Interplay between Type 1 Diabetes Mellitus and Celiac Disease: Implications in Treatment

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Keywords

Type 1 diabetes mellitus · Celiac disease · Genetics · Coexistence

Abstract

Background: A complex interplay between genetic and environmental factors contributes to disease etiology of most of the autoimmune disorders. Type 1 diabetes mellitus (T1DM) and celiac disease (CD) are polygenic autoimmune diseases that have high propensity to coexist due to shared etiological factors like genetics and clinico-pathological overlaps. **Summary:** The mean prevalence rate for coexistence of these diseases is 8%, and this value is a gross underestimation as reported from biopsy-proven symptomatic cases. The prevalence rate will rise when studies will excavate bottom layers of the “celiac iceberg” to detect potential and silent celiac cases. The concomitant presence of both these disorders is a complex situation immunologically as well as clinically. There is an accentuated breakdown of tolerance and proinflammatory cytokine storm that leads to the progression of organ-specific autoimmunity to systemic. No immunomodulating drugs are advocated as exogenous

insulin supplementation and gluten exclusion are recommended for T1DM and CD respectively. Nevertheless, these pose certain challenges to both the clinicians and the patients, as gluten free diet (GFD) has been described to have an impact on glycemic control, bone health, and vascular complications. Also intermittent gluten intake by these patients due to non-compliance with GFD also stimulates the autoreactive immune cells that result in an augmented immune response. **Key Messages:** Large public health studies are needed to estimate the prevalence of all forms of CD in T1DM patients. Strict global guidelines need to be formulated for the disease management and prognosis, and there is also a need for an extensive research on each front to thoroughly understand the co-occurrence of these diseases.

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Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic disorders prevalent in young individuals. It is an autoimmune disorder, which is characterized by β cell destruction that culminates into absolute insulin

deficiency resulting in a state of chronic hyperglycemia. The demise of β cell is not abrupt; rather it is preceded by a long prodromal phase that can last for about 10 years [1, 2]. This phase is characterized by $CD4^+$ $CD8^+$ T cell infiltration of the pancreatic islets that leads to insulinitis, which finally results in apoptosis of β cells [3]. In this phase, the patient is asymptomatic but tests positive for serum autoimmune markers for T1DM like anti glutamic acid decarboxylase-65 autoantibodies (GADA), anti-islet antigen 2 autoantibodies, and insulin autoantibodies [4, 5]. When only 10–30% of the islets mass remains, the patients present with symptoms related to hyperglycemia.

The next phase after the clinical onset of the disease is marked by management of elevated blood glucose levels and related complications. Like all autoimmune disorders, T1DM is also a complex genetic disorder in which environmental factors also contribute to the disease etiology. This is evident from the geoepidemiology [6], as the incidences of T1DM have increased by almost twofold in children below the age of 5. Due to shared genetic components and related environmental factors, the autoimmune diseases tend to cluster in “some” individuals. In T1DM, 10–30% of the individuals develop other autoimmune diseases and these usually develop after the clinical onset of the disease [7, 8]. These diseases can be autoimmune thyroid disease (AiTD), celiac disease (CD), uveitis, autoimmune gastritis, vitiligo, and adrenal autoimmunity. The concomitant presence of T1DM with other autoimmune disorders is referred to as autoimmune polyendocrine syndromes (APS). However, this term is a misnomer, as not all autoimmune diseases included in the different categories of APS are endocrine disorders. Nevertheless, 4 categories of APS, which are named as APS-1 to APS-4, have been described. APS-1, also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy is a monogenic disorder that results from mutation in the *Aire* gene and clinical manifestations include candidiasis, hypoparathyroidism, and Addison’s disease. APS-2 is diagnosed when Addison’s disease is present along with either T1DM or AiTD. When AiTD is present along with other autoimmune diseases, it is classified as APS-3 and coexistence of T1DM and CD is a subtype of APS-4, which [9, 10] represents a group that includes combinations not included in the above categories [11].

