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Endocrinological Disorders and Celiac Disease

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Celiac disease is a permanent intolerance to dietary gluten. Its well known features are abdominal symptoms, malabsorption of nutrients, and small-bowel mucosal inflammation with villous atrophy, which recover on a gluten-free diet. Diagnosis is challenging in that patients often suffer from subtle, if any, symptoms. The risk of clinically silent celiac disease is increased in various autoimmune conditions. The endocrinologist, especially, should maintain high suspicion and alertness to celiac disease, which is to be found in 2–5% of patients with insulin-dependent diabetes mellitus or autoimmune thyroid disease. Patients with multiple endocrine disorders, Addison's disease, alopecia, or hypophysitis may also have concomitant celiac disease. Similar heredity and proneness to autoimmune conditions are considered to be explanations for these associations. A gluten-free diet is essential to prevent celiac complications such as anemia, osteoporosis, and infertility. The diet may also be beneficial in the treatment of the underlying endocrinological disease; prolonged gluten exposure may even contribute to the development of autoimmune diseases. The diagnosis of celiac disease requires endoscopic biopsy, but serological screening with antiendomysial and antitissue transglutaminase antibody assays is an easy method for preliminary case finding. Celiac disease will be increasingly detected provided the close association with autoimmune endocrinological diseases is recognized. (*Endocrine Reviews* 23: 464–483, 2002)

Abbreviations: AIDDM, Autoimmune insulin-dependent diabetes mellitus; BMD, bone mineral density; GAD, glutamate decarboxylase antibodies associated with diabetes; HLA, human leukocyte antigen; MMP, matrix metalloproteinase.

I. Introduction

A. Celiac disease

CELIAC DISEASE, OR gluten-sensitive enteropathy, is an autoimmune disorder characterized by inflammation, villous atrophy, and crypt hyperplasia of the small-bowel mucosa. The mucosal lesion develops in genetically susceptible individuals after ingestion of dietary gluten and recovers when gluten-containing cereals, wheat, rye, and barley, are withdrawn from the diet (1). Population-based screening studies have shown that at least 0.5% of adults in Western countries suffer from the disease (2). Patients may present with only subtle, if any, symptoms (3), which is the main reason why the disease is highly underdiagnosed in the United States and elsewhere (4, 5). This notwithstanding, the disease should be detected as early as possible, because untreated celiac disease is associated with many, even severe, complications such as intestinal lymphoma or cancer (6) and osteoporosis (7).

B. Why should endocrinologists recognize celiac disease?

The disease is generally considered to affect mainly the gastrointestinal tract. Recent evidence has shown, however, that the condition may also involve a number of extraintestinal manifestations, and patients may thus be referred initially to specialists other than gastroenterologists. Circulating antibodies against gliadin, endomysium, and tissue transglutaminase are typical for the condition, and the development of sensitive and specific antibody assays (8) makes it easy to screen for celiac disease, especially in cases where typical gastrointestinal symptoms are not obvious.

Endocrinologists should consider celiac disease in different autoimmune conditions where the prevalence of the condition is distinctly higher than in the general population.

Symptoms suggestive of celiac disease should be recognized and should signal the need for further examinations. This article summarizes what is currently known about the association between various endocrinological diseases and celiac disease.

II. Diagnosis and Serological Screening of Celiac Disease

In untreated celiac disease the characteristic abnormalities in the small-bowel mucosa are villous atrophy, crypt hyperplasia, and an increased density of inflammatory cells in the epithelium and lamina propria (Fig. 1). This type of lesion is nowadays uncommon in other conditions (9). The mucosal lesion recovers with a gluten-free diet and deteriorates further if the patient resumes a gluten-containing diet (1). At the present time, a small intestinal biopsy is almost invariably taken with biopsy forceps by upper gastrointestinal endoscopy, but devices are also available by which to obtain biopsies in fluoroscopy.

The current diagnostic criteria comprise the finding of typical mucosal lesion, and the introduction of a gluten-free diet should result in clinical or histological recovery. The occurrence of further mucosal deterioration upon gluten challenge was earlier recommended to distinguish the condition from other diseases causing villous blunting (10); this is no longer necessary except in cases where the diagnosis has remained inconclusive (11).

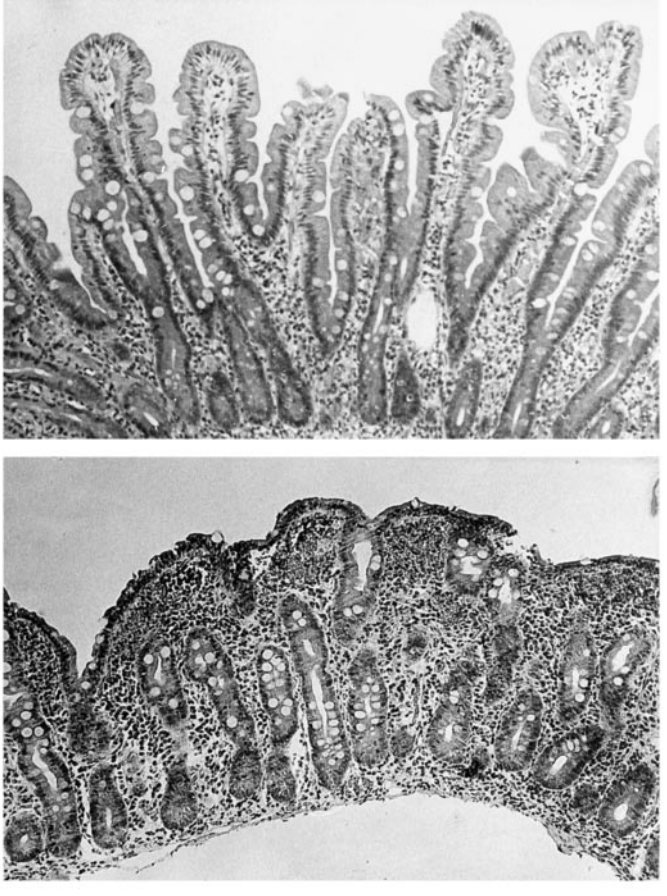

FIG. 1. *Top*, Normal small-bowel biopsy with finger-like villi. *Bottom,* Small-bowel biopsy from a patient with celiac disease showing villous atrophy and hypertrophy of crypts.

The occurrence of circulating antibodies against gliadin or intestinal matrix further supports a diagnosis of celiac disease. Various antibody assays have been developed to select patients for diagnostic small-bowel biopsy. Antireticulin (10) and antigliadin (12) antibodies were the first tests to be employed in screening, the latter still being widely in use. In the context of celiac screening in asymptomatic patients and in various risk groups, however, the benefits of the more recent IgA class antiendomysial antibody test (13, 14) and the latest antitissue-transglutaminase test (15, 16) would now seem obvious (Table 1).

First, the specificity of these tests is close to 100%, and the sensitivity is high enough for screening purposes. Antiendomysial antibody is a somewhat observer-dependent immunofluorescence test, whereas the antitissue transglutaminase antibody test is based on ELISA and is obviously easier to interpret and more suitable for large screening programs than the antiendomysial antibody. Both tests can well be applied in screening for celiac disease in patients with various endocrinological disorders, and the two can also be combined. A positive test result should always be confirmed by small-intestinal biopsy. However, 2–3% of patients with celiac disease have selective IgA deficiency (22, 23) and hence remain negative for IgA class gliadin and antiendomysial and antitissue transglutaminase antibodies; IgG class gliadin antibodies or serum total IgA can be applied in screening of these cases (23).

The small-bowel lesion develops gradually from mucosal inflammation to crypt hyperplasia and villous atrophy (24). A body of evidence shows that sometimes in cases where the first biopsy is normal or nondiagnostic, celiac disease can sometimes be observed subsequently when patients have continued on a gluten-containing diet (25–28). Thus, a normal small-bowel biopsy does not necessarily exclude celiac disease for life. Especially antiendomysial antibody-positive patients without villous atrophy, and relatives of celiac disease patients, seem to harbor this latent form of the condition (29, 30).

III. Common Manifestations of Celiac Disease

A. Typical symptoms

The classical features of celiac disease are well recognized. In small children, abnormal stools, steatorrhea, and abdominal distention may occur. Poor growth and failure to thrive are the most typical symptoms, and growth curves may reveal the condition early. In children aged 2 yr or more, symptoms appear to be milder and resemble those observed in adults (31). Subclinical isolated nutrient deficiencies may occur, and bone mineral density (BMD) may be impaired even in childhood (32). In adults, celiac disease typically produces diarrhea or steatorrhea, malaise, and weight loss. Abdominal distension after meals is a common, albeit unspecific symptom; only rarely do patients notice a relationship between the abdominal complaints and the ingestion of cereals (9). Symptoms that suggest the diagnosis of celiac

TABLE 1. The sensitivity and specificity of serological tests in the diagnosis of celiac disease

	Sensitivity (%)		Specificity (%)	
	Median	Range	Median	Range
IgA gliadin antibodies	87	31–100	85	82–100
IgA antiendomysial antibodies	93	85–100	100	95–100
IgA antitissue transglutaminase antibodies	95	92–98	95	94–99

Data from Refs. 15–21.

disease are bloating flatulence, chronic diarrhea, and lactose malabsorption. A great variety of malabsorption may exist, including anemia due to deficiency of iron or folic acid, and less commonly of cobalamin; serum calcium and fat-soluble vitamins D (7, 33), and less often K (34), may be low. Weight loss and fatigue may occur; however, even constipation, overweight, or obesity do not exclude celiac disease (9).

These common modes of presentation have remained, by and large, the same since 1960, but overall there has occurred, both in children and adults, a shift toward milder symptoms (35). Steatorrhea and profuse diarrhea are relatively rare, whereas patients often suffer only from occasional loose stools. Malabsorption may be subclinical, and severe forms are infrequent. Some celiac patients may experience abdominal discomfort mimicking irritable bowel syndrome (36).

Symptoms usually disappear on a gluten-free diet within a few weeks, whereas the recovery of the small-bowel mucosa may take much longer, 1 yr or even more. Apparently, a gluten-free diet often alleviates abdominal symptoms even in nonceliac patients (37). Hence, all approaches to detect celiac disease by dietary interventions are to be strongly discouraged: subsequently, the diagnosis may be difficult to establish, because possible mucosal lesions may have recovered as a result of gluten withdrawal.

Since the development of serological screening tests for celiac disease, it has become evident that the symptoms described above constitute only a minor component in the concept of celiac disease (29, 38). In many, perhaps in the majority of cases, celiac disease remains clinically silent, or symptoms emerge outside the gastrointestinal tract.

B. Extraintestinal and atypical symptoms

The recognition of atypical and clinically silent celiac disease has resulted in a marked increase in the incidence of the condition. Consequently, the overall prevalence of celiac disease in the population seems to be 0.5–1.0%—not less than 0.1% as was thought 20 yr ago (2). In first-degree relatives of celiac patients the risk is at least 10-fold (39, 40). The best known extraintestinal manifestation is dermatitis herpetiformis, an itching papulovesicular skin disease appearing predominantly at the knees, elbows, and buttock. Granular IgA deposition in the papillary dermis of the uninvolved skin is diagnostic for the condition (41). All untreated patients also evince at least some degree of small-bowel mucosal inflammation or atrophy, and both the skin symptoms and the mucosal lesion resolve on a gluten-free diet (42). The occurrence of autoimmune disorders in dermatitis herpetiformis is similar, by and large, to that in celiac enteropathy (43). Dermatitis herpetiformis is today considered one form of the celiac trait rather than an associated disease.

Recurrent oral aphthous ulcerations and enamel defects in the permanent teeth may be the only presenting manifestations of celiac disease (44). Neurological symptoms include peripheral neuropathy, memory loss, and ataxia (45). Sjögren's syndrome, nonspecific arthritis, and arthralgia have been described in connection with celiac disease (44).

Osteoporosis and infertility can be considered complications of celiac disease, because they are at least partially reversible on a gluten-free diet. In addition, a number of endocrinological autoimmune diseases, as reviewed below, belong to the category of celiac disease associations.

IV. Endocrinological Conditions Associated with Celiac Disease

A. Autoimmune insulin-dependent diabetes mellitus (AIDDM)

More than 30 yr ago, the association between celiac disease and AIDDM was recognized, especially by pediatricians. It was estimated that 1.0–1.5% of diabetic children suffered from celiac disease (46, 47). In these early reports, patients usually presented with classical symptoms such as steatorrhea, malabsorption syndrome, diarrhea, and failure to thrive. The metabolic control of diabetes mellitus was generally poor, and episodes of hypoglycemia were frequent (48). Diarrhea may easily have been misinterpreted as due to autonomic diabetic neuropathy or exocrine pancreatic insufficiency, and the diagnosis of celiac disease was therefore sometimes delayed. There also may have been confusion as to the etiology of villous atrophy, which might have been thought to be a direct complication of AIDDM instead of untreated celiac disease. In the absence of serological screening tests, celiac disease was invariably suspected only on the basis of overt symptoms, this obviously leading to underestimation of the frequency of the disease.

As to celiac disease, the frequency of AIDDM has been 1.4–3.5% (49–51), and in the latest studies somewhat higher, 5.4–7.4% (38, 52, 53).

