

## TYPE 1 DIABETES AND COELIAC DISEASE

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### INTRODUCTION

The association between Type 1 diabetes mellitus (DM) and coeliac disease (CD) has been recognised for more than five decades.<sup>1,2</sup> The first biopsy-confirmed case of CD in a patient with Type 1 DM was documented by Ellenberg and Bookman in 1960.<sup>3</sup> The prevalence of symptomatic CD in Type 1 DM is significantly higher than that of the general population,<sup>4</sup> and reported prevalence rates vary between 0.61%<sup>5</sup> and 16.4%<sup>6</sup> (Table 1).

It is now recognised that CD may be more common and of a more varied presentation than previously thought, especially in patients with Type 1 DM.<sup>7-13</sup> Many cases appear to be atypical, silent or latent in their presentation and are at risk of remaining undetected and untreated. If such patients are not treated, they risk complications such as anaemia, infertility, malabsorption, vitamin and mineral deficiencies, osteoporosis, osteomalacia, growth retardation and malignant disorders. In patients with Type 1 DM, untreated CD may be particularly associated with growth retardation, poor glycaemic control, recurrent hypoglycaemic attacks and delayed puberty.<sup>10, 14</sup> Complications of CD could be potentially averted with early detection and treatment. Moreover, recommended diet for patients with Type 1 DM includes large quantities of gluten-containing cereals, which undoubtedly provoke the symptoms of CD, thus further emphasising the importance of early recognition and treatment of CD.

Although a definite association between Type 1 DM and CD exists, it is controversial as to whether a screening programme should be instituted to detect clinically unrecognised CD, particularly whether implementation of a gluten free diet (GFD) in these patients may be practical as well as cost-effective. Some of the currently available data, studies and policies recommended on screening programmes to detect silent and atypical CD in patients with Type 1 DM will be analysed.

### METHODS

This literature search utilised Medline with the search being performed up until March 2001: search words used were 'diabetes' and 'coeliac disease'; other papers collected by the authors were also included.

### AUTOIMMUNITY AND HUMAN LEUCOCYTE ANTIGEN TYPES

Type 1 DM and CD are both autoimmune disorders. Autoimmunity may either be systemic (e.g. rheumatoid

arthritis, systemic lupus erythematosus) or organ-specific (such as Type 1 DM and autoimmune thyroid diseases). Autoimmune disorders are associated with the major histocompatibility complex (MHC) genes;<sup>15</sup> the MHC refers to the entire genetic region containing the genes encoding 'tissue antigens' or 'tissue types'. In humans, these genes lie on the short arm of chromosome 6 in the so-called human leucocyte antigen (HLA) region that includes dozens of genes<sup>15, 16</sup> whose products control a variety of functions concerned with regulation of immune responses.<sup>17</sup> The HLA has been evaluated in relation to autoimmune diseases with strong associations having been found.<sup>18, 19</sup>

Type 1 DM has a strong association with HLA markers DR3 and DR4<sup>20, 21</sup> and the heterozygous state DR3/DR4 is associated with a particularly high risk. Coeliac disease is associated with HLA markers DR3 in northern Europeans and DR5/DR7 in parts of southern Europeans and Latin Americans.<sup>22, 23</sup> Interestingly, HLA markers DR7 and DR9 in Afro Caribbeans and DR7 in Africans are associated with predisposition to Type 1 DM.<sup>24</sup>

Shanahan has reported the frequency of HLA markers DR3 in patients with CD and Type 1 DM (88%), patients with CD only (88%) and patients with Type 1 DM only (69%), which is significantly greater than in normal subjects (44%).<sup>24</sup> A high prevalence of HLA B8 in patients with both conditions has also been reported.<sup>25-7</sup>