CD or non-tropical sprue is also an autoimmune disorder that is characterized by intolerance to wheat gluten. It is marked by both intestinal and extraintestinal manifestations like anemia, delayed puberty, short stature, dermatitis herpetiformis, hypogonadism, and adrenal in-

sufficiency [10, 11]. T1DM patients, who are considered high-risk individuals for CD, usually present this disease in atypical, silent, or potential form [12]. In either of the forms, the presence of CD in T1DM patients can clinically complicate the disease management. Hence, in this review, we have tried to present a comprehensive scenario about the pathological and clinical severity of this APS-4 subtype that is emerging to be a more common disorder than expected and has serious implications in disease management and patient care.

Epidemiology

Walker-Smith first described the coexistence of T1DM-CD in 1969; nonetheless, not much data are available on the prevalence and incidence rates of this APS-4 subtype [13]. The prevalence of CD in T1DM patients is 5–7 times more than the general population. Four to nine percent of the T1DM patients have been described to have CD, compared to the incidence of 1% in general population [14]. However, this range is much broader as lowest incidence rates of 2.4% have been described in Finland and highest rate of 16.4% has been reported from Algeria [15, 16]. This statistics is also debatable, as Finland has a high prevalence rate of both T1DM ($>40/100,000$) and CD ($>39/100,000$); therefore, this may just be a gross underestimation, as it comes from a study dated back to 1996 [17]. Recently high frequencies have been reported from populations that have wheat or barley as their staple crop. These include Oran (Algeria) as described above, North India (11.1%), and Libya (10.3%) [18, 19]. The recent reports from other populations that are not mainly wheat consuming, but also have higher prevalence rate are Saudi Arabia (11.3%), Denmark (10.4%), Sweden (9.67%), Canada (7.7%), Italy (6.65%), and Iran (6.2%) [20–25]. However, comparatively lower rates have been reported from Australia (5.7%), Tunisia (5.3%), Austria (5%), United Kingdom (4.42%), and Egypt (4%) [26–30]. These prevalence rates have been illustrated in Figure 1. All these rates have been described for biopsy-proven CD cases, detected on screening of autoantibodies. Hence, these figures represent the classical CD incidences and lack the estimation of potential or silent forms of CD. The prevalence of CD has been described as a model of an iceberg, where symptomatic cases represent only the visible tip of the iceberg and the asymptomatic cases represent the main chunk of iceberg that is not visible. Thus, it can be speculated that when bottom layers of the “iceberg” are excavated to study the

Fig. 1. Described prevalence rates of coexistent type 1 diabetes and celiac disease in different countries and regions.

prevalence of asymptomatic cases, these figures might surge to an alarming level. Comparison of epidemiological parameters of T1DM, CD, and coexistent T1DM and CD in different geographical regions is shown in Table 1.

Genetic Basis of the Disease

The molecular basis of both T1DM and CD provides deep insights into the disease mechanisms. Both T1DM and CD are polygenic disorders, in which more than 30 genetic loci have been described to be associated with the diseases, thereby contributing to the genetic susceptibility. The significance of genetic factors in the etiology of the both T1DM and CD is very well evident from the familial aggregation and concordance rates observed in monozygotic twins. CD is seen in 8–18% of first-degree relatives and a concordance rate of 70–85% is seen in monozygotic twins [31, 32]. In T1DM patients, the rate of familial clustering is 6% in siblings compared to 0.4% in US white population and concordance rate of 50% is seen in monozygotic twins [33, 34].