After the introduction of serological antibody tests, a number of studies have been carried out to assess the frequency of celiac disease in patients with AIDDM. Virtually all have shown an increased frequency of the disorder compared with that (0.5–1.0%) in the population in general (Table 2). The prevalence figures shown here are based on biopsy-proven cases, and there are always some subjects with positive serological tests who will refuse the diagnostic small-bowel biopsy. There may be, on the other hand, some publication bias in favor of an increased frequency of celiac disease. Nevertheless, we can assume that approximately 4% of patients with AIDDM have concomitant celiac disease. Almost

TABLE 2. Serological screening studies on the prevalence of celiac disease in patients with AIDDM

Authors (Ref.)	Country	n	Screening method	Clinical celiac disease detected before screening (n)	Celiac disease detected by screening (n)	Overall prevalence of celiac disease n (%)
Boudraa *et al.,* 1996 (54)	Algeria	116 children	AGA,[a] EmA[b]	3	16	19 (16.4)
Gadd *et al.,* 1992 (55)	Australia	180 children	AGA	0	4	4 (2.2)
Verge *et al.,* 1994 (56)	Australia	273 children	AGA, EmA	0	5	5 (1.8)
Schober and Granditsch, 1994 (57)	Austria	164 children	AGA	0	0	0 (0.0)
Schober *et al.,* 2000 (58)	Austria	403 children	AGA, EmA	0	6	6 (1.5)
De Block *et al.,* 2001 (59)	Belgium	399 children and adults	EmA	0	3	3 (0.8)
Fraser-Reynolds *et al.,* 1998 (60)	Canada	236 children	EmA	0	12	12 (5.0)
Gillett *et al.,* 2001 (61)	Canada	233 children	EmA, tTg-ab[c]	4	14	18 (7.7)
Sumnik *et al.,* 2000 (62)	Czech	345 children	EmA	0	14	14 (4.1)
Hansen *et al.,* 2001 (63)	Denmark	106 children	AGA, EmA, tTg-ab	2	9	11 (10.4)
Mäki *et al.,* 1984 (64)	Finland	215 children	ARA	0	4	4 (2.3)
Savilahti *et al.,* 1986 (65)	Finland	201 children	AGA, ARA[d]	0	7	7 (3.5)
Collin *et al.,* 1989 (66)	Finland	195 adults	AGA, ARA	0	8	8 (4.1)
Kontiainen *et al.,* 1990 (67)	Finland	141 children	AGA, ARA	0	3	3 (2.0)
Saukkonen *et al.,* 1996 (68)	Finland	776 children	AGA, ARA	1	18	19 (2.4)
Koletzko *et al.,* 1988 (69)	Germany and Switzerland	1032 children	AGA	8	2	10 (1.0)
Kordonouri *et al.,* 2000 (70)	Germany	520 children	AGA, EmA, tTg-ab	0	9	9 (1.7)
Seissler *et al.,* 1999 (71)	Germany	305 children and adults	tTg-ab	0	5	5 (1.6)
Cronin *et al.,* 1997 (72)	Ireland	101 adults	EmA	0	5	5 (4.9)
Cacciari *et al.,* 1987 (73)	Italy	146 children	AGA	0	5	5 (3.4)
Barera *et al.,* 1991 (74)	Italy	498 children	AGA	0	16	16 (3.2)
Sategna-Guidetti *et al.,* 1994 (75)	Italy	383 adults	EmA	0	10	10 (2.6)
Pocecco and Ventura, 1995 (76)	Italy	4154 children	AGA	14	108	122 (2.7)
Nosari *et al.,* 1996 (77)	Italy	138 children	AGA, EmA	4	2	6 (4.4)
Lorini *et al.,* 1996 (78)	Italy	172 children	AGA, ARA, EmA	0	6	6 (3.5)
De Vitis *et al.,* 1996 (79)	Italy	639 adults	AGA, EmA	0	63	63 (7.0)
Not *et al.,* 2001 (80)	Italy	491 children and adults	EmA	0	28	28 (5.7)
Calero *et al.,* 1996 (81)	Spain	141 children	AGA	0	4	4 (2.9)
Roldan *et al.,* 1998 (82)	Spain	177 children	AGA, EmA	4	3	7 (3.9)
Vitoria *et al.,* 1998 (83)	Spain	93 children	AGA, EmA	0	6	6 (6.5)
Sigurs *et al.,* 1993 (84)	Sweden	459 children	AGA, ARA	6	15	21 (4.6)
Stenhammar *et al.,* 1993 (85)	Sweden	207 children	AGA	3	4	7 (3.4)
Sjöberg *et al.,* 1998 (86)	Sweden	848 adults	AGA, EmA	8	14	22 (2.6)
Carlsson *et al.,* 1999 (87)	Sweden	115 children	AGA, EmA	2	5	7 (6.2)
Page *et al.,* 1994 (88)	UK	767 adults	AGA	0	14	14 (2.0)
Acerini *et al.,* 1998 (89)	UK	167 children	AGA, EmA	0	8	8 (4.8)
Rossi *et al.,* 1993 (90)	USA	211 children	EmA	0	3	3 (1.4)
Rensch *et al.,* 1996 (91)	USA	47 adults	EmA	0	3	3 (6.0)
Talal *et al.,* 1997 (92)	USA	185 adults	EmA	0	4	4 (3.8)
Aktay *et al.,* 2001 (93)	USA	218 children	EmA	0	10	10 (4.6)
Median prevalence in 40 screening surveys (range)						4.1% (0–16.4)

[a] Gliadin antibodies.
[b] Antiendomysial antibodies.
[c] Antitissue transglutaminase antibodies.
[d] Antireticulin antibodies.

without exception, AIDDM has developed before the verification of celiac disease. However, the delay in the diagnosis of celiac disease is usually many years (94), which makes it difficult to specify the order in which the diseases appear.

These screening surveys (Table 2) have also taught us that many individuals with both AIDDM and celiac disease have suffered only from subtle, if any, gastrointestinal symptoms. Severe malabsorption is unusual, iron or folic acid deficiency with or without anemia being the most common laboratory abnormalities. Short stature has been reported in about one third of children with celiac disease (74, 76, 78), but in some series this has not been a prominent feature (60, 90, 95).

The impact of a gluten-free diet on the metabolic control of diabetes may depend on the symptoms of celiac disease in patients with both conditions. In severely malnourished subjects with AIDDM, the treatment of newly detected celiac disease has without doubt had an unequivocal positive effect: intestinal symptoms are rapidly alleviated and a significant weight gain is evident. In addition, the metabolic control of AIDDM has improved in general, and in particular the number of severe hypoglycemic episodes declined (46, 48).

This positive effect of a gluten-free diet is, at present, not as straightforward as it was previously, because today's ce-

liac patients are at the time of diagnosis in good condition and do not suffer from malabsorption. As shown in Table 3, the impact of dieting on metabolic control in patients with AIDDM and celiac disease cannot be considered unanimously positive.

We have investigated the influence of a strict gluten-free diet on the metabolic control of diabetes in a prospective and controlled 1-yr study, involving 22 adults with both AIDDM and celiac disease; 22 nonceliac patients matched for age, sex, and duration of AIDDM served as controls (97). Even though a definite improvement in the adherence to the gluten-free diet in the celiac group was achieved, this had no effect on the metabolic control of diabetes. Furthermore, the metabolic control in the celiac group was similar to that in nonceliac controls throughout the study. On the other hand, concomitant diabetic and celiac diets are not always easy to maintain, and glycemic control may theoretically even deteriorate after adopting a gluten-free diet. It was therefore significant that a strict celiac diet was observed to have no detrimental effect on the metabolic control of diabetes, which means that it is quite possible to treat both conditions appropriately at the same time.

An unanswered question is whether untreated celiac disease worsens the rate and progression of diabetic complications. In any case, neurological complications commonly occur in celiac disease (45), and it has not been excluded that untreated celiac disease may predispose diabetic patients to neuropathy.

When serological screening is used, most celiac cases will be detected within 1 yr of the onset of AIDDM (68). On the other hand, there are reports in which AIDDM patients who are initially celiac antibody negative have undergone seroconversion and contracted celiac disease during follow-up (68, 99–102). In general, positive antiendomysial (or antireticulin) antibodies especially seem to predict the eventual development of intestinal villous atrophy and celiac disease (103). Antiendomysial-positive individuals should therefore be kept under surveillance, and a new biopsy is recommended after 2–5 yr, or even earlier, in case symptoms emerge suggestive of celiac disease. It has been advocated further that serological screening for celiac disease in AIDDM should be carried out every fifth year due to the possibility of latent celiac disease, but prospective studies are lacking to substantiate this policy (68).

In contrast to what has been shown in AIDDM, there is no evidence that the risk of celiac disease in type 2 diabetes mellitus is increased compared with the population at large (86, 88).

B. Thyroid disorders

Recent evidence suggests that the association between autoimmune thyroid diseases and celiac disease is quite similar to that between AIDDM and celiac disease. In earlier series, approximately 5% of patients with celiac disease have been found to suffer from hyper- or hypothyroidism, even though the percentages are highly variable (Table 4). No clear difference in the occurrence of hypothyroidism *vs.* hyperthyroidism was seen. Again, it should be noted that clinically silent celiac cases probably remained mostly undetected. Moreover, thyroid disorders had not been rigorously sought in patients with celiac disease; hence subclinical cases were not found.

Previous to the wide application of serological screening tests, only few studies reported the prevalence of celiac disease in patients with autoimmune thyroid diseases. Siurala *et al.* (105) reported small-intestine mucosal biopsy findings in 32 patients with hyperthyroidism, but none showed villous atrophy. The same group (106) found six patients with concomitant spontaneous hypothyroidism or autoimmune thyroiditis and small-intestinal villous atrophy. However, the diagnosis of celiac disease remained inconclusive, as there was no definite response to a gluten-free diet. A few years later, Kuitunen *et al.* (107) performed small-bowel biopsies on 32 children with autoimmune thyroid disease; two (6%) of them were found to have small-bowel villous atrophy compatible with celiac disease.

An accurate perception as to the presence or the lack of association can be obtained by screening all patients with autoimmune thyroid conditions for celiac disease, and vice versa, by rigorously searching for even subclinical autoimmune thyroid conditions in celiac disease. Such studies should preferably be controlled. Over the past few years a number of prospective studies attempting to clarify the as-

TABLE 3. Metabolic control in patients with AIDDM and celiac disease: effect of gluten-free diet

Authors (Ref.)	n	Study design	Effect of gluten-free diet on metabolic control of AIDDM
Shanahan *et al.*, 1982 (48)	3 children, 11 adults	Cross-sectional uncontrolled	Fewer hypoglycemic events
Sategna-Guidetti *et al.*, 1994 (75)	6 adults	Prospective uncontrolled	HbA_{1c} increased in 4, no change in 2
Page *et al.*, 1994 (88)	14 adults	Prospective uncontrolled	No change in serum fructosamine level
Lorini *et al.*, 1996 (78)	5 children	Prospective uncontrolled	HbA_{1c} increased in 3, decreased in 1, no change in 1
Cronin *et al.*, 1997 (72)	5 adults	Prospective uncontrolled	No significant changes in HbA_{1c}
Acerini *et al.*, 1998 (89)	7 adults	Prospective uncontrolled	No significant changes in HbA_{1c}
Iafusco *et al.*, 1998 (96)	11 children	Prospective uncontrolled	Fewer hypoglycemic events
Kaukinen *et al.*, 1999 (97)	28 + 22 adults	Retrospective and prospective controlled	No effect on HbA_{1c} No effect on hypoglycemic events
Westman *et al.*, 1999 (95)	20 children	Cross-sectional controlled	HbA_{1c} not different from patients with AIDDM only
Mohn *et al.*, 2001 (98)	18 children	Retrospective and controlled	Fewer hypoglycemic events; no effect on HbA_{1c}

TABLE 4. Occurrence of thyroid abnormalities in adult celiac disease

Authors (Ref.)	n	Hyperthyroidism (%)	Hypothyroidism (%)
Lancaster-Smith *et al.*, 1974 (50)	57	5.2	0
Cooper *et al.*, 1978 (49)	314	1.0	2.2
Midhagen *et al.*, 1988 (104)	139	5.0	5.8
Snook *et al.*, 1989 (51)	148	1.4	2.7
Collin *et al.*, 1994 (52)	335	2.1	3.3
Reunala and Collin, 1997 (43)	383	2.3	3.7
	305[a]	1.0	3.3
Bottaro *et al.*, 1999 (38)	1026	0.1	0.1

[a] Patients with dermatitis herpetiformis.

sociation between thyroid and celiac diseases have been published.

Table 5 constitutes a summary of prospective or cross-sectional studies on the risk of clinical and subclinical thyroid disorder in those suffering from celiac disease. Accepted criteria for autoimmune thyroid diseases (120, 121) were applied in this table. Even though the study settings and results are to some extent varied, thyroid involvement would seem evident in as many as 10–15% of all celiac cases, and clearly more frequently than in controls. Table 5 further shows that subclinical hypothyroidism is an especially frequent finding in celiac disease. Thyroid gland volume as measured by ultrasound, in general, has been smaller in patients with celiac disease than in controls. Equally, the atrophic variant of autoimmune thyroiditis has been more common than the goitrous form (115, 118).

Similarly, the prevalence of celiac disease has invariably been higher in patients with autoimmune thyroid diseases than in controls. In serological screening studies with modern antibody assays, a celiac prevalence of approximately 2–4% has been obtained (Table 6). Again, some publication bias cannot be ruled out, and in some studies no increase in the prevalence of celiac disease has been obtained. A recent study indicated that as many as 43% of patients with Hashimoto's thyroiditis showed an increased density of $\gamma\delta^+$ T cell receptor bearing intraepithelial lymphocytes and signs of mucosal T cell activation, both typical for celiac disease (131).

It seems that a gluten-free diet has some, albeit limited, organ-specific effect on the thyroid gland in patients with celiac disease. There are only occasional reports of improvement in thyroid disease management after the detection and treatment of celiac disease (Table 6). The T_4 dosage could be tapered (125), and a recovery of clinical or subclinical autoimmune thyroid disease has been observed (117) in some cases in which celiac patients were placed on a gluten-free diet. On the other hand, symptoms of celiac disease and thyroid malfunction may mimic each other. Treatment failures may therefore be due to inadequate management either of celiac disease or of thyroid disease, or both.

C. Miscellaneous endocrinological conditions

As early as 1984, gluten intolerance was described as occurring concomitantly with at least 65 different diseases (132), most cases turning out to be fortuitous, however, when the high prevalence of celiac diseases came to be understood. One should therefore appraise critically the following associations where large controlled studies are lacking. Nevertheless, such plausible links should be recognized. Both undetected endocrinopathy and celiac disease may cause diagnostic difficulties in conditions in which the two disorders occur simultaneously.

There are case reports on the concomitant occurrence of Addison's and celiac disease (133–135). An association between these two conditions may indeed exist: in a recent screening survey, five (12.5%) of 41 patients with Addison's disease of autoimmune origin were found to be suffering from celiac disease (136).

The association between primary hyperparathyroidism and celiac disease is disputable, and only case reports have been published (137); there are no series actively screening for celiac disease in these patients. Moreover, compared with other endocrinological diseases, primary hyperparathyroidism seems to be a rare finding in celiac disease, detected, for instance, in only 0.3% of 1026 patients with celiac disease in Italy (38). Evidence thus suggests that the association between the two diseases is fortuitous. Secondary hyperparathyroidism may of course occur in celiac disease as a consequence of hypocalcemia (see below). Some case reports of autoimmune hypoparathyroidism and celiac disease have been published. In celiac patients with severe hypocalcemia or tetanic seizures this rare association should be borne in mind (138, 139).

Symptoms of celiac disease may be confusingly similar to those in concomitant autoimmune hypophysitis, which again may give rise to diagnostic delay of either condition. We described three celiac patients who also were found to be suffering from hypopituitarism (140). One diabetic patient experienced recurrent hypoglycemic events, one patient had muscle weakness without apparent etiology, and one exhibited growth failure. These symptoms were initially attributed to poor celiac control, but were found to be caused by concomitant hypopituitarism. This might have been of autoimmune origin: at least none of the subjects had a pituitary mass.

Alopecia areata has been found in approximately 2% of celiac disease patients (141); gluten-free diet treatment may initiate hair growth in some patients (141–143).

In general, the risk of celiac disease seems to be increased in patients with multiple autoimmune disorders. Apart from AIDDM and autoimmune thyroid disease, the involvement of the adrenal gland (144) and ovarian failure (145) have also been shown in some cases. Similarly alopecia may occur concomitantly with AIDDM or other endocrinological diseases (144).

TABLE 5. Autoimmune thyroid diseases (AITD) in adult patients with celiac disease: studies in which subclinical thyroid diseases had been actively sought

Authors (Ref.)	Year	No. of celiac patients	Overall AITD[a] (%)	Clinical hyperthyroidism (%)	Clinical hypothyroidism (%)	Subclinical or euthyroid AITD (%)	AITD in controls (%)
Cunningham and Zone (108)	1985	50[b]	34	2	10	22	No data
Weetman *et al.* (109)	1988	115[b]	48	0	5	43	16
Gaspari *et al.* (110)	1990	56	32	7	7	18	4
Counsell *et al.* (111)	1994	107	40	4	10	26	9[c]
Freeman (112)	1995	96	17	4	12	1	No data
Sategna-Guidetti *et al.* (113)	1998	185	20	3	4	13	11
Velluzzi *et al.* (114)	1998	47	30	0	4	26	10
Zettinig *et al.* (115)	2000	41	24	0	0	24	0
Toscano *et al.* (116)	2000	44	20	0	2	18	9
Sategna-Guidetti *et al.* (117)	2001	241	21	1	4	16	9
Hakanen *et al.* (118)	2001	79	24	4	10	10	5

[a] Compatible with American Thyroid Association guidelines: clinical or subclinical hyper- or hypothyroidism, or positive antithyroid antibodies in euthyroid (119).
[b] Patients with dermatitis herpetiformis.
[c] Based on national data.