Patients with one autoimmune condition are known to have a higher risk of developing other autoimmune disorders.<sup>25, 28-35</sup> Type 1 DM has a prevalence estimated at approximately four in 1,000 in the UK while that for CD is one in 200 in the same population.<sup>36</sup> Patients with Type 1 DM have been shown to have an increased prevalence of the antibodies found in CD, estimated at 2.3% to 11.6%, and is particularly prevalent among patients with Type 1 DM expressing the DQ2 and DQ8 class II HLA alleles.<sup>28</sup> Although the frequency of islet cell autoantibodies (ICA), insulin autoantibodies (IA) and glutamic acid decarboxylase autoantibodies (GAD) are increased in patients with CD, autoimmune thyroid disease and polyendocrine disorders,<sup>19</sup> the onset of Type 1 DM is delayed in this population.<sup>19, 21, 37-9</sup>

### PREVALENCE OF COELIAC DISEASE IN PATIENTS WITH TYPE 1 DIABETES

Payne suspected the likelihood of coexistence of Type 1 DM and CD in 1954.<sup>2</sup> This association was first proved

**TABLE 1**  
Prevalence of CD in patients with Type I diabetes.

Reference no.	Country	Number of patients with Type I diabetes screened	Screening test(s) used (serology)	Patient diagnosed before screening		Patient diagnosed after screening		Total number of patients with positive serology		Total number of patients with CD proved by histopathology		Symptomatic (including atypical symptoms) patients diagnosed after screening		Asymptomatic patients diagnosed after screening		IgA deficiency	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
43	UK	767	IgA-AGA	4	0.5%	11/763	1.4%	—	—	15/767	2%	7/11	63.6%	4/11	36.4%	1/767	0.13%
44	UK	167	IgA-EMA IgG-AGA (in IgA deficient subjects)	None	0%	8/167	4.8%	11/167	6.6%	8/167	4.8%	5/8	62.5%	3/8	37.5%	1/167	0.6%
45	Ireland	101	IgA-AEM	None	0%	5/101	5%	8/101	8%	8/101	8%	None/5	0%	5/5	100%	None/101	0%
42	Finland	215	IgA/IgG- ARA	1/215	0.5%	4/214 <sup>1</sup>	1.9%	9/214	4.2%	5/215	2.3%	4/4 all atypical	100%	None/4	0%	—	—
26	Finland	776	IgA-ARA IgA & IgG- AGA	1/776	0.1%	18/775 <sup>1</sup>	2.3%	76/775	9.8%	19/776 <sup>2</sup>	2.5%	—	—	—	—	—	—
47	Australia	403	IgA-AEM IgA/IgG- AGA	None	0%	9/403 <sup>4</sup>	2.2%	14/403	3.5%	9/403	2.2%	None	0%	9/403	2.2%	2/403	0.5%
27	Germany and Switzerland	1,032	IgA/IgG- AGA	8/1,032	0.8%	2–5/1,032	0.2– 0.5%	33/1,024 (17/1,024) <sup>5</sup>	3.2% (1.70%)	10/1,032	1% 1.1–1.3% <sup>5</sup>	None/2	0%	2/2	100%	1/305	0.33%
48	Germany	305	IgA/IgG-TG	None	0%	5/305	1.6%	12/305	3.9%	5/305	1.6% 1.6–3.9% <sup>7</sup>	4/12	33.3%	8/12	66.8%	1/305	0.33%
46	Sweden	848	IgA/IgG- AGA	8/848	1%	7/848	0.8%	14/848 <sup>8</sup>	1.7%	15/484– 22/848	1.8% (2.6%) <sup>7</sup>	None/7	0%	7/7	100%	—	—
49	Italy	383	IgA/IgG- AGA	None/383	0%	10/383 (12/383) <sup>8</sup>	2.6% (3.1%) <sup>8</sup>	12/383	3.1%	10/383	2.6%	1/10	10%	9/10	90%	—	—
10	Italy	172	IgA/IgG- AGA	None/172	0%	16/172	3.5%	—	—	6/172	3.5%	1/6	16.7%	5/6	83.3%	—	—