The role of human leukocyte antigens (HLA) class II genes in the genetic predisposition to both T1DM and CD has been well established. Perhaps, it is this shared genetic susceptibility that might be the major factor leading to the concomitant occurrence of T1DM and CD. HLA class II region that harbors on chromosome 6p21 comprises 3 loci – DR, DQ, and DP. The high-risk haplotypes for T1DM bank on DR and DQ, that is, DR3-DQA1*0501-DQB1*02:01 and DR4-DQA1*03:01-DQB1*03:02 and account for 30–50% of T1DM genetic risk [35]. The estimated risk of developing T1DM for the general population in children who have the HLA-DR3/DR4 genotype is approximately 1 in 15–25 versus 1 in 300 in general population. Furthermore, individuals with high-risk HLA genotypes and at least 2 family members with T1DM have a 50% of risk of developing T1DM. Also, 33% of the T1DM patients who are homozygous DR3/DQ2 have anti tissue transglutaminase (tTG) antibodies. Interestingly, the DQB1 alleles contributing to the T1DM risk, that is, DQB1*03:02 and DQB1*02:01, are also the high-risk alleles for CD. HLA DQ2 is found in 95% of CD patients and the remaining patients carry DQ8. Patients with refractory CD or enteropa-

Table 1. Epidemiology of T1DM, CD, and coexistent T1DM and CD

Incidence of T1DM (per 100,000 per year), %	Prevalence of CD, %	Prevalence of coexistent T1DM and CD, %
Algeria 4.7 [69]	North America 0.5–1 [76]	Finland 2.4 [14]
Australia 22.6 [70]	Europe 0.5–1 [77]	Algeria 16.4 [15]
Canada 39.7 [69, 71]	Ireland 1–1.5 [78]	North India 11.1 [17]
China 0.7 [72]	United Kingdom 1–1.5 [78]	Libya 10.3 [18]
Iceland 9 [73]	North Africa (Morocco, Algeria, Tunisia, Libya, Egypt) 0.28–5.6 [78]	Denmark 10.4 [19]
Israel 5 [69]	Australia 1.2 [78]	Sweden 9.67 [20]
Japan 1.7 [69]	Asia 5 [78]	Saudi Arabia 11.3 [21]
Libya 8.7 [69]	Middle east 2–8 [78]	Italy 6.65 [22]
New Zealand 12.9–23.8 [69, 74]		Iran 6.2 [23]
Peru 0.5 [69]		Canada 7.7 [24]
Thailand 1.65 [75]		Austria 5 [25]
United States 19.4 [69]		United Kingdom 4.42 [26]
		Egypt 4 [27]
		Tunisia 5.3 [28]
		Australia 5.7 [29]

thy associated T-cell lymphoma are often homozygous for DQ2. Both α and β heterodimers in cis/trans form, that is, DQ2.5 (DQA1*05:01-DQB1*02:01) or DQ2.2 (DQA1 (02:01-DQB1*0202, and DQA1*03:01-DQB1*03:02) have been implicated in CD development [36].

DR3 and DQ2 are in strong linkage disequilibrium and therefore, now it is speculated that it is actually the DQ2 molecule that predisposes to T1DM as well, as DQ2 influences the selection and binding of autoantigenic peptide. This is well elucidated for CD, in which negatively charged gliadin peptides as such or modified by tTG bind to DQ2/DQ8 with high affinity. The lysine position at β 71 in DQ2 binds to these residues at positions P4, P6, P7, and position β 57 in DQ8 binds at P9 [37, 38]. However, these mechanisms have not been fully resolved in T1DM, as the triggering factor is not known in the latter case, but it is anticipated that the “diabetogenic peptide” may be binding to DQ2 and DR3 accompanies it due to linkage disequilibrium. It has also been described that the individuals who are homozygous for DQ2.5 or DQ8 have fivefold higher risk for developing T1DM than those who are heterozygous [39].

Since the genetic predisposition conferred by HLA is not absolute; therefore, additional loci might be contributing significantly. Lately, genome wide association studies have identified several single nucleotide polymorphisms that are commonly associated with different autoimmune diseases. These include genes that play a role in T-cell differentiation, survival, migration, or activation like Runt-related transcription factor 3, ETS Proto-Onco-