D. Infertility

Celiac disease has been found in 4–8% of women with unexplained infertility (146–148), but the evidence of an association is not unambiguous (149). In some case reports, successful treatment of infertility has occurred after the diagnosis and dietary treatment of celiac disease (150, 151). Menarche takes place later and menopause earlier in celiac women, *i.e*, the fertility period is shortened, and celiac women on a normal diet suffer from spontaneous abortions and other complications of pregnancy more often than those maintaining a gluten-free diet (152). The issue of fertility problems in celiac men is poorly understood, and there are few studies available. Basal serum FSH and LH concentrations have been higher in untreated celiac men than in male controls with Crohn's disease (153). Plasma testosterone and free testosterone indices have been high, whereas dihydrotestosterone levels are reduced, indicating androgen resistance (154).

Problems of reproduction cannot be completely explained by malabsorption of nutrients in celiac women. It was recently reported that the children of celiac men had lower birth weight than age- and sex-matched nonceliac children (155). Genetic loci outside human leukocyte antigen (HLA) complex have been theorized to be implicated (155, 156); it also remains to be seen how substantial a role gonadal dysfunction plays in untreated celiac disease. In any case, a gluten-containing diet in women with celiac disease seems to carry an increased risk of an unfavorable outcome of pregnancy (148, 157, 158).

V. Pathogenetic Aspects of the Association Between Celiac Disease and Endocrinological Disorders

A. Genetic features

Susceptibility to celiac disease is determined to a significant extent by genetic factors. Liability to the disease runs in families, and concordance for celiac disease in first-degree relatives ranges between 10–15% (39) and reaches up to 80% in monozygotic twins (159–161). The coexistence of celiac disease and endocrinological autoimmune diseases appears to be at least partly due to a common genetic predisposition. Susceptibility to these diseases has been localized to the HLA region of chromosome 6. Approximately 90% of celiac disease patients share the HLA DR3-HLA DQ2 configuration (encoded by alleles DQA1*0501 and DQB1*0201) (162–165), and most of the remainder express the DR4-DQ8 haplotype encoded by DQA1*0301, DQB1*0302 alleles (163, 166).

The prevalence of HLA DQ2 is 20–30% in the population (162, 164), and only a minority of these will ever develop celiac disease. This implies the involvement of additional, probably non-HLA-linked genes in the pathogenesis of celiac disease. Genome-wide screening studies have resulted in a number of proposals for candidate non-HLA gene regions. In Irish celiac disease patients, five other chromosome locations have been identified: 6p23, 7q31, 11p11, 15q26, and 22cen (167). These findings could not be confirmed in the United Kingdom, because only one locus in chromosome 15 evinced a linkage to celiac disease (168). Studies elsewhere have pointed to candidate genes in chromosome 5q and 11q (169–171) as well as in the CTLA4/CD28 gene region (172). In a study by Lie *et al.* (173) an allele of locus D6S2223 seemed to protect against the development of celiac disease; an allele found in this locus was less frequent among HLA DR3-DQ2 homozygous celiac disease patients than in HLA DR3-DQ2 homozygous nonceliac controls. Interestingly, this allele has also been underrepresented among HLADR3-DQ2 homozygous AIDDM patients, and it was transmitted less often than expected from DR3-DQ2 homozygous parents to diabetic siblings (174). Taken together, no uniform gene or gene region has hitherto been found outside HLA DQ, and such additional genes are likely to have only a moderate effect in the pathogenesis of celiac disease (175).

The diabetic susceptibility, similarly to what has been observed in celiac disease, is associated with HLA DR3-DQ2 and DR4-DQ8. The association between the two diseases could thus be explained partially by the sharing of a common genetic factor in the HLA region (176, 177). Because first-degree relatives of patients with AIDDM also have an increased prevalence of these HLA-risk alleles, it is predictable that the prevalence of celiac disease will be increased in these subjects (178, 179). Moreover, Not *et al.* (80) showed that the

TABLE 6. Screening studies on the prevalence of adult celiac disease in autoimmune thyroid disorders

Authors (Ref.)	Thyroid disorders (n)	Criteria for thyroid disease	Controls (n)	Celiac disease in thyroid disorder (%)	Celiac disease in controls (%)	Symptoms of celiac disease in the study group	Screening test[a]
Collin *et al.,* 1994 (122)	83	Clinical disease	249 blood donors	4.8	0.4	1 detected clinically; 3 silent	ARA, AGA, EmA
			25 thyroid nodule		4		
Sategna-Guidetti *et al.,* 1998 (113)	152	ATA[b]	170	3.3	ND	All silent	EmA
Cuoco *et al.,* 1999 (123)	92	ATA	236 blood donors	4.3	0.4	All silent	AGA, EmA
			90 goiter, thyroid nodule cancer		1.1	(4/4 iron deficiency)	
Carroccio *et al.,* 1999 (124)	48	Clinical disease	Uncontrolled	0			AGA
							EmA
Valentino *et al.,* 1999 (125)	150	ATA	Uncontrolled	3.3		All silent	EmA
Seissler *et al.,* 1999 (71)	100	Not specified	100	0	0.5		tTg-ab
Berti *et al.,* 2000 (126)	172	Not specified	396 disease controls; 4000 blood donors	3.4	0.75	2 abdominal symptoms; 4 silent	EmA
					0.25		
Kumar *et al.,* 2001 (127)	132	Not specified	71 thyroid nodule or cancer	2.0	0	No data	EmA; no small-bowel biopsy
Meloni *et al.,* 2001 (128)	297	ATA	Uncontrolled	4.4		All silent	EmA
Volta *et al.,* 2001 (129)	220	ATA	250 blood donors	3.2	0.4	2 malabsorption; 5 silent	EmA, tTg-ab
			50 thyroid nodule		0.0		
Larizza *et al.,* 2001 (130)	90	ATA	Uncontrolled	7.8		3 symptoms	EmA
						4 silent	

[a] ARA, Antireticulin antibodies; AGA, gliadin antibodies; EmA, antiendomysial antibodies; tTg-ab, antitissue transglutaminase antibodies.
[b] Compatible with American Thyroid Association guidelines: clinical or subclinical hyper- or hypothyroidism, or positive antithyroid antibodies in euthyroid (119).

prevalence of other autoimmune diseases was significantly higher (18.7%) in first-degree relatives of AIDDM patients found to have silent celiac disease than in relatives without celiac disease antibodies (2.6%). On the other hand, Saukkonen *et al.* (180) observed that the prevalence of celiac disease in siblings of patients with AIDDM did not differ from that reported from population-based screening studies.

HLA DQ2 and DQ8 show only weak association with Hashimoto's thyroiditis; the HLA DQ2 association is less clear in Graves' disease (181, 182). DQA1*0501 seems to confer an increased susceptibility to Graves' disease (182, 183). Whether celiac disease and autoimmune thyroid disease share common gene expression outside the HLA region remains obscure. One candidate region might be CTLA4 on chromosome 2q33, a region that has been reported to confer susceptibility to both celiac (172) and Graves' disease (184). In all, genetic predisposition is not likely to explain entirely the association between celiac disease and autoimmune thyroiditis.

The HLA DR3-DQ2 and DR4-DQ8 haplotypes are common in many autoimmune diseases, *e.g.*, Addison's disease, Sjögren's syndrome, and autoimmune hepatitis (185). This HLA association presumably predisposes individuals to autoimmune conditions. Of note, many conditions, including celiac disease and autoimmune thyroid diseases, are more common among females.

B. Immunological features

At present, it is widely accepted that immunological mechanisms are implicated in the development of the mucosal damage in celiac disease. In untreated patients there are signs of activation of both mucosal cellular and humoral immune systems (186, 187). The major single environmental trigger is ingested gluten (gliadin). Recently, Dieterich *et al.* (188) established that serum antiendomysial antibody, a specific indicator of active celiac disease, recognizes enzyme tissue transglutaminase, of which activated endothelial, fibroblast, and mononuclear cells are a rich source. This enzyme seems to play a critical role in controlling cell homeostasis, regulating the cell cycle through its involvement in proliferation, differentiation, and apoptosis (189). Gliadin is an excellent substrate for tissue transglutaminase, which has now been shown to be the predominant autoantigen for celiac disease (188). Gluten-specific HLA DQ2- and DQ8-restricted T cells are present in the small-bowel mucosal lesion of celiac disease (190). Antigen-presenting cells in the lamina propria present digested gluten peptide to CD4+ T cells via their

HLA DQ2 molecules. Tissue transglutaminase modifies gliadin peptides through deamidation of glutamine residues to negatively charged glutamic acid, thus facilitating the binding of gliadin peptides to the peptic groove of HLA DQ2 and DQ8 molecules. This results further in better binding affinity and increased T cell reactivity (191–193). T cells that are customarily silent, once activated, induce a local inflammatory response that may continue as long as gliadin is present. Stimulated T cells secrete Th 1 cytokines such as TNFα and γ-interferon, which can further damage the small-bowel mucosa, leading to enteropathy (187, 194). For example, TNFα triggers intestinal fibroblasts to secrete matrix metalloproteinases (MMPs), which lead to mucosal destruction by dissolution of connective tissue. *In vitro* the inhibition of TNFα and MMP-3 has been seen to prevent such mucosal damage (195). Accordingly, expression of MMP-1 and MMP-3 mRNA is increased in fibroblasts of celiac small-bowel mucosa *in vivo* (196). A simultaneous Th 2 response at the intestinal level results in the formation of autoantibodies (197, 198). Antibodies against tissue transglutaminase may even play a direct role in the pathogenesis of small-bowel mucosal damage in celiac disease. In an *in vitro* model, antitissue transglutaminase antibody has been seen to inhibit epithelial differentiation on the crypt-villous axis (199). Whether antitissue transglutaminase antibody contributes to celiac-type small-bowel mucosal damage *in vivo* remains to be seen.

How are autoimmune endocrinological diseases such as AIDDM and autoimmune thyroid disorders associated with celiac disease? The coexistence of these diseases could be explained by molecular mimicry by which gliadin or tissue transglutaminase activates T cells that are cross-reactive with various self-antigens. Such inflammatory responses may have the capacity to persist in genetically susceptible hosts and lead to chronic organ-specific autoimmune disease via epitope spreading (200). However, it is unclear whether any sequence similarities exist between gliadin or tissue transglutaminase and, for example, glutamate decarboxylase antibodies associated with diabetes (GAD), insulin, thyroid peroxidase antibodies, or 21-hydroxylase.

It is also possible that, apart from gliadin, tissue transglutaminase can modify other external or self-antigens by cross-linking or deamidation and thus generate different neoantigens (200). These antigens and antibody production can further induce various autoimmune phenomena outside the intestine. On the other hand, apart from antiendomysial antibodies, celiac patients have an increased frequency of other autoantibodies; it is not known whether they play any pathological role (50, 201, 202). Furthermore, oxidative stress and inflammation may cause aberrant activation of transglutaminases in different tissues, which leads to the formation of inappropriate proteinaceous aggregates that may be cytotoxic and contribute to a variety of diseases (203).

There is evidence that in the development of autoimmunity in AIDDM, the failure to achieve tolerance to autoantigens derives from the gut. In patients with newly diagnosed AIDDM, the islet cell antigen GAD-reactive lymphocytes express the gut-specific homing receptor $\alpha 4\beta 7$ integrin (204). Furthermore, there are observations indicating that treatment of neonatal nonobese diabetic mice with monoclonal antibodies to $\alpha 4$ protects against insulitis (205). These findings suggest that autoreactive lymphocytes originate from the intestine and that tolerance to a self-antigen is broken in the gut-associated lymphocyte population. Interestingly, the prevalence of antitissue transglutaminase antibodies has been reported to be as high as 32% in HLA DQ2 homozygous AIDDM patients, as compared with 2% in patients without HLA DQ2 or DQ8 (206).

It has also been hypothesized that increased intestinal permeability in untreated celiac disease (207, 208) predisposes to other autoimmune disorders by facilitating further external antigens such as food proteins, bacterial products, and endotoxins to enter the intestinal lamina propria, thus leading to the activation of autoimmune phenomena (209). A role of food antigens in autoimmunity is supported by animal experiments in which hydrolyzed casein instead of nonhydrolyzed diet delayed the onset of AIDDM in BB rats, which develop AIDDM spontaneously (210). Likewise, a gluten-free diet for 320 d reduced the incidence of AIDDM from 64% to 15% in nonobese diabetic mice (211). In BB rats, increased paracellular permeability was observed even 3–4 wk before the development of insulitis and clinical diabetes (210). Zonulin, a human protein analog to the *Vibrio cholerae*-derived Zonula occludence toxin, is able to open small-bowel mucosal tight junctions, leading to increased molecule permeability, and in active celiac disease, zonulin expression is increased (212). Recently it was found that the increased intestinal permeability in the diabetic BB rat model is also associated with an increased concentration of intraluminal zonulin (213). On the whole, defects in the small-bowel mucosal barrier may be important in breaking oral tolerance and in mediating various autoimmune diseases.

C. Environmental factors

The principal environmental factor in celiac disease is dietary gluten, which is essential for the development of the disease. Apart from gliadin (wheat gluten), secalin (rye) and hordein (barley) are considered harmful, whereas oat protein avenin appears to lack a toxic effect in celiac disease (214). Additional environmental factors may be required for the breaking of oral tolerance in individuals genetically susceptible to celiac disease or other autoimmune conditions. Adenovirus serotype 12 has shown amino acid sequence homology with gliadin peptide (215). However, there is no evidence to suggest that celiac patients have a high prevalence of adenovirus infection (216), but virus infection may still initiate the cellular immune response (217). Sometimes celiac disease becomes manifest during the postnatal period (218). Transient postpartum thyroiditis is a well known entity and may later predispose to chronic thyroiditis (219). The postpartum period may also be a risk factor for Graves' disease in susceptible individuals (220). The body content of selenium may be low in untreated celiac disease (221). Interestingly, selenium deficiency may also impair thyroid hormone action (222, 223). So far there are no data on the association between thyroid function and selenium deficiency in untreated celiac disease.

Some studies have shown an inverse relationship between cigarette smoking and celiac disease (224). Smoking may influence the T- or B cell response and also decrease the

intestinal permeability that is a common feature in celiac disease; the role of smoking in the etiology of celiac disease is still controversial (225). On the other hand, smoking may be a risk factor for Graves' ophthalmopathy (226).

At the moment, apart from gluten, no additional environmental factors have been found to be involved in the development of celiac disease in genetically susceptible individuals. The period between the exposure of gluten and the disease development may be relatively short. This may indicate that additional genetic alleles are more likely to increase the risk of celiac disease (227).