Reference no.	Country	Number of patients with Type I diabetes screened	Screening test(s) used (serology)	Patient diagnosed before screening		Patient diagnosed after screening		Total number of patients with positive serology		Total number of patients with CD proved by histopathology		Symptomatic (including atypical symptoms) patients diagnosed after screening		Asymptomatic patients diagnosed after screening		IgA deficiency	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
50	Italy	1,114	IgA/IgG-AGA, IgA-AEM	None/1,114	0%	63/1,114	5.6%	121/1,114	10.7%	63/1,114 (98/1,114) <sup>8</sup>	5.6% (8.8%) <sup>8</sup>	15/63	23.8%	58/163	76.2%	—	—
51	Italy	133	IgA/IgG-AGA, ARA IgA-AEM	None/133	0%	5/133	3.7%	20/133 <sup>9</sup> 7/133 <sup>10</sup>	15% <sup>9</sup> 5.2% <sup>10</sup>	5/133	3.7%	—	—	—	—	—	—
39	Italy	419	IgA-AEM	3/419	0.7%	28/419	5.7%	28/419	5.2%	28/419	5.7%	7/28	25%	21/28	75%	—	—
52	USA	47	IgA-AEM	None/47	0%	3/47	6%	3/47	6%	3/47	6%	1/3	33%	2/3	67%	—	—
6	Algeria	116	IgA/IgG-AGA, IgA-AEM	3/116	2.6%	16/113	14%	19/116	16.8%	19/116	16.4%	8/19	4.2%	11/19	57.9%	—	—

#### ABBREVIATIONS

IgA Immunoglobulin A  
 IgG Immunoglobulin G  
 AGA Antigliadin antibodies  
 ARA Antireticulin antibodies  
 AEM Antiendomysial antibodies

<sup>1</sup> Patients with pre-existing CD excluded.

<sup>2</sup> Patients with pre-existing CD included.

<sup>3</sup> A fifth child had mild partial villous atrophy.

<sup>4</sup> Six with atypical and three with minor histological changes.

<sup>5</sup> Eight of 17 positive patients declined biopsy. Two patients left follow-up and one girl showed partial villous atrophy not fulfilling the criteria for CD diagnosis. Taking those patients, sensitivity and specificity of the test in consideration prevalence would be 1.1–1.3%.

<sup>6</sup> Only five of the 12 patients tested positive had biopsy, which showed CD changes in all. Taking that into consideration, estimated prevalence would be higher than 1.64% (1.64–3.93%).

<sup>7</sup> Only seven of 14 could be biopsied in all CD diagnosed.

<sup>8</sup> Estimated prevalence taking into consideration patients who refused biopsy.

<sup>9</sup> IgA-AGA positive.

<sup>10</sup> IgG-AGA positive.

by a small intestine biopsy by Ellenberg and Bookman, followed by Walker-Smith and Grigor in 1969.<sup>40</sup> Since then, Vasakorpi in 1969, Thain and co-workers in 1974, Sires and de Majo in 1977 and Maki and co-workers in 1984 have found that CD occurred in 1%, 1.5%, 2% and 2.3% of patients with Type I DM respectively.<sup>41,42</sup> More recently, other authors have also reported a high prevalence.<sup>5, 6, 9, 10, 13, 25, 26, 39, 42-8</sup> Use of more sensitive serological tests for screening and an increasing awareness of silent, oligosymptomatic and atypical CD have contributed to the identification of more cases, and not only the tip of the iceberg. Important studies that have looked at the prevalence of CD in patients with Type I DM are presented in Table 1.

Geographical variations occur in the prevalence of CD in patients with Type I DM (see Table 1).<sup>5, 6, 9, 10, 13, 25-7, 39, 42-56</sup> The highest prevalence was reported from Algeria<sup>6</sup> and Italy,<sup>39, 49-54</sup> and the lowest reported in Germany and Switzerland.<sup>27, 48</sup> In the UK, the reported prevalence was 2-4.8%.<sup>42, 43</sup> The majority of CD patients were asymptomatic, oligosymptomatic or presented with atypical symptoms and were only diagnosed by screening.<sup>5, 6, 11, 13, 25-7, 39, 42-54</sup>

From currently available data, the geographical variation in the prevalence of CD in patients with Type I DM is not parallel to the incidence rate of Type I DM.<sup>5, 6, 9, 10, 13, 25, 26, 39, 42-61</sup> It remains to be established whether the variation in the prevalence of CD in patients with Type I DM can be attributed to variations in genetic susceptibility, dietary habit of the population, other environmental factors or to a combination of all these.

