory condition of the large intestine (colon). Diverticulitis (inflammation of diverticula, pockets in the wall of the intestine) will be discussed at the end of this chapter.

**Constipation**

So far no publications are to be found in the medical literature in which constipation is associated with Sjögren’s syndrome. When recording the symptoms of patients diagnosed with Sjögren’s syndrome, it is striking that constipation symptoms often coincide with the start of other complaints. The problem is a complex one however, and it is therefore a good idea to first take a look at some of the causes of constipation.

**Causes of constipation**

*a. too little moisture in the intestines*

For normal soft bowel movements, stools should contain sufficient moisture. A diet with sufficient fibre plays an important role since fibre retains water. It may be deduced from this that constipation can occur as a result of too little dietary fibre or too little fluid in the intestines.

Table 9.1 shows how much fluid enters our gastrointestinal tract and what happens to it. Normally around 2 litres of fluid enter the body in the form of food and drink. The salivary glands add a further 1.5 litres, the stomach 2.5 litres, bile 0.5 litre, the pancreas 1.5 litres and the intestines themselves another 1 litre. This brings the total daily fluid intake in the gastrointestinal tract to around 9 litres. Remarkably little of this disappears via faeces; most of it is reabsorbed into the body. It is the large intestine that plays the most important role in this absorption process.

Although no data are available on how much fluid enters the gastrointestinal tract of patients with Sjögren’s syndrome, it may reasonably be assumed that this is considerably less than normal due to the impaired function of the intestinal exocrine glands.

On the other hand, patients with Sjögren’s syndrome will usually drink far more than normal due to dryness of the mouth and this may compensate to a certain extent for the consequences of the impaired function of the exocrine glands.

*b. abnormalities of intestinal muscle tissue*

Muscles are classified into striated muscle (including muscles that we consciously use for movement),

| Table 9.1 Amounts of fluid that enter and leave the gastrointestinal tract each day |
|-----------------|------------------|-----------------|
| **in (ml)**     | **out (ml)**     |
| food            | 2000             | reabsorption by intestine 8900 |
| saliva          | 1500             | faeces 100 |
| gastric juices  | 2500             |                |
| bile            | 500              |                |
| pancreatic juices | 1500          |                |
| intestinal juices | 1000           |                |
| **total**       | 9000             | 9000           |
smooth muscles (e.g. in intestines and blood vessels which do everything automatically) and heart muscle. The smooth muscle in the intestines plays an important role in moving food along the intestinal tract. These peristaltic movements are coordinated contractions that propel the food forward. This concerted propulsion is controlled by the (autonomous or involuntary) nervous system. It is not inconceivable to suspect that these contractions are not adequately coordinated in some Sjögren’s patients, giving rise to symptoms such as difficulty in swallowing, nausea, vomiting and perhaps also constipation. Inflammation of the smooth muscles possibly plays a subordinate role.

**c. impaired thyroid gland function**

A number of different thyroid disorders occur more frequently than normal in patients with Sjögren’s syndrome, probably in one-third.12,13 An underactive thyroid gland can be the cause of constipation and fatigue. Generally speaking, problems caused by an impaired thyroid gland are simple to treat with medication, but they first need to be diagnosed.

**d. medicine**

Medicine can be a significant cause of constipation and other gastrointestinal disorders. Codeine, for example, is a medication used in small quantities to treat a tickling cough. Patients with Sjögren’s syndrome are particularly susceptible to a tickling cough due to dryness in the throat. Too much or too frequent use of cough mixtures containing codeine can result in constipation.

It is less well-known, however, that many drugs used to treat inflammatory conditions of e.g. joints (the pros ta glandin synthesis inhibitors) often cause constipation as a side-effect (sometimes days later). This is no reason for not using these drugs, but it is useful to know about this side-effect. The same type of medication can also cause inflammation of the gastric mucosa (lining of the stomach) and sometimes gastric ulcers. Inflammation of the gastric mucosa and gastric ulcers can sometimes be the cause of constipation.

Drugs that contain aluminium or calcium salts can also cause constipation. Some antidepressants can cause constipation, in addition to exacerbating dryness of the mouth.

**Diarrhoea**

Intestinal infections are a well-known cause of diarrhoea. Food is a source of bacterial infection in the intestines. Food may already be contaminated when you buy it in the shop. Bacteria may increase to dangerous levels if food is kept too long (bacteria can also multiply in the refrigerator, albeit more slowly than at higher temperatures). Gastric acid is normally an important barrier against intestinal infection because many bacteria are unable to multiply further after spending time in the acid environment of the stomach.