VI. Can the Treatment of Celiac Disease Prevent the Development of Autoimmune Endocrinological Disorders?

As stated earlier, the effect of a gluten-free diet on the course of endocrinological disorders seems, in most cases, to be only moderate, but on the other hand, symptoms of celiac disease cannot always be distinguished from those of endocrinopathy. Even though symptoms of gluten intolerance are not restricted to the intestine, common genetic factors, *i.e.*, HLA DR3-DQ2 and DR4-DQ8, might explain the increased prevalence of autoimmune diseases in celiac disease. So far, there has been only circumstantial evidence that gluten in itself may induce other autoimmune conditions. In one study, the T_4 dosage could be tapered when patients were placed on a gluten-free diet (125). Thyroid abnormalities have been found to be more common in patients with dermatitis herpetiformis than in controls with HLA B8/-DR3 (110). Furthermore, the observation that AIDDM has been detected before, and less often after, the diagnosis and treatment of celiac disease has been taken as indirect evidence that a gluten-free diet protects from autoimmune diseases in celiac patients (76).

Recently, Ventura *et al.* (228) examined the relationship between the prevalence of autoimmune diseases and the duration of exposure to gluten. They observed that the development of autoimmune conditions was related to the age at diagnosis of celiac disease, which again was virtually the same as the time of gluten exposure. The number of autoimmune conditions in those celiac patients in whom the gluten-free diet was adopted in early childhood (5.1%) was not significantly different from that of controls (2.8%). By contrast, in celiac patients who had started a gluten-free diet at the age of 10 yr or more, the frequency of autoimmune conditions was significantly increased (23.6%). Age at diagnosis of celiac disease was the only independent predictor for the development of autoimmune conditions. The authors suggested that an early diagnosis and treatment of celiac disease might protect against the development of autoimmune diseases.

Since this observation, there has been an ongoing discussion as to whether a gluten-containing diet is involved in the pathogenesis of autoimmune conditions in genetically susceptible, *i.e.*, in HLA DQ2 and DQ8, individuals. A solution remains to be reached, because there are now reports for and against the hypothesis of Ventura *et al.* (228).

Diabetes-related GAD, islet cell antibodies, and insulin antibodies have been reported to occur in patients with celiac disease. In the study by Di-Mario *et al.* (229), 27% of 15 patients with untreated celiac disease had insulin antibodies, compared with 20% in 15 treated patients and in 0% of controls. Elsewhere, GAD and islet cell antibodies have also been found in 23% of 30 (230), and in 6.8% of 44 (231) celiac patients, who had been on a gluten-free diet. It is not known whether these antibodies in celiac patients are predictive of subclinical pancreatic damage and forthcoming AIDDM or whether they are simply indicators of a more general autoimmune diathesis. Toscano *et al.* (116) observed that thyroid peroxidase and other endocrine-related antibodies were more often and with higher titers elevated in untreated than in treated celiac disease patients: in 52.6% and 20%, respectively.

Ventura *et al.* (228) used an approach that would appear to strengthen their hypothesis that gluten is directly involved in the development of autoimmune conditions. They showed that diabetes-related antibodies, present in adolescents with untreated celiac disease, disappear when patients are put on a gluten-free diet (232). GAD, islet cell, and insulin antibodies were present in 11 (11.1%) of 90 newly detected celiac patients. During the gluten-free diet, all 11 became negative for these antibodies within 24 months. The glucose tolerance test was normal in all individuals having initially diabetes-related antibodies. Similarly, thyroid antibodies were present in 14.4% when on a normal diet, but in only 2.2% after gluten-free dietary treatment.

By contrast, the data presented by Sategna-Guidetti *et al.* (117, 233) on the prevalence of thyroid involvement in adult celiac disease did not unequivocally support the above mentioned hypothesis. They investigated thyroid function outcome in 128 patients with celiac disease, who had been placed on a gluten-free diet 1 yr earlier (117). The dietary compliance was not good, because only 57% showed a mucosal recovery. Nevertheless, thyroid function improved in three of five with subclinical autoimmune hypothyroidism; two were compliant with the diet. Of the 16 patients with euthyroid autoimmune thyroiditis, three developed subclinical hypothyroidism and one developed subclinical hyperthyroidism (three were noncompliant). On the other hand, two of 91 patients who initially had no signs of thyroiditis developed euthyroid autoimmune thyroiditis, and one developed subclinical hyperthyroidism while maintaining a gluten-free diet. Moreover, the authors observed that it was the age of patients and not the duration of gluten exposure that predicted the occurrence of autoimmune diseases in celiac patients (233). One problem seems to lie in defining the time of actual gluten exposure, which should also include periods of dietary lapses after the diagnosis of celiac disease. Furthermore, it is difficult to estimate the actual gluten exposure before the development of autoimmune diseases: these conditions may have existed subclinically for many years, which again means that the gluten exposure time needed for the manifestation of autoimmune condition will be overestimated. Extensive prospective follow-up studies are clearly indicated here. Meanwhile, in the absence of evidence to the contrary, it seems justified to detect and treat celiac disease as early as possible.

VII. Bone and Celiac Disease

It has long been recognized that osteomalacia, osteoporosis, bone pain, and fractures are complications of celiac disease (132). Even here, the clinical spectrum of celiac disease has changed. Osteomalacia and severe bone disease are relatively rare, whereas a low BMD seems to follow dermatitis herpetiformis as the most common extraintestinal manifestation of the disease. This has been ascertained in several cross-sectional and prospective studies (Table 7).

In a recent study of 128 North American patients, who had been on gluten-free diet from 0 months to 46 yr (mean, 7.5 yr), osteoporosis (T score < -2.5) was present in 34% of the patients at the lumbar spine, 27% at the femoral neck, and 32% at the radius (255). Evidence shows that osteoporosis and osteopenia are alleviated on a gluten-free diet, although not always completely. Even children may carry an increased risk of osteopenia, which in this age group, however, seems to be cured completely with an appropriate diet (32, 251).

There are fewer data on the occurrence of celiac disease in patients with osteoporosis. Lindh *et al.* (256) found biopsy-proven celiac disease in 3.2% of patients suffering from osteoporosis. They used the IgA antigliadin antibody test, which may yield a number of false negative results. Recently, Nuti *et al.* (257) found IgA class antitissue transglutaminase antibodies in 9.4% of patients with osteoporosis. Unfortunately, no more than 10 of 24 antibody-positive patients underwent small-bowel biopsy, and only six (2.4%) had biopsy-proven celiac disease. Mather *et al.* (258) in their series of 96 patients with idiopathic low BMD found seven (7.3%) to be positive for antiendomysial antibodies at low titers, but none had small-bowel villous atrophy. In these two studies, the specificity of antitissue transglutaminase and antiendomysial antibody test, respectively, was low. In the absence of villous atrophy, it is possible that positive test results forecast the early onset of celiac disease (latent stage), and villous atrophy will appear later (258). Clearly, more studies are needed to estimate the prevalence of silent celiac disease in patients suffering from low BMD. On the other hand, it seems that the risk of low BMD is by no means reduced in adults with symptom-free celiac disease (252, 259).

A study carried out in Argentina (260) showed that patients with celiac disease seem to have an increased risk of fractures. Twenty-five per cent of 165 celiac patients had experienced one or more fractures, compared with 8% of 165 hospital controls. The risk seemed to be associated with poor adherence to a gluten-free diet and late diagnosis of celiac disease. The majority of fractures occurred before the diagnosis of celiac disease.

The mechanisms of disturbances in bone metabolism in celiac disease are poorly understood. The initial and probably main event is calcium malabsorption (261), which is primarily caused by villous atrophy (238) and secondarily by coexisting vitamin D deficiency (243, 249). Impaired intestinal calcium malabsorption leads to secondary hyperparathyroidism, which is often present and may serve to asseverate the bone disease by increasing bone turnover (7, 243, 250, 253, 254). Consequently, markers of bone formation (serum osteocalcin, bone alkaline phosphatase, carboxy-terminal propeptide of type I procollagen) and bone resorption (serum type I carboxy-terminal telopeptide, urinary N- and C-terminal telopeptides of type I collagen, pyridinolines) are often increased (7, 250, 262).

IGF is involved in the regulation of bone metabolism: circulating levels have been reported to be low in osteoporosis (263). It is uncertain whether this plays any pathogenetic role or simply constitutes a secondary phenomenon to malabsorption. As discussed earlier, there is now evidence that celiac disease is associated with infertility. In women, celiac disease can lead to amenorrhea and early menopause (264), which are associated with high risk for osteoporosis. Direct adverse immunological effects of gluten on bone are not excluded; similar mechanisms have been suggested to be involved in the development of enamel defects in the permanent teeth in untreated celiac disease (265). There are no studies to date to support this hypothesis.

VIII. Discussion

A. Time to change clinical practice

It is obvious that a number of patients with diverse endocrinological disorders suffer from celiac disease, the symptoms of the disease being sometimes, if not mostly, subtle or atypical. For this reason the majority of patients remain undetected. The diagnosis of celiac disease is based on intestinal biopsy samples usually taken by upper gastrointestinal endoscopy. Many individuals consider this investigation unpleasant and inconvenient. Fortunately, endoscopy can now be limited to subjects with a great likelihood of celiac disease and those found positive in screening surveys. For initial screening purposes, up-to-date serological tests, IgA class antiendomysial and antitissue transglutaminase antibodies, are highly specific and sensitive enough in cases in which symptoms do not clearly indicate celiac disease.

There is some evidence that the dietary treatment improves the quality of life in silent celiac disease (266), and that even asymptomatic patients with celiac disease may suffer from osteopenia or osteoporosis (252, 259). The natural course of silent celiac disease remains poorly understood. It is not yet unanimously accepted that population-based screening programs for celiac disease should be carried out. However, it is a different issue to employ screening in individuals known to run an increased risk of the disease. For several reasons, autoimmune endocrine diseases belong without doubt to such a risk group. First, it is expected that screening will yield positive results in this group more (3–5%) than in an unselected population (0.3–1.0%). Second, it is often possible to confuse symptoms of thyroid dysfunction, for instance, with those of celiac disease. Third, both patients with endocrinological disorders and those with celiac disease run an increased risk of osteopenia, which is possible to prevent and even treat by means of a gluten-free diet, provided that the proper diagnosis of gluten intolerance is made. Moreover, gluten-free dietary treatment, in some cases, will be of benefit in associated conditions, *e.g.*, in infertility or miscarriage problems (152). Nor can the risk of lymphoma be ignored (6), although its likelihood would seem to be low in symptom-free celiac disease (267); the same applies to neurological complications.

TABLE 7. BMD in celiac disease

Authors (Ref.)	No. of celiac disease patients		BMD in untreated celiac disease	BMD on gluten-free diet	Other remarks
Molteni *et al.,* 1990 (234)	29 untreated; 23 treated	Adolescents and adults	Decreased	Similar to controls	14 of 29 untreated patients had subclinical celiac disease
Bode *et al.,* 1991 (235)	22 treated	Adults	No data	Decreased	BMD did not correlate to symptoms or strictness of the diet
Mora *et al.,* 1993 (236)	33 untreated; 14 treated	Children	Decreased	Improvement	
Mazure *et al.,* 1994 (237)	8 untreated (asymptomatic); 20 untreated (symptomatic); 14 treated	Adults	In symptomatic decreased more than in asymptomatic	Similar to untreated asymptomatic patients	
Valdimarsson *et al.,* 1994 (238)	13 treated (villous atrophy); 17 treated (normal mucosa)	Adults	No data	Lower in patients with persistent villous atrophy	BMD correlated to adherence to diet and presence of villous atrophy; D vitamin lower in patients with villous atrophy
McFarlane *et al.,* 1995 (239)	55 treated	Adults	No data	Decreased in 20% of patients	Low BMD correlated to low body mass index and low calcium intake
Pistorius *et al.,* 1995 (240)	81 treated	Adults (female)	No data	Decreased in postmenopause	
Corazza *et al.,* 1995 (7)	17 untreated; 14 treated	Adults	Decreased	Improvement	Bone turnover increased in untreated, decreased during the diet
Walters, 1994 (241)	10 untreated; 14 treated	Adults	Decreased	Decreased in some	7 of 8 treated patients with low BMD had villous atrophy
McFarlane *et al.,* 1996 (242)	21 before and after treatment (1 yr)	Adults	Decreased	Improvement, but still low	
Valdimarsson *et al.,* 1996 (33)	63 before and after treatment (1 yr)	Adults	Decreased	Improvement, but still low	Improvement in serum vitamin D, PTH,[a] Afos,[b] and calcium levels during diet
Corazza *et al.,* 1996 (243)	14 untreated (asymptomatic); 10 untreated (symptomatic); 8 treated	Adults	In symptomatic decreased more than in asymptomatic	In asymptomatic similar to controls, in symptomatic low in some cases	
Mautalen *et al.,* 1997 (244)	14 patients before and after treatment (1 yr)	Adults	Decreased	Improvement, but still low in some cases	Bone turnover decreased during diet; calcium and vitamin D substitution did not further improve BMD
Ciacci *et al.,* 1997 (245)	41 before and after treatment (1 yr)	Adults	Decreased	Improvement, but still low in some cases	
Smecuol *et al.,* 1997 (246)	25 before and after treatment (37 months)	Adults	Decreased	Improvement, but still low in some cases	Improvement of BMD especially on strict diet
Scotta *et al.,* 1997 (247)	66 before and after treatment (1–2 yr)	Children	Decreased	Normalization with strict diet	
Mora *et al.,* 1998 (248)	44 before and after treatment (1 yr)	Children	Decreased	Normalization with a strict diet	
Kemppainen *et al.,* 1999 (249)	28 before and after treatment (1–5 yr)	Adults	Decreased	Improvement within 1 yr in most cases	PTH normalized during the diet

TABLE 7. Continued

Authors (Ref.)	No. of celiac disease patients		BMD in untreated celiac disease	BMD on gluten-free diet	Other remarks
Selby *et al.,* 1999 (250)	35 treated	Adults	No data	Decreased	Decreased BMD related to secondary hyperparathyroidism
Mora *et al.,* 1999 (251)	30 treated	Children	No data	Similar to controls	BMD normal in children with long-term diet
Mustalahti *et al.,* 1999 (252)	19 asymptomatic before and after treatment (1 yr); 30 symptomatic	Adults	Decreased in asymptomatic and symptomatic	Improvement	
Sategna-Guidetti *et al.,* 2000 (253)	86 before and after treatment (1–2 yr)	Adults	Decreased	Improvement	Bone turnover increased in untreated cases, improved during diet
Valdimarsson *et al.,* 2000 (254)	105 before and after treatment (1–3 yr)	Adults	Decreased	Improvement, low in those with initially secondary hyperparathyroidism	Low BMD associated with secondary hyperparathyroidism
Mora *et al.,* 2001 (32)	19 before and after treatment (1–4 yr)	Children	Decreased	Improvement	

[a] Parathyroid hormone.
[b] Alkaline phosphatase.

In celiac disease, we have an effective dietary treatment that enables the patient to live a normal life. Even though large cost-benefit analyses are still lacking, there seems to be a good case for the following recommendation. All patients with AIDDM, autoimmune thyroid diseases, or Addison's disease or those with multiple endocrinological disorders should undergo serological screening for celiac disease. Celiac disease should be considered in patients with osteoporosis (255), even when there are no signs of vitamin D deficiency or hypocalcemia.

Harewood and Murray (268) have shown that the endomysial antibody test is less expensive in screening for celiac disease in a population where the expected prevalence of the disease is approximately 5–10%; the costs of the antitissue transglutaminase test were not analyzed in this study. Whether to select IgA class antiendomysial or antitissue transglutaminase antibody as a screening assay depends on the facilities of local laboratories; the combination of these two tests increases the sensitivity of screening without incurring any significant loss of specificity. A positive antibody result should always be verified by small-bowel biopsy. Biopsy should similarly be considered whenever the clinical suspicion of celiac disease is high: celiac patients with IgA deficiency and a few other cases (Table 1) remain antibody negative. The concept of latent celiac disease is not yet fully understood. At the moment, we recommend that antiendomysial and antitissue transglutaminase antibody-positive patients without small-bowel villous atrophy should continue on a gluten-containing diet and be kept under surveillance. In patients that remain antibody positive, a repeat biopsy should be carried out, for instance within 1–3 yr depending on symptoms.