**CLINICAL IMPLICATIONS OF UNDIAGNOSED COELIAC DISEASE**

Unrecognised and untreated CD is associated with a high mortality and morbidity.<sup>7, 61-2</sup> In one study the mortality reached 12% prior to the introduction of a strict GFD. The risk of upper gastrointestinal malignancies and

intestinal lymphoma is increased by 8- and 30-100-fold respectively.<sup>31, 62, 63</sup> In addition, serious extra-intestinal complications have also been recognised (Table 2)<sup>31, 62-84</sup> and undiagnosed CD may first present with a benign or malignant complication.<sup>7, 10, 78, 79, 84-6</sup>

However, benign and malignant complications of CD can be avoided by early diagnosis and compliance with GFD.<sup>10, 68-70, 76, 77, 80, 81, 88-92</sup> Once the disease is in remission with GFD, the risk of malignancy decreases and approaches that of the normal population.<sup>52</sup> After adopting a GFD hypertransaminasaemia normalises.<sup>10, 65, 66</sup> Treatment of CD with a GFD appears to prevent infertility (both in men and women), amenorrhoea, delayed menarche, early menopause, recurrent abortions and hyperprolactinaemia.<sup>82, 83</sup> A GFD also prevents bone loss, improves or even completely normalises bone mineral density and serum markers of bone metabolism.<sup>80, 87, 89</sup> In adults with a late diagnosis and institution of a GFD these parameters tend to improve, but would not reach a normal level.

Interestingly, CD may present with neuropsychiatric symptoms and neurological signs such as ataxia, depression, anxiety, peripheral neuropathy, epilepsy and other neurological dysfunctions,<sup>71-81, 88, 90, 91</sup> epilepsy with cerebral calcification only occurred in patients following an unrestricted diet. However, a GFD beneficially affects the course of epilepsy, but only when started soon after the onset of epilepsy,<sup>90</sup> but also has a beneficial effect on depression and behavioural changes. These neurological manifestations could be associated with neurotoxic autoantibodies.<sup>71, 75, 92</sup> A GFD also prevents, and even reverses, nutritional, haemopoetic and dermatological complications, arthritic symptoms, growth retardation, delayed puberty and a host of other non-specific symptoms.<sup>10, 12, 36-54, 63, 69, 76, 77, 80, 81, 89, 91-3</sup>

The prevalence of autoimmune disorders tends to increase with the duration of untreated CD.<sup>68</sup> Indeed, non-coeliac related organ-specific autoantibodies tend

**TABLE 2**  
**Complications of undiagnosed and untreated CD.**

Organ or system	Complication
Gastrointestinal	Malabsorption, intestinal lymphoma, bowel adenocarcinoma, oesophageal and pharangeal squamous cell carcinoma, unexplained hypertransaminemia.
Endocrine, reproductive, gynaecology and obstetrics	Hypogonadism, reduced semen quality, immature secondary sex characteristics, hyperprolactinaemia (25% of CD patients), amenorrhoea, infertility, impotence, late menarche, early menopause, recurrent abortions, delayed puberty, short stature, intrauterine growth retardation among infants of mothers with undiagnosed CD.
Musculoskeletal	Osteopenia, osteomalasia, arthritis, fatigue, myopathy.
Neuropsychiatric	Ataxia, peripheral neuropathy, epilepsy, cerebral calcification, demylineating central nervous system lesions, depression, anxiety.
Haematological and nutrition	Anaemia, nutritional deficiencies, bleeding tendency.
Autoimmune diseases	Increased prevalence of autoimmune disorders such as Type I DM, collagen vascular diseases, autoimmune thyroiditis. Autoantibodies increase with the duration of undetected CD.