Table 2. Genetic loci implicated in susceptibility to coexistent T1DM and CD

Locus/gene	Description
DR3-DQ2	Human leucocyte antigen class II genes
DR4-DQ3	
RUNX3	Runt-related transcription factor 3
ETS2	ETS Proto-Oncogene 2
FASLG	Fas ligand
TNFSF18	Tumor necrosis factor superfamily member 18
CTLA-4	Cytotoxic T lymphocyte associate protein 4
ICOS/ICOSLG	Inducible T cell costimulator/ligand
CD28	Costimulatory molecule
CD247	T cell surface glycoprotein
SH2B3	SH2B adaptor family
RGS1	Regulator of G protein Signaling
IL18R1	Interleukin 18 receptor
IL1R1	Interleukin 1 receptor
IL1RL2	Interleukin 1 receptor ligand 2

gene 2, Fas ligand, tumor necrosis factor superfamily member 18, regulator of G protein signaling 1, cytotoxic T lymphocyte associated protein 4, ICOS (Inducible T cell costimulator/ligand), CD28, CD247, SH2B3 (SH2 domain containing protein B adaptor family), and so on. Genes involved in B-cell activation or maturation (ICOSLG, Regulator of G protein Signaling 1) or cytokine genes (IL18R1, IL1R1, IL1RL2) have also been described as the key players. Table 2 shows list of all these genes. However, the association of these single nucleotide poly-

Fig. 2. Pathophysiological mechanisms in type 1 diabetes and celiac disease that lead to immune-mediated killing of β cells of islets and enterocytes.

morphisms is weak, compared to the association seen with HLA, as indicated by comparatively lower relative risk and odds ratio. In order to elucidate, the shared loci in T1DM and CD, Smyth et al. [40] have reported that there is considerable overlap in variants, associated with these two conditions. Out of the 8 CD loci, 6 loci showed association with T1DM as well and out of the 17 loci described in T1DM, 8 showed an association with CD. Several of these loci also show an association with other autoimmune diseases.

Pathophysiology

Both T1DM and CD are marked by the selective destruction of β cells of islets and enterocytes respectively. The triggering factor for the cascade of events is not known in T1DM, but the triggering factor is wheat gluten in CD. Because the causing factor is well known in CD, the pathogenic mechanisms of CD are far more precisely known compared to the mechanisms of T1DM. However, other than gluten, different infectious agents like viruses

(adenovirus type 12, hepatitis C virus, rotavirus) [41] have also been implicated as the risk factors for CD. This is evident from the fact that not all individuals who carry the genetic risk factors develop CD. Similarly, viruses such as enteroviruses and herpesviruses [42] have also been described as the triggering factors for T1DM [43]. Since in most of the cases, T1DM manifests first followed by CD, so here we will try to elucidate the cascade of events in APS-4 subtype in this manner and is shown in Figure 2.

Due to some kind of triggering factor/event, the β cells upregulate interferon (IFN)- α , and subsequently, major histocompatibility complex (MHC) class I on cell surface. This exposes the β cells to attack by the autoreactive CD8⁺ T cells with specificity for antigens in the pancreas [44]. Type 1 interferons also activate the dendritic cells (DCs) and promote the presentation of β cell antigens to T cells. The DCs activate CD4⁺ T cells, which promote macrophage-mediated killing through the production of cytokines and reactive oxygen species. The CD4⁺ T cells also activate antigen-specific B cells, which differentiate into antibody-producing plasma

Table 3. Classical and non-classical symptoms of T1DM and CD

Type 1 diabetes mellitus	Celiac disease
Hyperglycemia	Abdominal discomfort/bloating
Osmotic symptoms-polyuria, polydipsia, polyphagia	Weight loss, fatigue, growth abnormalities
Vomiting/abdominal discomfort/constipation/headache	Infertility, hypogonadism
Nocturia, pyogenic skin infections, recurrent candida rash	Recurrent aphthous stomatitis
Urine ketones	Low bone mineralization
	Compensatory hyperthyroidism
	Dermatitis herpetiformis
	Dental hypoplasia