In celiac patients, on the other hand, thyroid function should be assessed at the time of diagnosis and always when there is even minor clinical suspicion of thyroid dysfunction. Hypopituitarism or Addison's disease appear not to be as rare in celiac disease patients as in the general population; therefore, these conditions should be remembered when celiac patients have any symptoms suggestive of them.

Ideally, BMD should be investigated in all patients with celiac disease. In this way, calcium and vitamin D supplementation could be precisely targeted. The detection of osteopenia or osteoporosis would further be important when considering specific treatments of osteoporosis. Furthermore, motivation to maintain a gluten-free diet, especially in subjects with low BMD, is essential.

B. Future aspects

Cost-benefit analyses of screening for celiac disease in risk groups or in the whole population are warranted, and the importance of measuring health-related quality of life should be recognized. The impact of early diagnosis and gluten-free dietary treatment on the occurrence of autoimmune endocrinological conditions should be further investigated in prospective surveys. These should comprise individuals with silent and developing latent celiac disease. Research into common genetic involvement in endocrine conditions and celiac disease should be carried out. The finding that tissue transglutaminase is the target for celiac antibodies makes it possible to study the role of this enzyme in nonintestinal organ-specific involvements in celiac individuals. This may make possible, in the future, specific treatments of celiac complications, such as osteoporosis or infertility, and perhaps even prevent the development of autoimmune conditions. The development of curative treatment in celiac disease is still far away. It is as difficult to induce oral tolerance as it is to block the T cell response to gluten. Serious side effects prevent the use of immunosuppressive drugs in clinical practice. The development of wheat free of toxic peptides may be possible, but at the risk of losing its baking properties (227).

C. Conclusions

There is no doubt that many patients with celiac disease primarily contact specialists other than gastroenterologists. The majority of cases thus remain undetected. A close association between various autoimmune endocrinological disorders and celiac disease has been shown in numerous studies. The diagnosis of celiac disease requires a small-bowel biopsy, usually taken by endoscopy. However, sensitive and specific antibody assays, the antiendomysial and antitissue transglutaminase tests, are helpful in preliminary screening for gluten intolerance in cases where symptoms are atypical, appear outside the gastrointestinal tract, or are totally absent. The need to prevent osteoporosis advocates the early diagnosis and treatment of even asymptomatic celiac disease. The benefits of screening for celiac disease in autoimmune disease remain to be proved by prospective follow-up studies. However, there seems to be a good case for extensive screening.

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References

1. **Trier JS** 1991 Celiac sprue. N Engl J Med 325:1709–1719
2. **Fasano A, Catassi C** 2001 Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. Gastroenterology 120:636–651
3. **Corazza GR, Frisoni M, Treggiari EA, Valentini RA, Filipponi C, Volta U, Gasbarrini G** 1993 Subclinical celiac sprue. Increasing occurrence and clues to its diagnosis. J Clin Gastroenterol 16:16–21
4. **Not T, Horvath K, Hill ID, Partanen J, Hammed A, Magazzu G, Fasano A** 1998 Celiac disease risk in the USA, high prevalence of antiendomysium antibodies in healthy subjects. Scand J Gastroenterol 33:494–498
5. **Ferguson A** 1997 Celiac disease, an eminently treatable condition, may be underdiagnosed in the United States. Am J Gastroenterol 92:1252–1254
6. **Holmes GKT, Prior P, Lane MR, Pope D, Allan RN** 1989 Malignancy in coeliac disease—effect of a gluten free diet. Gut 30:333–338
7. **Corazza GR, Di Sario A, Cecchetti L, Tarozzi C, Corrao G, Bernardi M, Gasbarrini G** 1995 Bone mass and metabolism in patients with celiac disease. Gastroenterology 109:122–128
8. **Mäki M** 1995 The humoral immune system in coeliac disease. Baillieres Clin Gastroenterol 9:231–249
9. **Murray JA** 1999 The widening spectrum of celiac disease. Am J Clin Nutr 69:354–365
10. **Meeuwisse GW** 1970 Diagnostic criteria in coeliac disease. Acta Paediatr Scand 59:461–463
11. **Walker-Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK** 1990 Revised criteria for diagnosis of coeliac disease. Arch Dis Child 65:909–911
12. **O'Farrelly C, Kelly J, Hekkens W, Bradley B, Thompson A, Feighery C, Weir DG** 1983 α-Gliadin antibody levels: a serological test for coeliac disease. Br Med J 286:2007–2010
13. **Chorzelski TP, Beutner EH, Sulej J, Tchorzewska H, Jablonska S, Kumar V, Kapuscinska A** 1984 IgA anti-endomysium antibody. A new immunological marker of dermatitis herpetiformis and coeliac disease. Br J Dermatol 111:395–402
14. **Ladinser B, Rossipal E, Pittschieler K** 1994 Endomysium antibodies in coeliac disease: an improved method. Gut 35:776–778
15. **Dieterich W, Laag E, Schopper H, Volta U, Ferguson A, Gillett H, Riecken EO, Schuppan D** 1998 Autoantibodies to tissue transglutaminase as predictors of celiac disease. Gastroenterology 115:1317–1321
16. **Sulkanen S, Halttunen T, Laurila K, Kolho K-L, Korponay-Szabo I, Sarnesto A, Savilahti E, Collin P, Mäki M** 1998 Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology 115:1322–1328
17. **Volta U, Molinaro N, Fusconi M, Cassani F, Bianchi FB** 1991 IgA antiendomysial antibody test. A step forward in celiac disease screening. Dig Dis Sci 36:752–756
18. **McMillan SA, Haughton DJ, Biggart JD, Edgar JD, Porter KG, McNeill TA** 1991 Predictive value for coeliac disease of antibodies to gliadin, endomysium, and jejunum in patients attending for jejunal biopsy. Br Med J 303:1163–1165
19. **Mäki M, Holm K, Lipsanen V, Hällström O, Viander M, Collin P, Savilahti E, Koskimies S** 1991 Serological markers and HLA genes among healthy first-degree relatives of patients with coeliac disease. Lancet 338:1350–1353
20. **Ferreira M, Davies SL, Butler M, Scott D, Clark M, Kumar P** 1992 Endomysial antibody: is it the best screening test for coeliac disease? Gut 33:1633–1637
21. **Sblattero D, Berti I, Trevisoli C, Marzari R, Tommasini A, Bradbury A, Fasano A, Ventura A, Not T** 2000 Human recombinant tissue transglutaminase ELISA: an innovative diagnostic assay for celiac disease. Am J Gastroenterol 95:1253–1257
22. **Savilahti E, Pelkonen P, Visakorpi JK** 1971 IgA deficiency in children. A clinical study with special reference to intestinal findings. Arch Dis Child 46:665–670
23. **Cataldo F, Marino V, Bottaro G, Greco P, Ventura A** 1997 Celiac disease and selective immunoglobulin A deficiency. J Pediatr 131: 306–308
24. **Marsh MN** 1992 Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 102:330–354
25. **Troncone R** 1995 Latent coeliac disease in Italy. Acta Paediatr 84:1252–1257
26. **Weinstein WM** 1974 Latent celiac sprue. Gastroenterology 66: 489–493
27. **Collin P, Helin H, Mäki M, Hällström O, Karvonen A-L** 1993 Follow-up of patients positive in reticulin and gliadin antibody tests with normal small bowel biopsy findings. Scand J Gastroenterol 28:595–598
28. **Corazza GR, Andreani ML, Biagi F, Bonvicini F, Bernardi M, Gasbarrini G** 1996 Clinical, pathological, and antibody pattern of latent celiac disease: report of three adult cases. Am J Gastroenterol 91:2203–2207
29. **Ferguson A, Arranz E, O'Mahony S** 1993 Clinical and pathological spectrum of coeliac disease—active, silent, latent, potential. Gut 34:150–151
30. **Holmes GKT** 2001 Potential and latent coeliac disease. Eur J Gastroenterol Hepatol 13:1057–1060
31. **Visakorpi JK, Mäki M** 1994 Changing clinical features of coeliac disease. Acta Paediatr Suppl 83:10–13
32. **Mora S, Barera G, Beccio S, Menni L, Proverbio MC, Bianchi C, Chiumello G** 2001 A prospective, longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. J Pediatr 139:516–521
33. **Valdimarsson T, Löfman O, Toss G, Ström M** 1996 Reversal of osteopenia with diet in adult coeliac disease. Gut 38:322–327
34. **Graham DR, Bellingham AJ, Alstead E, Krasner N, Martindale J** 1982 Coeliac disease presenting as acute bleeding disorders. Postgrad Med J 58:178–179
35. **Logan RFA, Tucker G, Rifkind EA, Heading RC, Ferguson A** 1983 Changes in clinical features of coeliac disease in adults in Edinburgh and the Lothians 1960–79. Br Med J 286:95–97
36. **Wahnschafffe U, Ullrich R, Riecken EO, Schulzke JD** 2001 Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. Gastroenterology 121:1329–1338
37. **Kaukinen K, Turjanmaa K, Mäki M, Partanen J, Venäläinen R,**

Reunala T, Collin P 2000 Intolerance to cereals is not specific for coeliac disease. Scand J Gastroenterol 35:942–946
38. **Bottaro G, Cataldo F, Rotolo N, Spina M, Corazza GR** 1999 The clinical pattern of subclinical/silent celiac disease: an analysis on 1026 consecutive cases. Am J Gastroenterol 94:691–696
39. **MacDonald WC, Dobbins WO, Rubin CE** 1965 Studies on the familial nature of coeliac sprue using biopsy of the small intestine. N Engl J Med 272:448–456
40. **Mäki M, Collin P** 1997 Coeliac disease. Lancet 349:1755–1759
41. **van der Meer JB** 1969 Granular deposits of immunoglobulins in the skin of patients with dermatitis herpetiformis. An immunofluorescent study. Br J Dermatol 81:493–503
42. **Reunala T, Kosnai I, Karpati S, Kuitunen P, Török E, Savilahti E** 1984 Dermatitis herpetiformis: jejunal findings and skin response to gluten-free diet. Arch Dis Child 59:517–522
43. **Reunala T, Collin P** 1997 Diseases associated with dermatitis herpetiformis. Br J Dermatol 136:315–318
44. **Collin P, Mäki M** 1994 Associated disorders in coeliac disease: clinical aspects. Scand J Gastroenterol 29:769–775
45. **Hadjivassiliou M, Gibson A, Davies-Jones GAB, Lobo AJ, Stephenson TJ, Milford-Wars A** 1996 Does cryptic gluten sensitivity play a part in neurological illness? Lancet 347:369–371
46. **Thain ME, Hamilton JR, Ehrlich RM** 1974 Coexistence of diabetes mellitus and celiac disease. J Pediatr 85:527–529
47. **Visakorpi JK** 1969 Diabetes and coeliac disease. Lancet 2:1192
48. **Shanahan F, McKenna R, McCarthy CF, Drury MI** 1982 Coeliac disease and diabetes mellitus: a study of 24 patients with HLA typing. Q J Med 51:329–335
49. **Cooper BT, Holmes GKT, Cooke WT** 1978 Coeliac disease and immunological disorders. Br Med J 1:537–539
50. **Lancaster-Smith MJ, Perrin J, Swarbrick ET, Wright JT** 1974 Coeliac disease and autoimmunity. Postgrad Med J 50:45–48
51. **Snook JA, de Silva HJ, Jewell DP** 1989 The association of autoimmune disorders with inflammatory bowel disease. Q J Med 72:835–840
52. **Collin P, Reunala T, Pukkala E, Laippala P, Keyriläinen O, Pasternack A** 1994 Coeliac disease-associated disorders and survival. Gut 35:1215–1218
53. **de Freitas IN, Sipahi AM, Damiao AO, de Brito T, Cancado EL, Leser PG, Laudanna AA** 2002 Celiac disease in Brazilian adults. J Clin Gastroenterol 34:430–434
54. **Boudraa G, Hachelaf W, Benbouabdellah M, Belkadi M, Benmansour FZ, Touhami M** 1996 Prevalence of coeliac disease in diabetic children and their first-degree relatives in West Algeria: screening with serological markers. Acta Paediatr Suppl 412:58–60
55. **Gadd S, Silink M, Kamath KR, Skerritt JH** 1992 Co-existence of coeliac disease and insulin-dependent diabetes mellitus in children: screening sere using an ELISA test for gliadin antibody. Aust NZ J Med 22:256–260
56. **Verge CF, Howard NJ, Rowley MJ, Mackay IR, Zimmet PZ, Egan M, Hulinska H, Hulinsky I, Silvestrini RA, Kamath S, Sharp A, Arundel T, Silink M** 1994 Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population-based study. Diabetologia 37:1113–1120
57. **Schober E, Granditsch G** 1994 IDDM and celiac disease. Diabetes Care 17:1549–1550
58. **Schober E, Bittmann B, Granditsch G, Huber WD, Huppe A, Jager A, Oberhuber G, Rami B, Reichel G** 2000 Screening by anti-endomysium antibody for celiac disease in diabetic children and adolescents in Austria. J Pediatr Gastrenterol Nutr 30:391–396
59. **De Block CE, De Leeuw IH, Vertommen JJ, Rooman RP, Su Caju MV, Van Campenhout CM, Veyler JJ, Winnock F, Van Autreve J, Gorus FK** 2001 β-Cell, thyroid, gastric, adrenal and coeliac autoimmunity and HLA-DQ types in type 1 diabetes. Clin Exp Immunol 126:184–186
60. **Fraser-Reynolds KA, Butzner JD, Stephure DK, Trussell RA, Scott RB** 1998 Use of immunoglobulin A-antiendomysial antibody to screen for celiac disease in North American children with type 1 diabetes. Diabetes Care 21:1985–1989
61. **Gillett PM, Gillett HR, Israel DM, Metzger DL, Stewart L, Chanoine JP, Freeman HJ** 2001 High prevalence of celiac disease in patients with type I diabetes detected by antibodies to endomysium and tissue transglutaminase. Can J Gastroenterol 15:297–301
62. **Sumnik Z, Kolouskova S, Cinek O, Kotalova R, Vavrinec J, Snajderova M** 2000 HLA-DQA1*05-DQB1*0201 positivity predisposes to coeliac disease in Czech diabetic children. Acta Paediatr 89:1426–1430
63. **Hansen D, Bennedbaek FN, Hansen LK, Hoier-Madsen M, Hegedu LS, Jacobsen BB, Husby S** 2001 High prevalence of coeliac disease in Danish children with type I diabetes mellitus. Acta Paediatr 90:1238–1243
64. **Mäki M, Hällström O, Huupponen T, Vesikari T, Visakorpi JK** 1984 Increased prevalence of coeliac disease in diabetes. Arch Dis Child 59:739–742
65. **Savilahti E, Simell O, Koskimies S, Rilva A, Åkerblom HK** 1986 Celiac disease in insulin-dependent diabetes mellitus. J Pediatr 108:690–693
66. **Collin P, Salmi J, Hällström O, Oksa H, Oksala H, Mäki M, Reunala T** 1989 High frequency of coeliac disease in adult patients with type-I diabetes. Scand J Gastroenterol 24:81–84
67. **Kontiainen S, Schlenzka A, Koskimies S, Rilva A, Mäenpää J** 1990 Autoantibodies and autoimmune diseases in young diabetics. Diabetes Res 13:151–156
68. **Saukkonen T, Savilahti E, Reijonen H, Ilonen J, Tuomilehto-Wolf E, Åkerblom HK** 1996 Coeliac disease: frequent occurrence after clinical onset of insulin-dependent diabetes mellitus. Diabet Med 13:464–470
69. **Koletzko S, Burgin-Wolff A, Koletzko B, Knapp M, Burger W, Gruneklee D, Herz G, Ruch W, Thon A, Wendel U, Zuppinger K** 1988 Prevalence of coeliac disease in diabetic children and adolescents. A multicentre study. Eur J Pediatr 148:113–117
70. **Kordonouri O, Dietrich W, Schuppan D, Webert G, Muller C, Sarioglu N, Becker M, Danne T** 2000 Autoantibodies to tissue transglutaminase are sensitive serological parameters for detecting silent coeliac disease in patients with type I diabetes mellitus. Diabet Med 17:441–444
71. **Seissler J, Schott M, Boms S, Wohlrab U, Ostendorf B, Morgenthaler NB, Scherbaum WA** 1999 Autoantibodies to human tissue transglutaminase indetify silent coeliac disease in type I diabetes. Diabetologia 42:1440–1441
72. **Cronin C, Feighery A, Ferriss BJ, Liddy C, Shanahan F, Feighery C** 1997 High prevalence of celiac disease among patients with insulin-dependent (type I) diabetes mellitus. Am J Gastroenterol 92:2210–2212
73. **Cacciari E, Salardi S, Volta U, Biasco G, Partesotti S, Mantovani A, Cicognani A, Tonioli S, Tassoni P, Pirazzoli P, Bianchi FB, Barboni F, Pisi E** 1987 Prevalence and characteristics of coeliac disease in type 1 diabetes mellitus. Acta Paediatr Scand 76:671–672
74. **Barera G, Bianchi C, Calisti L, Cerutti F, Dammacco F, Frezza E, Illeni MT, Mistura L, Pocecco M, Prisco F, Sacchetti C, Saggese G, Stoppoloni G, Tonini G, Chiumello G** 1991 Screening of diabetic children for coeliac disease with antigliadin antibodies and HLA typing. Arch Dis Child 66:491–494
75. **Sategna-Guidetti C, Grosso S, Pulitano R, Benaduce E, Dani F, Carta Q** 1994 Celiac disease and insulin-dependent diabetes mellitus. Screening in an adult population. Dig Dis Sci 39:1633–1637
76. **Pocecco M, Ventura A** 1995 Coeliac disease and insulin-dependent diabetes mellitus: a causal association? Acta Paediatr 84:1432–1433
77. **Nosari I, Casati A, Mora C, Astulfoni A, Cortinovis F, Maglio ML, Lepore G** 1996 The use of IgA-antiendomysial antibody test for screening coeliac disease in insulin-dependent diabetes mellitus. Diabetes Nutr Metab 9:267–272
78. **Lorini R, Scaramuzza A, Vitali L, d'Annunzio G, Avanzini A, De Giacomo C, Severi F** 1996 Clinical aspects of coeliac disease in children with insulin-dependent diabetes mellitus. J Pediatr Endocrinol Metab 9:101–111
79. **De Vitis I, Ghirlanda G, Gasbarrini G** 1996 Prevalence of coeliac disease in type I diabetes: a multicentre study. Acta Paediatr Suppl 412:56–57
80. **Not T, Tommasini A, Tonini G, Buratti E, M. P, Tortul C, Valussi M, Crichiutti G, Berti I, Trevisiol C, Azzoni E, Neri E, Torre G, Martelossi S, Soban M, Lenhardt A, Cattin L, Ventura A** 2001 Undiagnosed coeliac disease and risk of autoimmune disorders in subjects with type I diabetes mellitus. Diabetologia 44:151–155
81. **Calero P, Ribes-Koninckx V, Albiach V, Carles C, Ferrer J** 1996 IgA antigliadin antibodies as a screening method for nonovert