to disappear 6–12 months after adopting a GFD.<sup>39</sup> It is tempting to conclude that an early GFD could prevent, or at least reduce, the risk of developing other autoimmune conditions.<sup>39, 68, 92, 94</sup>

## IMPLICATIONS OF UNDETECTED COELIAC DISEASE IN PATIENTS WITH TYPE 1 DIABETES

Patients with both conditions have an earlier age of onset of Type 1 DM than the general population,<sup>9, 47</sup> with a female excess<sup>18, 46, 47, 65</sup> which is inconsistent with the prevalence of CD in the general population.<sup>95</sup> In the majority of cases the clinical onset of DM precedes that of CD.<sup>5, 6, 9, 10, 13, 25–7, 39, 48–53, 83</sup> In contrast to Andrew *et al.*, who have reported that the presence of CD-related antibodies has not been influenced by the duration of Type 1 DM,<sup>53</sup> most authors have reported that the presence of these antibodies and the prevalence of CD are both significantly related to the duration of the onset of Type 1 DM.<sup>26, 46</sup> Antibody-negative patients may also seroconvert during follow-up.<sup>26</sup> Recurrent hypoglycaemic attacks<sup>25, 97, 99</sup> and poor glycaemic control<sup>26, 47</sup> tend to be more frequent in patients with untreated CD (Table 3).

Changes in the small bowel of CD may be responsible for abnormal concentrations of gastrointestinal hormones; plasma gastric inhibitory polypeptide (GIP) levels are low in CD patients.<sup>97</sup> Because of its significant insulinotropic role, the decreased release of GIP eventually leads to a decrease in insulin release.<sup>98</sup> The plasma enteroglucagon level is elevated in patients with untreated CD.<sup>98</sup> Unlike pancreatic glucagon, enteroglucagon has no hyperglycaemic effect. However, *in vitro* transformation of enteroglucagon into pancreatic glucagon has been convincingly demonstrated in an experimental study.<sup>99</sup> These changes in intestinal hormones may contribute to the earlier onset of Type 1 DM in patients with both conditions.

Compliance with a GFD leads to intestinal mucosal recovery, improvement of malabsorption and absorption fluctuations<sup>36, 69, 70, 77–9, 96</sup> as well as restoring the nutritional balance,<sup>97, 98, 101</sup> which will in turn result in an improvement of growth rate in children and adolescence, better glycaemic control and a decrease in the frequency of hypoglycaemic attacks. However, some have reported minor, or no, improvement in glycaemic control after adoption of a GFD,<sup>47</sup> but adherence to GFD was not strict, making a proper assessment difficult. Furthermore, an increase in insulin requirements has also been noted.<sup>25, 49, 50, 94</sup> On balance, a GFD tends to improve glycaemic control, reduce hypoglycaemic episodes, decrease circulating autoantibodies, increase insulin requirement and improve growth.

## THE CAUSAL RELATIONSHIP ISSUE

The genetic link between Type 1 DM and CD is beyond any doubt but it is not entirely clear whether the association between these two autoimmune disorders is

entirely genetic.<sup>102–05</sup> Gluten may have a broader role in autoimmunity, especially in genetically predisposed subjects. Similar to other food proteins such as bovine albumin peptide, it may be a possible trigger for autoimmune reactions that subsequently result in a pancreatic beta-cell destruction and Type 1 DM. Therefore, long-standing exposure to gluten in patients with silent CD is likely to predispose to other autoimmune disorders including Type 1 DM. Indeed, this hypothesis is further supported by two facts. First, non-coeliac-related organ-specific antibodies tend to disappear six to 12 months after adopting a GFD, and second, the progression of the autoimmunity stage to clinical Type 1 DM is related to autoantibody titres and the simultaneous presence of at least two Type 1 DM-related autoantibodies.<sup>106, 107</sup> These autoantibodies do have a predictive role and serve as surrogate markers of Type 1 DM.<sup>108</sup> Therefore, intervention with a GFD could play a role in preventing Type 1 DM in high-risk subjects such as first degree relatives of Type 1 diabetics. Subjects with autoimmune diseases diagnosed with CD by screening showed a relative improvement in the associated diseases, such as primary sclerosing cholangitis and alopecia areata, when placed on a GFD.<sup>109, 110</sup>