Some Sjögren’s patients are unable to secrete gastric acid (achlorhydria), or use medication that either neutralises the acid or inhibits its production. In both situations bacteria in the food can pass through the stomach unhindered and then multiply. This means that all those who are unable to produce gastric acid or who take antacid medication run a greater risk of intestinal infections when consuming food containing excessive bacteria. To avoid problems, meat such as chicken or pork - which are often infected - should be thoroughly cooked before consumption.

Some people are unable to tolerate certain foods, without there being any clear reason why, and diarrhoea may be one of the consequences. If there is a clear link between the diarrhoea and consumption of the food, the food item in question can usually be avoided to prevent any recurrence.

Coeliac disease was discussed at the beginning of this chapter as a cause of diarrhoea.

Impaired function of the pancreas can also cause diarrhoea, particularly due to the fact that as a result of an enzyme deficiency fat is inadequately absorbed into the body and consequently has the effect of a dose of castor oil on the large intestine. This leads to diarrhoea and weight loss. Research has shown that in many Sjögren’s syndrome patients the pancreas does not function 100%, but usually causes no problems.

Inflammation of the large intestine (colitis) has already been mentioned as a possible cause of diarrhoea. Blood and/or mucus often occur in the stools and this is an important signal for further investigation to exclude the possibility of bowel cancer for instance.

**Irritable bowel syndrome**

Irritable bowel syndrome (IBS) is a functional bowel disorder in which the key symptom of abdominal pain or discomfort is associated with defecation or a change in bowel habit, and with features of disordered defecation.16,22 IBS was previously called spastic bowel or spastic colitis but these terms should be avoided.

Functional bowel disorders are identified only by symptoms.

Subtypes of IBS are recognized by predominant stool pattern such as hard or lumpy stools, loose or watery stools, mixed and unsubtyped stools. The Rome III diagnostic criteria allow the diagnosis in patients with recurrent abdominal pain or discomfort (= uncomfortable sensation not described as pain) at
least 3 days per month in the last 3 months associated with 2 or more of the following:
- improvement with defecation;
- onset associated with a change in frequency of stool;
- onset associated with a change in form (appearance) of stool.
Supportive symptoms that are not part of the diagnostic criteria include abnormal stool frequency, abnormal stool form, defecation straining, urgency, or also a feeling of incomplete bowel movement, passing mucus, and bloating.16 Heartburn, fibromyalgia, headache, backache, urinary symptoms, and others are often associated with IBS, but are not useful in diagnosing it.16 The course of IBS is uncomplicated but symptoms may vary at different periods.

Constipation increases the risk of diverticulae in the sigmoid. Diverticulae may become inflamed (diverticulitis), thereby causing severe disease.

Few tests are required for patients who have typical IBS symptoms and no alarm features. Alarm symptoms such as fever, gastrointestinal bleeding, weight loss, anaemia, abdominal mass are not due to IBS but may accompany it.23

The cause of IBS is unknown but it is suggested that IBS, like fibromyalgia and interstitial cystitis (bladder pain syndrome, see chapter on urogenital disorders), belongs to the central pain syndromes in which disease manifestation depends on a genetic background and environmental stressors such as peripheral pain due to inflammation or to infections.14

IBS occurs in 3-15% of the population. It generally starts in adulthood and is diagnosed 4x more frequently in women than in men. IBS clearly aggregates within families and first-degree relatives of IBS patients are twice as likely to have IBS as control subjects.27 Twin studies suggest a strong environmental contribution to IBS but no significant genetic contribution.15 In patients with Sjögren’s syndrome, IBS has been found in 39-65% as compared to 9-15% in healthy controls.28,33 Treatment consists of explanation as to why symptoms occur, adapting diet and lifestyle, or drug therapy.

Dietary fibre for IBS is poorly substantiated by clinical trials. Bran may exacerbate flatulence and not relieve pain.24,25

Drug therapy is directed towards the dominant symptoms. Examples are loperamide or cholestyramine (IBS with diarrhoea), psyllium or lactulose (IBS with constipation) and smooth-muscle relaxants, tricyclic antidepressants or selective serotonin reuptake inhibitors (IBS with abdominal pain).