celiac disease in children with insulin-dependent diabetes mellitus. J Pediatr Gastroenterol Nutr 23:29–33
82. **Roldan MB, Barrio R, Roy G, Parra C, Alonso M, Yturriaga R** 1998 Diagnostic value of serological markers for celiac disease in diabetic children and adolescents. J Pediatr Endocrinol Metab 11:751–756
83. **Vitoria JC, Castano L, Rica I, Bilbao JR, Arrieta A, Garcia-Masdevall MD** 1998 Association of insulin-dependent diabetes mellitus and celiac disease: a study based on serological markers. J Pediatr Gastroenterol Nutr 27:47–52
84. **Sigurs N, Johansson C, Elfstrand P-O, Viander M, Lanner A** 1993 Prevalence of coeliac disease in diabetic children and adolescents in Sweden. Acta Paediatr 82:748–751
85. **Stenhammar L, Strömberg L, Fälth-Magnusson K, Ludvigsson J** 1993 Celiac disease and diabetes mellitus. Ann Allergy 71:80–81
86. **Sjöberg K, Eriksson KF, Brendberg A, Wassmuth R, Eriksson S** 1998 Screening for coeliac disease in adult insulin-dependent diabetes mellitus. J Intern Med 243:133–140
87. **Carlsson AK, Axelsson IEM, Borulf SK, Bredberg ACA, Lindberg BA, Sjöberg KG, Ivarson SA** 1999 Prevalence of IgA-antiedomysium and IgA-antigliadin autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children and adolescents. Pediatrics 103:1248–1252
88. **Page SR, Lloyd CA, Hill PG, Peacock I, Holmes GKT** 1994 The prevalence of coeliac disease in adult diabetes mellitus. Q J Med 87:631–637
89. **Acerini CL, Ahmed ML, Ross KM, Sullivan PB, Bird G, Dunger DB** 1998 Coeliac disease in children and adolescents with IDDM: clinical characteristics and response to gluten-free diet. Diabet Med 15:38–44
90. **Rossi TM, Albini CH, Kumar V** 1993 Incidence of celiac disease identified by the presence of serum endomysial antibodies in children with chronic diarrhea, short stature, or insulin-dependent diabetes mellitus. J Pediatr 123:262–264
91. **Rensch MJ, Merenich JA, Lieberman M, Long BD, Davis DR, McNally PR** 1996 Gluten-sensitive enteropathy in patients with insulin-dependent diabetes mellitus. Ann Intern Med 124:564–567
92. **Talal AH, Murray JA, Goeken JA, Sivitz WI** 1997 Celiac disease in an adult population with insulin-dependent diabetes mellitus: use of endomysial antibody testing. Am J Gastroenterol 92:1280–1284
93. **Aktay AN, Lee PC, Kumar V, Parton E, Wyatt DT, Werlin SL** 2001 The prevalence and clinical characteristics of celiac disease in juvenile diabetes in Wisconsin. J Pediatr Gastroenterol Nutr 33: 462–465
94. **Gregory C, Ashworth M, Eade OE, Holdstock G, Smith CL, Wright R** 1983 Delay in diagnosis of adult coeliac disease. Digestion 28:201–204
95. **Westman E, Ambler G, Royle M, Peat J, Chan A** 1999 Children with coeliac disease and insulin dependent diabetes mellitus—growth, diabetes control and dietary intake. J Pediatr Endocrinol Metab 12:433–442
96. **Iafusco D, Rea F, Prisco F** 1998 Hypoglycemia and reduction of the insulin requirement as a sign of celiac disease in children with IDDM. Diabetes Care 21:1379–1380
97. **Kaukinen K, Salmi J, Lahtela J, Siljamäki-Ojansuu U, Koivisto A-M, Oksa H, Collin P** 1999 No effect of gluten-free diet on the metabolic control of type 1 diabetes in patients with diabetes and celiac disease. Retrospective and controlled prospective survey. Diabetes Care 22:1747–1748
98. **Mohn A, Cerruto M, Iafrusco D, Prisco F, Tumini S, Stoppoloni O, Chiarelli F** 2001 Celiac disease in children and adolescents with type 1 diabetes: importance of hypoglycemia. J Pediatr Gastroenterol Nutr 32:37–40
99. **Mäki M, Hällström O, Vesikari T, Visakorpi JK** 1984 Evaluation of a serum IgA-class reticulin antibody test for the detection of childhood celiac disease. J Pediatr 105:901–905
100. **Catassi C, Natalini G, Ratsch IM, Gabrielli O, Coppa GV, Giorgi PL** 1991 Documented latent coeliac disease in a child with insulin-dependent diabetes mellitus. Eur J Pediatr 150:832–834
101. **Cacciari E, Bianchi FB, Salardi S, Bazzoli F, De Franceschi L, Volta U** 1997 Late development of IgA antiendomycial antibodies and small intestinal mucosal atrophy after insulin dependent diabetes mellitus onset. Arch Dis Child 77:465
102. **Lorini R, Scotta MS, Cortona L, Avanzini MA, Vitali L, De Giacomo C, Scaramuzza A, Severi F** 1996 Celiac disease and type I (insulin-dependent) diabetes mellitus in childhood: follow-up study. J Diabetes Complications 10:154–159
103. **Mäki M, Huupponen T, Holm K, Hällström O** 1995 Seroconversion of reticulin autoantibodies predicts coeliac disease in insulin dependent diabetes mellitus. Gut 36:239–242
104. **Midhagen G, Järnerot G, Kraaz W** 1988 Adult coeliac disease within a defined geographic area in Sweden. A study of prevalence and associated diseases. Scand J Gastroenterol 23:1000–1004
105. **Siurala M, Julkunen H, Lamberg BA** 1966 Gastrointestinal tract in hyperthyroidism before and after treatment. Scand J Gastroenterol 1:79–85
106. **Siurala M, Varis K, Lamberg BA** 1968 Intestinal absorption and autoimmunity in endocrine disorders. Acta Med Scand 184:53–64
107. **Kuitunen P, Mäenpää J, Krohn K, Visakorpi JK** 1971 Gastrointestinal findings in autoimmune thyroiditis and non-goitrous juvenile hypothyroidism in children. Scand J Gastroenterol 6:335–341
108. **Cunningham MJ, Zone JJ** 1985 Thyroid abnormalities in dermatitis herpetiformis. Ann Intern Med 102:194–196
109. **Weetman AP, Burrin JM, Mackay D, Leonard JN, Griffiths CEM, Fry L** 1988 The prevalence of thyroid autoantibodies in dermatitis herpetiformis. Br J Dermatol 118:377–383
110. **Gaspari AA, Huang C-M, Davey RJ, Bondy C, Lawley TJ, Katz SI** 1990 Prevalence of thyroid abnormalities in patients with dermatitis herpetiformis and in control subjects with HLA-B8/-DR3. Am J Med 88:145–150
111. **Counsell CE, Taha A, Ruddell WSJ** 1994 Coeliac disease and autoimmune thyroid disease. Gut 35:844–846
112. **Freeman HJ** 1995 Celiac-associated autoimmune thyroid disease: a study of 16 patients with overt hypothyroidism. Can J Gastroenterol 9:242–246
113. **Sategna-Guidetti C, Bruno M, Mazza E, Carlino A, Predebon S, Tagliabue M, Brossa C** 1998 Autoimmune thyroid diseases and coeliac disease. Eur J Gastroenterol Hepatol 10:927–931
114. **Velluzzi F, Caradonna A, Boy MF, Pinna MA, Cabula R, Lai MA, Piras E, Corda G, Mossa P, Atzeni F, Loviselli A, Mariotti S** 1998 Thyroid and celiac disease: clinical, serological and echographic study. Am J Gastroenterol 93:976–979
115. **Zettinig G, Weissel M, Flores J, Dudczak R, Vogelsang H** 2000 Dermatitis herpetiformis is associated with atrophic but not with goitrous variant of Hashimoto's thyroiditis. Eur J Clin Invest 30: 53–57
116. **Toscano V, Conti FG, Anastasi E, Mariani P, Tiberti C, Poggi M, Montuori M, Monti S, Laureti S, Cipolletta E, Gemme G, Caiola S, Di Mario U, Bonamico M** 2000 Importance of gluten in the induction of endocrine autoantibodies and organ dysfunction in adolescent celiac patients. Am J Gastroenterol 95:1742–1748
117. **Sategna-Guidetti C, Volta U, Ciacci C, Usai P, Carlino A, De Francesci L, Camera A, Pelli A, Brossa C** 2001 Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. Am J Gastroenterol 96:751–757
118. **Hakanen M, Luotola K, Salmi J, Laippala P, Kaukinen K, Collin P** 2001 Clinical and subclinical autoimmune thyroid disease in adult celiac disease. Dig Dis Sci 46:2631–2635
119. **Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH** 1990 American Thyroid Association guideline for use of laboratory tests in thyroid disorders. JAMA 263:1529–1532
120. **Weetman AP** 2000 Graves' disease. N Engl J Med 343:1236–1248
121. **Dayan CM, Daniels GH** 1996 Chronic autoimmune thyroiditis. N Engl J Med 335:99–105
122. **Collin P, Salmi J, Hällström O, Reunala T, Pasternack A** 1994 Autoimmune thyroid disorders and coeliac disease. Eur J Endocrinol 130:137–140
123. **Cuoco L, Certo M, Jorizzo RA, De Vitis I, Tursi A, Papa A, De Marinis L, Fedeli P, Fedeli G, Gaspar G** 1999 Prevalence and early diagnosis of coeliac disease in autoimmune thyroid disorders. Ital J Gastroenterol Hepatol 31:283–287
124. **Carroccio A, Custro N, Montalto G, Giannitrapani L, Soresi M, Notarbartolo A** 1999 Evidence of transient IgA-endomysial antibody positivity in a patient with Graves' disease. Digestion 60: 86–88