Although an increase in intestinal permeability has been reported in some subjects with Type 1 DM this is more likely to be secondary to undiagnosed latent or potential CD in these subjects rather than a primary defect related to Type 1 DM. These factors, as well as the low plasma GIP and high enteroglucagon, may play a role in the aetiology of Type 1 DM and explain the earlier onset of Type 1 DM in patients with both conditions.

## SHOULD WE SCREEN PATIENTS WITH TYPE 1 DIABETES FOR CD?

Coeliac disease in patients with Type 1 DM fulfil almost all of the criteria which render a condition suitable for screening:

1. it is a well-defined disorder;
2. it has a silent phase that could last for years;
3. untreated CD is associated with increased morbidity and mortality;
4. an estimate of its prevalence and progression is available;
5. a GFD is an effective treatment;
6. a simple, safe and reliable screening test is available;
7. those with a positive serology test have a sufficiently high chance of being affected; and
8. the facilities for the screening programme are available.

(No data are available on the cost-effectiveness of a screening programme).

The main justification for embarking on a screening programme for the presence of CD in patients with Type 1 DM would be prevention or reduction of malignant

**TABLE 3**  
**Characteristics of patients with both Type I diabetes and CD.**

- In the majority of patients CD is silent, if any symptoms or signs are displayed, they usually present with atypical rather than typical.
- Female/male ratio of CD prevalence is more than one.
- The onset of Type I diabetes precedes that of CD in the majority of cases.
- Earlier age of onset of Type I diabetes.
- Prevalence of CD increases with the duration of Type I diabetes.
- Some patients who are antibody negative may later test positive.
- Recurrent hypoglycaemia, poor glycaemic control and growth retardation is more common in patients with untreated CD.
- GFD has a significant beneficial effect on glycaemic control, reducing hypoglycaemic control and growth.
- Autoimmune disorders as well as autoantibodies are more common in individuals with both Type I diabetes and CD than those with either condition alone. Prevalence of autoimmune disorders increases with the duration of untreated CD.

and non-malignant complications associated with untreated CD, aversion of symptoms, improved growth rate and glycaemic control with subsequent decrease in morbidity and mortality. Undoubtedly, better glycaemic control in such patients would be likely to lead to a significant reduction in micro- and macrovascular complications.<sup>111–13</sup>

#### How to screen?

It is now clear that the spectrum of gluten sensitivity includes latent and potential CD.<sup>114</sup> In latent CD, patients have a normal intestinal biopsy while on a normal diet that at some other time, while still on normal diet, becomes flat and recovers on GFD. Potential CD is used to describe patients who have a normal appearing villi but subtle changes are present such as an increased number of lymphocytes and aberrant HLA-DR expression in crypt epithelial cells; the serology test may be positive and in time the mucosa may become flat.

Accurate diagnosis of CD is essential, as it requires a life-long commitment to a GFD. Serological tests are highly sensitive and specific,<sup>114</sup> but a negative serology does not exclude gluten sensitivity.<sup>114</sup> Therefore, small bowel mucosal biopsy remains the 'gold standard' of diagnosis of CD.<sup>115</sup> The use of serological tests alone for screening will underestimate the prevalence of CD due to false-negative results.<sup>114</sup> However, serological testing could increase the identification of CD in the general population as well as patients with Type I DM and is also very useful for a better selection of patients to undergo small bowel biopsy.<sup>116, 117</sup>