cells. The antibodies bind to β cells and Fc receptors on macrophages and mediate complement killing. The activated B cells can also function as antigen-presenting cells, further enhancing the anti β cell immune response. Interaction of β cell with antigen-specific CD4⁺ T cells and the presence of proinflammatory cytokines can license the DCs to cross-present antigen to β cell antigen-specific CD8⁺ T cells so that they upregulate their cytotoxic properties. These cytolytic CD8⁺ T cells can kill β cells through the release of cytolytic granules containing perforin and granzymes, as well as through apoptotic Fas–FasL cell death pathway. These immune mechanisms can be tempered by regulatory cell subsets such as the IL-4-producing natural killer T cells and forkhead box (Fox) p3⁺ regulatory T (Treg) cells [45]. However, Treg cells can be incapacitated in the presence of certain cytokines, such as IL-21, which release the β cell destructive immune response. A remitting relapsing phenomenon results, sometimes with Tregs overpowering the CD8⁺ T-cell-mediated killing of β cells. This may be called the “honeymoon phase”, where transiently the dependency on insulin is decreased. Eventually T1DM results, when only 10–30% of the functional β cell mass remains [46].

Even after the onset of the disease, immunological remittance is not observed in the patients, as titers of auto-antibodies and auto reactive T cell persist for a long duration. It is not known if this is because of the continuous exposure to the “triggering factor” or constant auto antigen exposure. Few of the T1DM patients with long-standing disease or others even with new onset of diabetes develop CD. This is also favored by the dysfunctional state of Tregs and “inflammatory milieu” leading to the persistence of the autoimmune state. Due to immune perturbations and neuropathy induced by hyperglycemia, the gut permeability is affected and the site of the autoimmune reaction now shifts from the pancreas to the gut. It has

also been described by researchers that the gut immune system is activated in T1DM patients, as initial priming of diabetogenic cells takes place in the gut and further activation of the immune response takes place in the regional lymph nodes [47].

The pathogenesis of CD can be divided into 3 phases: luminal and early mucosal events, activation of pathogenic CD4⁺ T cells, and events leading to tissue damage that involves both innate and adaptive immunity. The pathogenesis of CD is largely attributed to trigger by wheat gluten. “Gluten” refers to the protein complex of wheat that may include more than 100 different molecules. These proteins can be divided on the basis of solubility into gliadins and glutenins [48]. Some incompletely digested peptides of wheat gluten, rye, or barley can cross the epithelium and enter the lamina propria of the small intestine due to increased gut permeability. When gluten is ingested during the first phase, it is digested to form peptides, but due to lack of prolylendopeptidases, the proline- and glutamine-rich residues remain undigested [49]. These glutamine residues can be converted to negatively charged glutamic acids by tTG, which is a calcium-dependent enzyme that mediates deamidation of gliadins that eventually lead to the formation of epitope that binds efficiently to DQ2, which is then recognized by gut T cells [50]. The peptides generated like the 19 mer trigger an innate immune response that is characterized by the production of IL-15. This affects the epithelial barrier either by increasing the permeability through disruption of tight junctions or by acting on intra epithelial lymphocytes promoting IFN- γ production as well as potent cytotoxic activity particularly by natural killer group 2, member D, natural killer group 2, member C receptors which recognize (MHC class I chain related antigen A and MHC class I chain related antigen B and HLA-E on epithelial cells), leading to epithelial destruction either by T-cell receptor killing or by cytokine production like IL-21 and IFN- γ .

As a result of increased permeability caused by the events described above, peptides like 33 mer can now reach lamina propria where subsequent binding of these peptides to the HLA molecules results in peptide complexes that can activate host gluten-specific CD4⁺ T cells in lamina propria. These activated CD4⁺ T cells lead to the production of a number of cytokines that can in turn promote inflammation and villous damage in the small intestine through the release of metalloproteinases by fibroblasts and inflammatory cells. Activated gluten-specific CD4⁺ T cells can also stimulate B cell production of anti-gluten as well as anti-tTG antibodies [51]. It has been shown that the anti-tTG antibodies in CD can interfere with tTG activity and have a deleterious impact on epithelial cell differentiation [52, 53].