The possible beneficial effect of probiotics is not yet established. Excellent guidelines for the management of IBS have recently been published by the British

---

**Table 9.2 Adaptation of diet and lifestyle in irritable bowel syndrome**

<table>
<thead>
<tr>
<th>high-fibre “bulk”-forming foods</th>
<th>bran, psyllium: gradually increase the quantity and drink plenty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- fibre binds moisture: liquid stools become more solid, while hard stools become softer</td>
</tr>
<tr>
<td></td>
<td>- in 20%: first an increase in symptoms, after several weeks an improvement</td>
</tr>
<tr>
<td><strong>do not postpone an urge to defecate</strong></td>
<td>get into the habit of going to the toilet at a regular time (after breakfast)</td>
</tr>
<tr>
<td><strong>diet</strong></td>
<td>symptoms may be exacerbated by coffee, sorbitol (sweetener), milk products, certain vegetables, cabbage</td>
</tr>
<tr>
<td><strong>change your lifestyle</strong></td>
<td>eat regularly, physical exercise, relaxation</td>
</tr>
<tr>
<td><strong>particular symptoms</strong></td>
<td><strong>abdominal pain</strong>: if necessary smooth-muscle relaxants, tricyclic antidepressants or selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td></td>
<td><strong>diarrhoea</strong>: if necessary (for preventive and occasional use): loperamide or cholestyramine</td>
</tr>
<tr>
<td></td>
<td><strong>constipation</strong>: if necessary psyllium or lactulose; in general, fibre increases bloating; constipation may be treated with magnesium oxide tablets of 500 mg, 1-5x daily</td>
</tr>
<tr>
<td><strong>flatulence</strong></td>
<td>- eat slowly</td>
</tr>
<tr>
<td></td>
<td>- do not chew chewing-gum</td>
</tr>
<tr>
<td></td>
<td>- do not drink carbonated drinks or drinks containing caffeine</td>
</tr>
<tr>
<td></td>
<td>- do not use artificial sweeteners (sorbitol)</td>
</tr>
<tr>
<td></td>
<td>- do not eat cabbage</td>
</tr>
</tbody>
</table>
Diverticula are pocket-like openings in the intestinal wall. The occurrence of diverticula is called diverticulosis (see figures 9.2 and 8.3). They most frequently occur in the sigmoid colon and especially at points where the blood vessels enter the intestine (weak points). It is estimated that 20-50% of the population over the age of 50 years in the western world have diverticula. Low-fibre diet and constipation increase the risk of diverticulosis.

The term diverticulitis is used when the diverticula become inflamed. This is probably caused by faecal residue in the diverticula, resulting in poor blood supply to the diverticula and allowing intestinal bacteria to set up inflammation of the diverticular wall. The symptoms of diverticulitis depend on the severity of the inflammation. They may consist of fever, pain in the lower left abdomen and blood in the stools.17,18

The development of diverticulitis and diverticulosis has no direct link with Sjögren’s syndrome. Nevertheless, the possibility cannot be excluded that diverticula may occur slightly more frequently in patients with Sjögren’s syndrome than normal, perhaps because Sjögren’s patients suffer more commonly from constipation, due on the one hand to the disease itself and on the other to the use of anti-inflammatory drugs (the prostaglandin synthesis inhibitors).

Treatment of diverticulitis in Sjögren’s syndrome is the same as in people without Sjögren’s syndrome. In addition, a high-fibre diet is important to prevent constipation.19

Muscarinic M3-receptors (see chapter 3) play a role in the contraction of the muscles in the intestinal tract and urinary bladder. It is therefore possible that antibodies to M3-receptors, that are now known to cause dryness of the eyes and mouth in Sjögren’s syndrome, may also affect the functioning of the intestines and bladder.

References
32. Kelly CP. Diagnosis of celiac disease. Uptodate 2009; v17.3.

<table>
<thead>
<tr>
<th>Latest additions or modifications (date: dd.mm.yyyy)</th>
<th>date</th>
<th>addition/modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.09.2010 data on functional dyspepsia, impaired gastric emptying and gastroparesis; references 28-31</td>
<td>21.09.2010</td>
<td>data on functional dyspepsia, impaired gastric emptying and gastroparesis; references 28-31</td>
</tr>
<tr>
<td>22.09.2010 information on coeliac disease extended</td>
<td>22.09.2010</td>
<td>information on coeliac disease extended</td>
</tr>
<tr>
<td>03.10.2010 information on irritable bowel syndrome updated</td>
<td>03.10.2010</td>
<td>information on irritable bowel syndrome updated</td>
</tr>
</tbody>
</table>