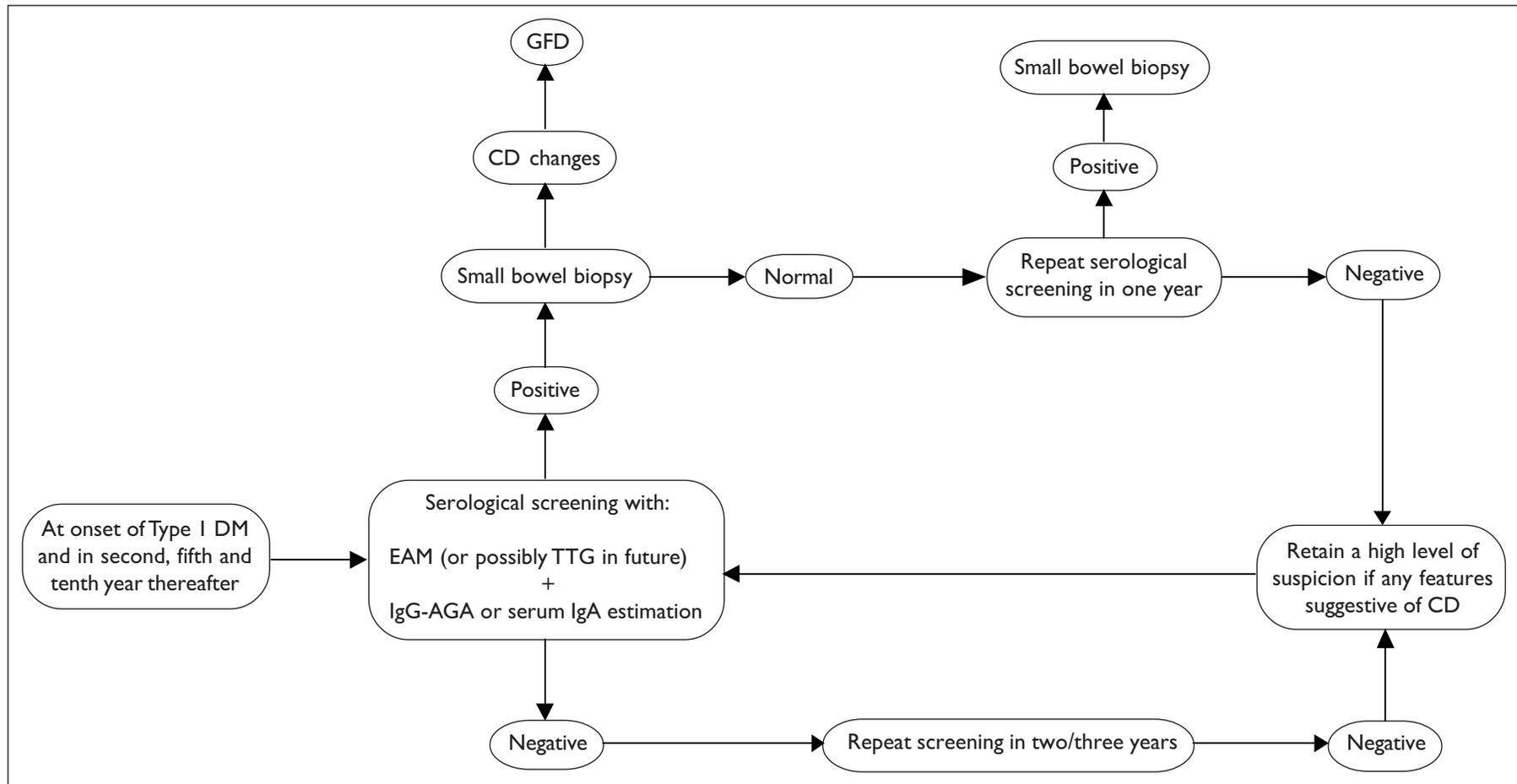
Currently, IgA-anti-endomyseal antibody (IgA-AEM) is the most reliable of the serological markers with a high sensitivity and specificity of 74–100% and 96–100% respectively.<sup>114</sup> IgA-anti-endomyseal antibody is more reliable than IgA-antigliadin antibody (IgA-AGA), IgG-antigliadin antibody (IgG-AGA), IgA-anti-reticulin

antibody (IgA-ARA) and IgA-anti-jejunal antibodies (IgA-AJB).<sup>114, 116, 118</sup>