125. **Valentino R, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, Micillo M, Paparo F, Petrone E, Lombardi G, Troncone R** 1999 Prevalence of coeliac disease in patients with thyroid disease. Horm Res 51:124–127
126. **Berti I, Trevisiol C, Tommasini A, Citta A, Neri E, Geatti O, Giammarini A, Ventura A, Not T** 2000 Usefulness of screening program for celiac disease in autoimmune thyroiditis. Dig Dis Sci 45:403–406
127. **Kumar V, Rajadhyaksha M, Wortsman J** 2001 Celiac disease-associated autoimmune endocrinopathies. Clin Diagn Lab Immunol 8:678–685
128. **Meloni GF, Tomasi PA, Bertoncelli A, Fanciulli G, Delitala G, Meloni T** 2001 Prevalence of silent celiac disease in patients with autoimmune thyroiditis from Northern Sardinia. J Endocrinol Invest 24:298–302
129. **Volta U, Ravaglia G, Granito A, Forti P, Petrolini N, Zoli M, Bianchi FB** 2001 Coeliac disease in patients with autoimmune thyroiditis. Digestion 64:61–65
130. **Larizza D, Calcaterra V, De Giacomo C, De Silvestri A, Asti M, Badulli C, Autelli M, Coslovich E, Martinetti M** 2001 Celiac disease in children with autoimmune thyroid disease. J Pediatr 139: 738–740
131. **Valentino R, Savastano S, Maglio M, Paparo F, Ferrara F, Dorato M, Lombardi G, Troncone R** 2002 Markers of potential coeliac disease in patients with Hashimoto's thyroiditis. Eur J Endocrinol 146:479–483
132. **Cooke WT, Holmes GKT** 1984 Coeliac disease. Edinburgh: Churchill Livingstone
133. **Reunala T, Salmi J, Karvonen J** 1987 Dermatitis herpetiformis and celiac disease associated with Addison's disease. Arch Dermatol 123:930–932
134. **Zelissen PMJ, Bast EJEG, Croughs RJM** 1995 Associated autoimmunity in Addison's disease. J Autoimmun 8:121–130
135. **Henegan MA, McHugh P, Stevens FM, McCarthy CF** 1997 Addison's disease and selective IgA deficiency in two coeliac patients. Scand J Gastroenterol 32:509–511
136. **O'Leary C, Walsh CH, Wieneke P, O'Regan P, Buckley B, O'Halloran DJ, Ferriss JB, Quigley EMM, Annis P, Shanahan FL, Cronin CC** 2002 Celiac disease and autoimmune Addison's disease: a clinical pitfall. Q J Med 95:79–82
137. **Raymakers JA** 1987 Autonomous hyperparathyroidism in a patient with adult coeliac disease. Neth J Med 31:308–311
138. **Kumar V, Valeski JE, Wortsman J** 1996 Celiac disease and hypoparathyroidism: cross-reaction of endomysial antibodies with parathyroid tissue. Clin Diagn Lab Immunol 3:143–146
139. **Matsueda K, Rosenberg IH** 1982 Malabsorption with idiopathic hypoparathyroidism responding to treatment for coincident celiac sprue. Dig Dis Sci 27:269–273
140. **Collin P, Hakanen M, Salmi J, Mäki M, Kaukinen K** 2001 Autoimmune hypopituitarism in patients with coeliac disease—symptoms confusingly similar. Scand J Gastroenterol 36:558–560
141. **Corazza GR, Andreani ML, Venturo N, Bernardi M, Tosti A, Gasbarrini G** 1995 Celiac disease and alopecia areata: report of a new association. Gastroenterology 109:1333–1337
142. **Volta U, Bardazzi F, Zauli D, DeFranceschi L, Tosti A, Molinaro N, Ghetti S, Tetta C, Grassi A, Bianchi FB** 1997 Serological screening for coeliac disease in vitiligo and alopecia areata. Br J Dermatol 136:801–802
143. **Barbato M, Viola F, Grillo R, Franchin L, Lo Russo L, Lucarelli S, Frediani T, Mazzilli MC, Cardi E** 1998 Alopecia and coeliac disease: reports of two patients showing response to gluten-free diet. Clin Exp Dermatol 23:230–240
144. **Kaukinen K, Collin P, Mykkänen A-H, Partanen J, Mäki M, Salmi J** 1999 Celiac disease and autoimmune endocrinologic disorders. Dig Dis Sci 44:1428–1433
145. **Valentino R, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, Lombardi G, Troncone R** 1999 Unusual association of thyroiditis, Addison's disease, ovarian failure and celiac disease in a young woman. J Endocrinol Invest 22:390–394
146. **Collin P, Vilska S, Heinonen PK, Hällström O, Pikkarainen P** 1996 Infertility and coeliac disease. Gut 39:382–384
147. **Meloni GF, Dessole S, Vargiu N, Tomasi PA, Musumeci S** 1999 The prevalence of coeliac disease in infertility. Hum Reprod 14: 2759–2761
148. **Gasparrini A, Torre E, Trivellini C, De Carolis S, Caruso A, Gasparrini G** 2000 Recurrent spontaneous abortion and intrauterine fetal growth retardation as symptoms of coeliac disease. Lancet 356:399–400
149. **Kolho K-L, Tiitinen A, Tulppala M, Unkila-Kallio L, Savilahti E** 1999 Screening for coeliac disease in women with a history of recurrent miscarriage and infertility. Br J Obstet Gynaecol 106: 171–173
150. **Ferguson R, Holmes GKT, Cooke WT** 1982 Coeliac disease, fertility and pregnancy. Scand J Gastroenterol 17:65–68
151. **McCann JP, Nicholls DP, Verzin JA** 1988 Adult coeliac disease presenting with infertility. Ulster Med J 57:88–89
152. **Sher KS, Jayanthi V, Probert CS, Stewart CR, Mayberry JF** 1994 Infertility, obstetric and gynaecological problems in coeliac sprue. Dig Dis 12:186–190
153. **Farthing MJ, Rees LH, Dawson AM** 1983 Male gonadal function in coeliac disease. III. Pituitary regulation. Clin Endocrinol (Oxf) 19:661–671
154. **Farthing MJG, Rees LH, Edwards CRW, Dawson AM** 1983 Male gonadal function in coeliac disease. 2. Sex hormones. Gut 24: 127–135
155. **Ludvigsson JF, Ludvigsson J** 2001 Coeliac disease in the father affects the newborn. Gut 49:169–175
156. **Greco L** 2001 The father figure in coeliac disease. Gut 49:163
157. **Martinelli P, Troncone R, Paparo F, Torre P, Trapanese E, Fasano C, Lamberti A, Budillon G, Nardone G, Greco L** 2000 Coeliac disease and unfavourable outcome of pregnancy. Gut 46:332–335
158. **Norgard B, Fonager K, Sorensen H, Olsen J** 1999 Birth outcomes of women with celiac disease: a nationwide historical cohort study. Am J Gastroenterol 94:2435–2440
159. **Polanco I, Biemond I, van Leeuwen A, Schreuder I, Meera Khan P, Guerrero J, D'Amaro J, Vazques C, van Rood JJ, Pena AS** 1981 Gluten sensitive enteropathy in Spain: genetic and environmental factors. In: McConell RB, ed. The genetics of coeliac disease. Lancaster, UK: MTP Press; 211–234
160. **Mearin ML, Biemond I, Pena AS, Polanco I, Vazquez C, Schreuder GT, de Vries RR, van Rood JJ** 1983 HLA-DR phenotypes in Spanish coeliac children: their contribution to the understanding of the genetics of the disease. Gut 24:532–537
161. **Hervonen K, Karell K, Holopainen P, Collin P, Partanen J, Reunala T** 2000 Concordance of dermatitis herpetiformis in monozygous twins. J Invest Dermatol 115:990–993
162. **Sollid LM, Markussen G, Ek J, Gjerde H, Vartdal F, Thorsby E** 1989 Evidence for a primary association of celiac disease to a particular HLA-DQ α/β heterodimer. J Exp Med 169:345–350
163. **Michalski JP, McCombs CC, Arai T, Elston RC, Cao T, McCarthy CF, Stevens FM** 1996 HLA-DR, DQ genotypes of celiac disease patients and healthy subjects from the West of Ireland. Tissue Antigens 47:127–133
164. **Polvi A, Eland C, Koskimies S, Mäki M, Partanen J** 1996 HLA DQ and DP in Finnish families with coeliac disease. Eur J Immunogen 23:221–234
165. **Balas A, Vicario JL, Zambrano A, Acuna D, Garcia-Novo D** 1997 Absolute linkage of celiac disease and dermatitis herpetiformis. Tissue Antigens 50:52–56
166. **Polvi A, Arranz E, Fernandez-Arquero M, Collin P, Mäki M, Sanz A, Calvo C, Maluenda C, Westman P, de la Concha EG, Partanen J** 1998 HLA-DQ2-negative celiac disease in Finland and Spain. Hum Immunol 59:169–175
167. **Zhong F, McCombs CC, Olson JM, Elston RC, Stevens FM, McCarthy CF, Michalski JP** 1996 An autosomal screen for genes that predispose to celiac disease in the western counties of Ireland. Nat Genet 14:329–333
168. **Houlston RS, Tomlinson IP, Ford D, Seal S, Marossy AM, Ferguson A, Holmes GKT, Hosie KB, Howdle PD, Jewell DP, Godkin A, Kerr GD, Kumar P, Logan RF, Love AH, Johnston S, Marsh MN, Mitton S, O'Donoghue D, Roberts A, Walker-Smith JA, Stratton MF** 1997 Linkage analysis of candidate regions for coeliac disease genes. Hum Mol Genet 6:1335–1339
169. **Greco L, Corazza G, Babron M-C, Clot F, Fulchignoni-Lataud M-C, Percopo S, Zavattari P, Bouguerra F, Dib C, Tosi R, Tron-**

cone R, Ventura A, Mantavoni W, Magazzu G, Gatti R, Lazzari R, Giunta A, Perri F, Iacono G, Cardi E, de Virgiliis S, Cataldo F, De Angelis G, Musumeci S, Ferrari R, Balli F, Bardella M-T, Volta U, Catassi C, Torre G, Eliaou J-F, Serre J-L, Clerget-Darpoux F 1998 Genome search in celiac disease. Am J Hum Genet 62:669–675

170. **Greco L, Babron MC, Corazza GR, Percopo S, Sica R, Clot F, Fulchignoni-Lataud MC, Zavattari P, Momigliano-Richiardi P, Casari G, Gasparini P, Tosi R, Mantovani V, De Virgilis S, Iacono G, DÁlfonso A, Selinger-Leneman H, Lemainque A, Serre JL, Clerget-Darpoux F** 2001 Existence of a genetic risk factor on chromosome 5q in Italian coeliac disease families. Ann Hum Genet 65:35–41
171. **Holopainen P, Mustalahti K, Uimari P, Collin P, Mäki M, Partanen J** 2001 Candidate gene regions and genetic heterogeneity in gluten sensitivity. Gut 48:696–701
172. **Holopainen P, Arvas M, Sistonen P, Mustalahti K, Collin P, Mäki M, Partanen J** 1999 CD28/CTLA4 gene region on chromosome 2q3 confers genetic susceptibility to celiac disease. A linkage and family-based association study. Tissue Antigens 53:470–475
173. **Lie BA, Sollid LM, Ascher H, Ek J, Akselsen HE, Ronningen KS, Thorsby E, Undlien DE** 1999 A gene telomeric of the HLA class I region is involved in predisposition to type I diabetes and coeliac disease. Tissue Antigens 54:162–168
174. **Lie BA, Todd JA, Pochiot F, Nerup J, Akselsen HE, Joner G, Dahl-Jorgensen K, Ronningen KS, Thorsby E, Undlien DE** 1999 The predisposition to type I diabetes linked to the human leucocyte antigen complex includes at least one non-class II gene. Am J Hum Genet 64:793–800
175. **Liu J, Juo SH, Holopainen P, Terwilliger J, Tong X, Grunn A, Brito M, Green P, Mustalahti K, Mäki M, Gilliam TC, Partanen J** 2002 Genomewide linkage analysis of celiac disease in Finnish families. Am J Hum Genet 70:51–59
176. **Buzetti R, Quattrocchi CC, Nistico L** 1998 Dissecting the genetics of type I diabetes: relevance for familial clustering and differences in incidence. Diabetes Metab Rev 14:111–128
177. **Atkinson MA, Eisenbarth GS** 2001 Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet 358:221–229
178. **Hummel M, Bonafacio E, Stern M, Becker M, Dittler J, Schimmel A, Ziegler AG** 2000 Development of celiac disease-associated antibodies in offspring of parents with type I diabetes. Diabetologia 43:1005–1011
179. **Williams AJK, Norcross AJ, Lock RJ, Unsworth DJ, Gale EAM, Bingley PJ** 2001 The high prevalence of autoantibodies to tissue transglutaminase in first-degree relatives of patients with type 1 diabetes is not associated with islet autoimmunity. Diabetes Care 24:504–509
180. **Saukkonen T, Ilonen J, Åkerblom HK, Savilahti E** 2001 Prevalence of coeliac disease in siblings of patients with type I diabetes is related fo the prevalence of DQB1*02 allele. Diabetologia 44: 1051–1053
181. **Stenzsky V, Balazs C, Kraszits E, Juhasz F, Kozma L, Balazs G, Farid NR** 1987 Assocation of goitrous autoimmune thyroiditis with HLA-DR3 in Eastern Hungary. J Immunogenet 14:143–148
182. **Weetman AP, McGregor AM** 1994 Autoimmune thyroid disease: further developments in our understanding. Endocr Rev 15: 788–830
183. **Yanagawa T, Manglabruks A, Chang Y-B, Okamoto Y, Fisfalen M-E, Curran PG, de Groot LJ** 1993 Human histocompatibility leucocyte antigen-DQa*0501 allele associated with genetic susceptibility to Graves' disease in a Caucasian population. J Clin Endocrinol Metab 76:1569–1574
184. **Heward JM, Allahabadia A, Armitage M, Hattersley A, Dodson PM, Macleod K, Carr-Smith J, Daykin J, Daly A, Sheppard MC, Holder RL, Barnett AH, Franklyn JA, Gough SC** 1999 The development of Graves' disease and the CTLA-4 gene on chromosome 2q33. J Clin Endocrinol Metab 84:2398–2401
185. **Dalton TA, Bennet JC** 1992 Autoimmune disease and major histocompatibility complex: therapeutic implications. Am J Med 92: 183–188
186. **Tredjosiewics LK, Howdle PD** 1995 T-cell responses and cellular immunity in coeliac disease. Baillieres Clin Gastroenterol 9:251–272
187. **Sollid LM, Molberg O, McAdam S, Lundin KEA** 1997 Autoantibodies in coeliac disease: tissue transglutaminase—guilt by association. Gut 41:851–852
188. **Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, Schuppan D** 1997 Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 3:797–801
189. **Piacentini M, Colizzi V** 1999 Tissue transglutaminase: apoptosis *vs.* autoimmunity. Immunol Today 3:130–134
190. **Lundin KEA, Scott H, Hansen T, Paulsen G, Halstensen TS, Fausa O, Thorsby E, Sollid LM** 1993 Gliadin-specific, HLA-DQ(α1*0501, β1*0201) restricted T cells isolated from the small intestinal mucosa of celiac disease patients. J Exp Med 178:87–96
191. **Molberg O, Mcadam SN, Korner R, Quarsten H, Kristiansen C, Madsen L, Fugger L, Scott H, Noren O, Roepstorff P, Lundin KE, Sjöström H, Sollid LM** 1998 Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. Nat Med 4:713–717
192. **Molberg O, McAdam S, Lundin KEA, Kristiansen C, Arentz-Hansen H, Kett K, Sollid LM** 2001 T cells from celiac disease lesions recognize gliadin epitopes deamidated *in situ* by endogenous tissue transglutaminase. Eur J Immunol 31:1317–1323
193. **van de Wal Y, Kooy Y, van Veelen P, Pena S, Mearin L, Papadopoulos G, Koning F** 1998 Cutting edge: selective deamidation by tissue transglutaminase strongly enhances gliadin-specific T cell reactivity. J Immunol 161:1585–1588
194. **Nilsen EM, Jahnsen FL, Lundin KEA, Johansen F-E, Fausa O, Sollid LM, Jahnsen J, Scott H, Brandtzaeg P** 1998 Gluten induces an intestinal cytokine response strongly dominated by interferon γ in patients with celiac disease. Gastroenterology 115:551–563
195. **Pender SL, Tickle SP, Docherty AJ, Howie D, Wathen NC, MacDonald TT** 1997 A role of matrix metalloproteinases in T cell injury in the gut. J Immunol 158:1582–1590
196. **Daum S, Bauer U, Foss HD, Schuppan D, Stein H, Riecken EO, Ullrich R** 1999 Increased expression of mRNA for matrix metalloproteinase-1 and -3 and tissue inhibitor of metalloproteinases-1 in intestinal biopsy specimens from patients with coeliac disease. Gut 44:17–25
197. **Picarelli A, Maiuri L, Frate A, Greco M, Auricchio S, Londei M** 1996 Production of antiendomysial antibodies after in-vitro gliadin challenge of small intestine biopsy samples from patients with coeliac disease. Lancet 348:1065–1067
198. **Marzari R, Sblattero D, Florian F, Tongiorgi E, Not T, Tommasini A, Ventura A, Brandbury A** 2001 Molecular dissection of tissue transglutaminase autoantibody response in celiac disease. J Immunol 166:4170–4176
199. **Halttunen T, Mäki M** 1999 Serum immunoglobulin A from patients with celiac disease inhibits human T84 intestinal crypt epithelial cell differentiation. Gastroenterology 116:566–572
200. **Schuppan D** 2000 Current concepts of celiac disease pathogenesis. Gastroenterology 119:234–242
201. **Lerner A, Blank M, Lahat N, Shoenfeld Y** 1998 Increased prevalence of autoantibodies in celiac disease. Dig Dis Sci 43:723–726
202. **da Rosa Utiyama SR, Da Silva Kotze LM, Nisihara RM, Carvalho RF, de Carvalho EG, de Sena MG, de Messias Reason IJ** 2001 Spectrum of autoantibodies in celiac patients and relatives. Dig Dis Sci 46:2624–2630
203. **Kim S-Y, Jeitner TM, Steinert PM** 2002 Transglutaminases in disease. Neurochem Int 20:85–103
204. **Paronen J, Klemetti P, Kantele JM, Savilahti E, Perheentupa J, Åkerblom HK, Vaarala O** 1997 Glutamate decarboxylase-reactive peripherial blood lymphocytes from patients with IDDM express gut-specific homing receptor $\alpha4\beta7$-integrin. Diabetes 46:583–588
205. **Yang XD, Michie SA, Tisch R, Karin N, Steinman L, McDevitt H** 1994 A predominant role of inte $\alpha4$ in the spontaneus development of autoimmune diabetes in non-obese diabetic mice. Proc Natl Acad Sci USA 91:12604–12608
206. **Bao F, Yu L, Babu S, Wang T, Hoffenberg EJ, Rewers M, Eisenbarth GS** 1999 One third of HLA DQ2 homozygous patients with type I diabetes express celiac disease-associated transglutaminase antibodies. J Autoimmun 13:143–148
207. **Juby LD, Dixon MF, Axon AT** 1987 Abnormal intestinal permeability and jejunal morphometry. J Clin Pathol 40:714–718
208. **Bjarnason I, Peters TJ, Veall N** 1983 A persistent defect in intestinal