There is an emerging evidence that gut microbiome has a strong impact on shaping the autoimmune response in several diseases including T1DM and CD [54]. With many contraindicating reports, it is an ongoing debate whether altered microflora is a causative factor or a consequence of autoimmunity. Priming of autoimmune effector cells takes place in gut in both T1DM and CD. The hypersensitive innate receptors for bacteria and viruses like toll like receptors can trigger an immune response that is autoreactive. Gram-positive bacteria have been shown to be strong inducers of Th1 response [55] leading to proinflammation; furthermore, antibiotic treatment of these bacteria in non-obese diabetic [56] mouse decreases the incidence of T1DM. Children in the prodrome phase show changes in fecal microflora [57]. We have also reported isolation of pathogenic strain of *Nesterenkonia jeotgali* from duodenal mucosa of CD patient [58]. The exact role of the gut microbiome in pathophysiology is not known currently, but these studies strongly suggest that it modulates the disease mechanism.

Symptomatology, Clinical Presentation, and Diagnosis

In 90% of the patients with this APS-4 subtype, T1DM manifests first followed by CD and in less than 10% of the patients, other patterns are seen. The exact cause of this manner of disease presentation is not known, but it is speculated that it may be because of the long prodromal phase in which epitope spreading takes place that finally leads to celiac-specific antibodies.

Due to prolonged hyperglycemia, patients present with typical osmotic symptoms like marked weight loss, polyuria, polydipsia, and polyphagia. Besides these spe-

cific manifestations, certain nonspecific symptoms also require to be dealt with, to either diagnose or exclude diabetes. These include vomiting, abdominal discomfort, constipation, and headache. Additionally, enuresis in a previously trained child, nocturia, pyogenic skin infections, and recurrent candida rash need consideration for diagnosis/exclusion of T1DM. The presence of urine ketones is also an important marker for diabetes. T1DM patients are generally young, lean, and have a sudden onset of disease and usually the serum C peptide is virtually absent. In the presence of the above-mentioned symptoms, diagnosis of diabetes is done by blood glucose measurements as per American Diabetes Association guidelines [59]. These include random plasma glucose conc ≥ 11.1 mmol/L, fasting plasma glucose conc ≥ 7.0 mmol/L, 2 h post oral glucose tolerance test ≥ 11.1 mmol/L, and HbA1c $\geq 6.5\%$. These patients also have absolute insulin dependency for glycemic control and this is used as a criterion for differentiating T1DM from other forms of diabetes like type 2 diabetes in young, slowly progressive insulin-dependent diabetes mellitus, latent autoimmune diabetes in young as well as latent autoimmune diabetes in adults [60]. About 30% of the T1DM patients present with hyperglycemic emergencies like diabetic ketoacidosis, but hyperglycemic hyperosmolar state is rarely seen in T1DM patients, though it has a high mortality rate.

At least 90–95% of the patients with T1DM test positive for either of the autoantibodies at the onset of the diseases. The autoantibodies can be detected against insulin, islet cell antigen, GAD-65, or zinc transporter 8. Insulin autoantibodies have been implicated as the first antibody to appear in T1DM patients and have been shown to be present years before the onset of the overt diabetes [61]. GADA have been considered the general markers of the autoimmunity and therefore, the correlation of GADA with other disease-specific antibodies such as CD and AiTD autoantibodies has been described.

Clinical features of CD in T1DM patients may be subtle, atypical, or may be completely lacking. This implies that the T1DM patients may harbor florid CD, silent CD or potential CD. In whatsoever form, detection of CD is crucial in T1DM patients, as inclusion of gluten free diet (GFD) in T1DM patients improves the blood glycemic control, and also has a positive impact on biochemical parameters. Therefore, periodic screening of T1DM patients for CD is highly recommended. The features that need to be evaluated for CD diagnosis are mild abdominal discomfort and bloating, weight loss, fatigue, growth abnormalities mimicking constitutional growth delay, infertility, recurrent aphthous stomatitis, low bone mineral-

ization and compensatory hyperthyroidism, and rarely enteropathy-associated T-cell lymphoma. Iron and folic acid deficiency with or without anemia is also one of the most common laboratory findings [62]. T1DM patients with CD have higher propensity for hypoglycemic episodes and are also at increased risk for diabetic retinopathy and nephropathy. The classical and non-classical symptoms of T1DM and CD are summarized in Table 3.