The identification of tissue transglutaminase (TTG) in 1997 led to a rapid progress in our understanding of the pathogenesis of CD.<sup>119</sup> Tissue transglutaminase is known to play an important role in many biological processes.<sup>119, 120</sup> In CD it has been shown that TTG may generate antigenic T-cell modified gliadin peptides,<sup>121</sup> and these peptides are involved in modulating the reactivity of gliadin specific T-cells; they also contribute to the breaking of tolerance and initiation of autoimmune reactions in CD.<sup>120</sup> Transglutaminase antibodies also contribute to the jejunal mucosal lesions.<sup>121</sup> Furthermore, the availability of highly sensitive and specific recombinant serology tests for IgA-anti-tissue transglutaminase (IgA-TTG) antibody is promising and it may replace IgA-AEM as the most reliable serological test in the future.<sup>122, 123</sup> Despite the reliability of serological tests, problems still exist in the standardisation of serological methods and reference ranges, but there are efforts to develop an international protocol and quality control.

Selective IgA deficiency (SIgAD) is the commonest primary immunodeficiency with a prevalence of 0.14–0.20% in the general population,<sup>124, 125</sup> and in patients with Type I DM the reported prevalence varies between 0.13–0.60%. In patients with SIgAD, IgA-AEM is not reliable and it has been suggested that IgG-AGA or serum IgA levels in combination with IgA-AEM should be determined whenever screening for CD to avoid false-negative serology results.<sup>114, 115, 120, 121</sup> Overall, the use of a combination of serological tests is the most reliable approach.<sup>114, 126</sup>

Patients with Type I DM may have latent or potential CD, and at this stage in their disease the mucosa has normal villi; subtle mucosal changes could be present and serology may be positive. These patients should



**FIGURE 1**  
Algorithm demonstrating a proposed programme for screening of CD in patients with Type I diabetes.

continue taking a normal diet and be re-biopsied after an interval of one to two years as many later develop villous atrophy. If available, immunohistochemical studies may reveal subtle changes characteristic to those of CD. As the prevalence of CD in patients with Type I DM increases with time and some patients may sero-convert after the onset of Type I DM, it is proposed to screen patients at the onset of Type I DM then two, five and ten years afterwards. Figure 1 demonstrates an algorithm for a proposed screening programme.

### Compliance

Symptomatic patients are more likely to accept and adhere to a GFD than asymptomatic patients because they have more to gain.<sup>43, 127</sup> However, the sense of improved wellbeing and vitality after adopting a GFD in those who regard themselves as asymptomatic is expected to lead to a better compliance. In fact, in one study patients newly diagnosed with CD, including asymptomatic patients, showed an excellent compliance with GFD. A gluten free diet and diabetic diet can be combined quite readily, and all patients should have access to a skilled dietician. This should encourage the policy makers to introduce a screening programme for patients with Type I DM.

### Cost of screening

Serological screening, as proposed in Figure 1, costs about £18 per patient and a diagnostic upper gastrointestinal endoscopy costs about £280;<sup>128</sup> these costs will vary according to different laboratories and hospitals. Holmes calculated the cost per case and found it to be £860 and £950 in patients known to have Type I DM and new cases of Type I DM respectively,<sup>128</sup> but no data are available on cost-effectiveness. Although direct comparison between different screening is difficult to make, it may be worthwhile to look at the cost per case found in other screening programmes: this is £4,500 for cystic fibrosis, £14,860 for congenital hypothyroidism and £25,000 for phenylketonuria.<sup>129</sup> The NHS breast screening programme costs £25,142 per death prevented and £2,522 per life year saved.<sup>130</sup>

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