permeability in coeliac disease demonstrated by a 51Cr-labelled EDTA absorption test. Lancet 1:323–325
209. **Fasano A** 2001 Intestinal zonulin: open sesame! Gut 49:159–162
210. **Meddings JB, Jarand S, Urbanski SJ, Hardin J, Gall G** 1999 Increased gastrointestinal permeability in an early lesion in the spontaneously diabetic BB rat. Am J Physiol 276:G951–G957
211. **Funda DP, Kaas A, Bock T, Tlaskalova-Hogenova H, Buschard K** 1999 Guten-free diet protects diabetes in NOD mice. Diabetes Metab Res Rev 15:323–327
212. **Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Glodblum SE** 2000 Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. Lancet 355: 1518–1519
213. **Watts T, Berti I, Not T, Asmar R, Pierro MD, Margaretten K, Fasano A** 2000 Zonulin secretion may indicate changes in intestinal permeability associated with the onset of diabetes in BB/Wor diabetic rats. Gastroenterology 118:A603
214. **Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma V-M, Järvinen RMK, Uusitupa MIJ, Julkunen RJK** 1995 A comparison of diets with and without oats in adults with celiac disease. N Engl J Med 333:1033–1037
215. **Kagnoff MF, Austin RK, Hubert JJ, Bernardin JE, Kasarda DD** 1984 Possible role for a human adenovirus in the pathogenesis of celiac disease. J Exp Med 160:1544–1557
216. **Mahon J, Blair GE, Wood GM, Scott BB, Losowsky MS, Howdle PD** 1991 Is persistent adenovirus 12 infection involved in coeliac disease? A search for viral DNA using the polymerase chain reaction. Gut 32:1114–1116
217. **Brandtzaeg P, Halstensen TS, Kett K, Krajci P, Kvale D, Rognum TO, Scott H, Sollid LM** 1989 Immunobiology and immunopathology of human gut mucosa: humoral immunity and intraepithelial lymphocytes. Gastroenterology 97:1562–1584
218. **Stewart K, Willoughby JM** 1988 Postnatal presentation of coeliac disease. Br Med J 297:1245
219. **Othman S, Phillips DIW, Parkes AB, Richards CJ, Harris B, Fung H, Darke C, John R, Hall R, Lazarus JH** 1990 A long-term follow-up of postpartum thyroiditis. Clin Endocrinol (Oxf) 32: 559–564
220. **Jansson R** 1986 Postpartum thyroid disease. Mol Biol Med 3: 201–211
221. **Hinks LJ, Inwards KD, Lloyd B, Clayton BE** 1984 Body content of selenium in coeliac disease. Br Med J 288:1862–1863
222. **Sher L** 2000 Selenium and human health. Lancet 356:233–241
223. **Chanoine JP, Neve J, Wu S, Vanderpas J, Bourdoux P** 2001 Selenium decreases thyroglobilin concentrations but does not affect the increased thyroxine-to-triiodothyronine ratio in chidren with congenital hypothyroidism. J Clin Endocrinol Metab 86:1160–1163
224. **Vazquez H, Smecuol E, Flores D, Mazure R, Pedreira S, Niveloni S, Maurino E, Bai JC** 2001 Relation between cigarette smoking and celiac disease: evidence from a case-control study. Am J Gastroenterol 96:798–802
225. **Patel AH, Loftus EV, Murray JA, Harmsen WS, Zinsmeister AR, Sandborn WJ** 2001 Cigarette smoking and celiac sprue: a case-control study. Am J Gastroenterol 96:2388–2391
226. **Bartalena L, Martino E, Marcocci C, Bogazzi F, Panicucci M, Velluzzi F, Loviselli A, Pinchera A** 1989 More on smoking habits and Graves' ophthalmopathy. J Endocrinol Invest 12:733–737
227. **Papadopoulos GK, Wijmenga C, Koning F** 2001 Interplay between genetics and the environment in the development of celiac disease: perspectives for a healthy life. J Clin Invest 108:1261–1266
228. **Ventura A, Magazzu G, Greco L** 1999 Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. Gastroenterology 117:297–303
229. **Di-Mario U, Anastasi E, Mariani P, Ballati G, Perfetti R, Triglione P, Morellini M, Bonamico M** 1992 Diabetes-related autoantibodies do appear in children with coeliac disease. Acta Paediatr 81: 593–597
230. **Galli-Tsinopoulou A, Nousia-Arvanitakis S, Dracoulacos D, Xefteri M, Karamouzis M** 1999 Autoantibodies predicting diabetes mellitus type I in celiac disease. Horm Res 52:119–124
231. **Rapaport MJ, Bistritzer T, Vardi O, Broide E, Azizi A, Vardi P** 1996 Increased prevalence of diabetic-related autoantibodies in celiac disease. J Pediatr Gastroenterol Nutr 23:524–527
232. **Ventura A, Neri E, Ughi C, Leopaldi A, Citta A, Not T** 2000 Gluten-dependent diabetes-related and thyroid-related autoantibodies in patients with celiac disease. J Pediatr 137:263–265
233. **Sategna Guidetti C, Solerio E, Scaglione N, Aimo G, Mengozzi G** 2001 Duration of gluten exposure in adult coeliac disease does not correlate with the risk of autoimmune disorders. Gut 49: 502–505
234. **Molteni N, Caraceni MP, Bardella MT, Ortolani S, Gandolini GG, Bianchi P** 1990 Bone mineral density in adult celiac patients and the effect of gluten-free diet from childhood. Am J Gastroenterol 85: 51–53
235. **Bode S, Hassager C, Gudmand-Hoyer E, Christiansen C** 1991 Body composition and calcium metabolism in adult treated coeliac disease. Gut 32:1342–1345
236. **Mora S, Weber G, Barera G, Bellini A, Pasolini D, Prinster C, Bianchi C, Chiomello G** 1993 Effect of gluten-free diet on bone mineral content in growing patients with celiac disease. Am J Clin Nutr 57:224–228
237. **Mazure R, Vazquez H, Gonzalez D, Mautalen C, Pedreira S, Boerr L, Bai JC** 1994 Bone mineral affection in asymptomatic adult patients with celiac disease. Am J Gastroenterol 89:2130–2134
238. **Valdimarsson T, Toss G, Ross I, Lofman O, Ström M** 1994 Bone mineral density in coeliac disease. Scand J Gastroenterol 29: 457–461
239. **McFarlane XA, Bhalla AK, Reeves DE, Morgan LM, Robertson DA** 1995 Osteoporosis in treated adult coeliac disease. Gut 36: 710–714
240. **Pistorius LR, Sweidan WH, Purdie DW, Steel SA, Howey S, Bennett JR, Sutton DR** 1995 Coeliac disease and bone mineral density in adult female patients. Gut 37:639–642
241. **Walters JR** 1994 Bone mineral density in coeliac disease. Gut 35: 150–151
242. **McFarlane XA, Bhalla AK, Robertson DA** 1996 Fractures and low bone mineral density in adult coeliac disease. Gut 39:180–184
243. **Corazza GR, DiSario A, Gecchetti L, Jorizzo LA, Di-Stefano M, Minguzzi L, Brusco G, Bernardi M, Gasparrini G** 1996 Influence of pattern of clinical presentation and of gluten-free diet on bone mass and metabolism in adult coeliac disease. Bone 18:525–530
244. **Mautalen C, Gonzalez D, Mazure R, Vazquez H, Lorenzetti MP, Maurino E, Niveloni S, Pedreira S, Smecuol E, Boerr LA, Bai JC** 1997 Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients. Am J Gastroenterol 92:313–318
245. **Ciacci C, Maurelli L, Klain M, Savino G, Salvatore M, Mazzacca G, Cirillo M** 1997 Effects of dietary treatment on bone mineral density in adults with celiac disease: factors predicting response. Am J Gastroenterol 92:992–996
246. **Smecuol E, Gonzalez D, Mautalen C, Siccardi A, Cataldi M, Niveloni S, Mazure R, Vazquez H, Pedreira S, Soifer G, Boerr LA, Maurino E, Bai JC** 1997 Longitudinal study on the effect of treatment on body composition and anthropometry of celiac disease patients. Am J Gastroenterol 92:639–643
247. **Scotta MC, Salvatore S, Salvatoni A, De Amici M, Ghiringhelli G, Broggini M, Nespoli L** 1997 Bone mineralization and body composition in young patients with celiac disease. Am J Gastroenterol 92:1331–1334
248. **Mora S, Barera G, Ricotti A, Weber G, Bianchi C, Chiumello G** 1998 Reversal of low bone density with a gluten-free diet in children and adolescents with celiac disease. Am J Clin Nutr 67:477–481
249. **Kemppainen T, Kroger H, Janatuinen E, Arnala I, Lambert-Allard C, Kärkkäinen M, Kosma VM, Julkunen R, Jurvelin J, Alhava E, Uusitupa M** 1999 Bone recovery after a gluten-free diet: a 5-year follow-up study. Bone 25:355–360
250. **Selby PL, Davies M, Adams JE, Mawer EB** 1999 Bone loss in celiac disease is related to secondary hyperparathyroidism. J Bone Miner Res 14:652–657
251. **Mora S, Barera G, Beccio S, Proverbio MC, Weber G, Bianchi C, Chiumello G** 1999 Bone density and bone metabolism are normal after long-term gluten-free diet in young celiac patients. Am J Gastroenterol 94:398–403
252. **Mustalahti K, Collin P, Sievänen H, Salmi J, Mäki M** 1999 Osteopenia in patients with clinically silent coeliac disease warrants screening. Lancet 354:744–745

253. **Sategna-Guidetti C, Grosso SB, Grosso S, Mengozzi G, Aimo G, Zaccaria T, Di Stefano M, Isaia GC** 2000 The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutrional status. Aliment Pharmacol Ther 14:35–43
254. **Valdimarsson T, Toss G, Lofman O, Ström M** 2000 Three years' follow-up of bone density in adult coeliac disease: significance of secondary hyperparathyroidism. Scand J Gastroenterol 35:274–280
255. **Meyer D, Stavropolous S, Diamond B, Shane E, Green PH** 2001 Osteoporosis in a North American adult population with celiac disease. Am J Gastroenterol 96:112–119
256. **Lindh E, Ljunghall S, Larsson K, Lavö B** 1992 Screening for antibodies against gliaidin in patients with osteoporosis. J Intern Med 231:403–406
257. **Nuti R, Martini G, Valenti R, Giovani S, Salvadori S, Avanzati A** 2001 Prevalence of undiagnosed coeliac syndrome in osteoporotic women. J Intern Med 250:361–366
258. **Mather KJ, Meddings JB, Beck PL, Scott RB, Hanley DA** 2001 Prevalence of IgA-endomysial antibody in asymptomatic low bone mineral density. Am J Gastroenterol 96:120–125
259. **Cellier C, Flobert C, Cormier C, Roux C, Schmitz J** 2000 Severe osteopenia in symptom-free adults with a childhood diagnosis of coeliac disease. Lancet 355:806
260. **Vazquez H, Mazure R, Gonzalez D, Flores D, Pedreira S, Niveloni S, Smecuol E, Maurino E, Bai JC** 2000 Risk of fractures in celiac disease patients: a cross-sectional, case-control study. Am J Gastroenterol 95:183–189
261. **Molteni N, Bardella MT, Vezzoli G, Pozzoli E, Bianchi P** 1995 Intestinal calcium absorption as shown by stable strontium test in celiac disease before and after gluten-free diet. Am J Gastroenterol 90:2025–2028
262. **Keaveny AP, Freaney R, McKenna MJ, Masterson J, O'Donoghue DP** 1996 Bone remodeling indices and secondary hyperparathyroidism in celiac disease. Am J Gastroenterol 91:1226–1231
263. **Valdimarsson T, Arnqvist HJ, Toss G, Järnerot G, Nyström F, Ström M** 2000 Low circulating insulin-like growth factor I in coeliac disease and its relation to bone mineral density. Scand J Gastroenterol 35:894–896
264. **Smecuol E, Maurino H, Vasquez S, Pedeira S, Niveloni S, Mazure R, Boerr L, Bai J** 1996 Gynecological and obstetric disorders in celiac disease: frequent clinical onset during pregnancy or the puerperium. Eur J Gastroenterol Hepatol 8:63–67
265. **Aine L** 1996 Coeliac-type permanent tooth enamel defects. Ann Med 28:9–12
266. **Mustalahti K, Lohiniemi S, Collin P, Vuolteenaho N, Laippala P, Mäki M** 2002 Gluten-free diet and quality of life in patients with screen-detected celiac disease. Eff Clin Pract 5:105–113
267. **Carrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Sategna-Guidetti C, Usai P, Cesari P, Pelli MA, Loperfido S, Volta U, Calabro A, Certo M** 2001 Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 358:356–361
268. **Harewood GC, Murray JA** 2001 Diagnostic approach to a patient with suspected celiac disease. A cost analysis. Dig Dis Sci 46:2510–2514