Diagnosis of CD is done by following a protocol that is widely recommended and accepted. It consists of 2 stages that comprise serological testing and histopathological investigation. In the first stage, the patients are screened for autoantibodies anti tTG immunoglobulin A (IgA) and anti EMA (endomysium) IgA. If any patient is detected negative, but is still suspected of CD, then IgA levels are checked for selective IgA deficiency. In case of selective IgA deficiency, tTG IgG and EMA IgG are checked. Other than these 2 antibodies, anti gliadin IgA and IgG as well as anti deamidated gliadin peptide IgA antibodies are also detected in these patients and may be useful in the diagnosis of atypical CD.

If the patient is detected positive for antibodies, then biopsy of small intestine is required to confirm the diagnosis. The characteristic histological changes include an increased no of intraepithelial lymphocytes (>25 per 100 enterocytes), elongation of the crypts, and partial to total villous atrophy [63]. Although there are no strict guidelines formulated by any of the organizations like American Diabetes Association, International Society for Pediatric and Adolescent Diabetes, Canadian Diabetes Association, North American Society of Pediatric Gastroenterology, Hepatology and Nutrition regarding screening of CD in T1DM patients in lieu of controversial reports, periodic screening is recommended irrespective of symptomatic presentation [64].

Treatment and Outcome

Exogenous insulin supplementation and GFD, which excludes wheat, rye, and barley, are the treatments of choice for T1DM and CD respectively. There is no consensus over the safe limit of gluten that can be included in the daily diet. Henceforth, complete abstinence is recommended. Diet plays a pivotal role in management of both these disorders.

In patients with T1DM, low glycemic index food is recommended; however, dietary options in GFD often have high glycemic index. Therefore, dietary management is complicated when both the diseases coexist. The metabol-

ic aspect of these diseases can have influence on several of the associated manifestations as well as on the disease pathogenesis. There are limited numbers of studies that have explored the implications of these treatment regimens on crisscross associated parameters. T1DM patients with undiagnosed or newly diagnosed CD often have poor glycemic control, low total cholesterol, lower high density cholesterol, low diastolic blood, higher prevalence of nephropathy, and retinopathy [65]. These patients often have impaired height, weight, bone mineral density as well body mass index. Few recent studies indicate that these parameters improve within 1 year on compliance with GFD [66, 67]. A study by Cianci et al. [68] shows significant positive impact of GFD on inflammatory immune response.

Future Perspectives

This review brings out a comprehensive scenario about the coexistence of T1DM and CD. So far the information on the epidemiology, etiology, disease progression and several other aspects of this APS-4s is limited as well as scattered. Though the full understanding of APS-4s is a formidable challenge, insights into the genetic, environmental factors and their functional consequences may serve as an illuminator for multifactorial autoimmune diseases that often coexist. Consistent efforts are needed to search other genetic loci with substantial penetrance power, which may be done by genome wide association studies spanning the intronic regions as well.

Though gluten is the triggering factor for CD, it needs to be found out if there is any common environmental factor for both T1DM and CD that leads to their concurrence. Studies on immunological perturbations to delineate disease pathogenesis would also yield great insights. Finally, we need to study implications of different factors on disease management like the effect of GFD on metabolism, glycemic control, bone health, microvascular complications, and other laboratory derangements. There is also an immediate need for multicentric, collaborative, prospective studies to define algorithms for management of multi-endocrine disorders.

Conclusion

T1DM and CD coexist in patients more frequently than expected. These patients may present with nonclassical or asymptomatic diseases. Therefore, periodic

screening of the T1DM patients for CD is highly recommended. The patients often present with additional laboratory derangements and thus necessitate discreet evaluation.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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