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REVIEW ARTICLE

Celiac Disease in Type1 Diabetes: Prevalence, Pathogenesis and Clinical Implications

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ABSTRACT

Absolute insulin insufficiency and persistent hyperglycemia are symptoms of type 1 diabetes mellitus (T1DM), an autoimmune illness marked by the immune-mediated death of pancreatic β-cells. Shared genetic and immunological processes, especially involving HLA-DQ2 and DQ8 alleles, sometimes link type 1 diabetes (T1DM) with celiac disease (CD), another autoimmune condition that is induced by gluten consumption. Type 1 diabetes mellitus (T1DM) and chronic kidney disease (CD) occurring together constitute a subtype of autoimmune polyendocrine syndrome (APS-4), which makes metabolic regulation and therapeutic care more challenging. With variations depending on regional and dietary variables, the frequency of CD among T1DM patients is much greater (4-10%) than in the general population. It is essential to screen T1DM patients for CD since many individuals do not show symptoms or have unusual signs including growth retardation, anemia, or hypoglycemia. Adherence to a gluten-free diet (GFD) and prompt diagnosis greatly enhance metabolic parameters, development, and overall quality of life. The significance of routine screening, early diagnosis, and integrated treatment for best results is highlighted in this review that outlines the genetic, pathophysiological, and clinical intersections of type 1 diabetes and chronic kidney disease.

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1- INTRODUCTION

Celiac disease (CD) and type 1 diabetes (T1D) are immune-mediated disorders that co-cluster far beyond chance, creating a clinically important “autoimmune overlap” in which one diagnosis should prompt vigilance for the other. Contemporary pooled estimates indicate that CD affects a substantial minority of people with T1D, although rates vary by geography and critically by screening strategy and case definition; a recent global meta-analysis focusing on screening studies using anti-tissue transglutaminase (tTG) reported an overall prevalence around (1 in 16) and higher estimates in some regions, underscoring that CD is not a rare comorbidity in T1D care and that under-recognition remains plausible when systematic screening is inconsistent [1]. This matters because CD is frequently silent or presents with non-specific intestinal and extra-intestinal features, while its complications (e.g., nutrient deficiencies and bone health concerns) can intersect with diabetes management priorities; major diabetes guidance therefore continues to justify screening of people with T1D for CD based on prevalence, subtle presentations, and preventable morbidity [2, 3]. In parallel, the gluten-free diet (GFD) the core therapy for CD introduces practical burdens that are uniquely complex in T1D, where carbohydrate counting, hypoglycemia prevention, and dietary quality already demand sustained behavioral work; thus, clarifying when, how, and in whom

to screen and confirm CD has immediate downstream implications for patient-centered care and outcomes [4, 5]. The majority of people with type 1 diabetes mellitus (T1DM) are either children or young adults. This chronic autoimmune condition affects millions of people worldwide [11]. This condition is characterized by the immune system destroying the β-cells in the pancreas, which results in an insulin shortage and ongoing high blood sugar. Progressive β-cell autoimmunity normally occurs during the prodromal period of type 1 diabetes, which may last up to a decade and is usually preceded by the asymptomatic development of the illness [12, 13]. The entry of CD8+ CD4+ T lymphocytes into the pancreatic islets characterizes this stage, leading to insulitis and, ultimately, the death of β cells [14]. Insulin autoantibodies, anti-islet antigen 2 autoantibodies, and anti-glutamic acid decarboxylase-65 autoantibodies (GADA) are positive blood markers for type 1 diabetes, albeit the patient is asymptomatic throughout this time [15]. When just ten to thirty percentages of the islet mass remains; patients begin to experience hyperglycemic symptoms [16].

Following the onset of symptoms, the subsequent stage of the illness is characterized by the treatment of hyperglycemia and its complications. Like all autoimmune diseases, type1 diabetes is a complex hereditary condition whose etiology is also influenced by environmental variables. The geoepidemiology shows that the incidence of T1DM has nearly doubled in children under the age of five [17]. Autoimmune disorders tend to cluster in "some" people due to similar genetic components and associated environmental variables. Ten to thirty percent of people with type 1 diabetes acquire other autoimmune disorders, which typically appear after the disease's clinical beginning [16]. These diseases can be vitiligo, autoimmune gastritis, uveitis, celiac disease (CD), autoimmune thyroid disease (AiTD), and adrenal autoimmunity [18, 19]. The combination of type 1 diabetes with additional autoimmune diseases is known as autoimmune polyendocrine syndromes (APS). On the other hand, not all autoimmune illnesses that belong to the different types of APS are endocrine disorders, therefore this phrase is inaccurate. However, four APS categories designated APS-1 through APS-4 has been identified [20, 21]. Autoimmune polyendocrinopathy is another name for APS-1. Addison's disease, hypoparathyroidism, and candidiasis are among the clinical signs of candidiasis ectodermal dystrophy, a monogenic ailment caused by a mutation in the *Aire* gene [22]. When Addison's illness coexists with either AiTD or T1DM, APS-2 is identified. A subtype of APS-4, is the coexistence of CD and T1DM, which denotes a category that contains combinations not covered in the aforementioned categories. AiTD is classed as APS-3 when it coexists with other autoimmune disorders [16, 23, 24]. Another autoimmune condition that is typified via intolerance to gluten of wheat is CD or non-tropical sprue. Adrenal insufficiency, hypogonadism, dermatitis herpetiformis, small stature, delayed puberty and anemia, are among its intestinal and extraintestinal symptoms [25, 26]. CD typically manifests in an unusual, silent, or prospective form in patients with T1DM, who are regarded as high-risk individuals for the disease [27]. Mechanistically, the T1D–CD association is biologically coherent rather than merely epidemiologic. CD pathogenesis is among the best-characterized HLA-associated immune diseases, where gluten exposure in genetically susceptible individuals drives a defined cascade culminating in characteristic intestinal injury and highly disease-specific serology [6, 7]. Importantly, recent work in a leading diabetes journal adds immunologic granularity by demonstrating gliadin-reactive T cell responses in the gut in children with T1D (with or without diagnosed CD), reinforcing the concept that intestinal immune activation relevant to gluten may be present along a spectrum in T1D and could complicate interpretation of early or borderline serology in routine practice [8].

From a clinical standpoint, the literature since 2022 has increasingly highlighted that the central challenge is not whether CD occurs in T1D, but how to optimize detection and confirmation while minimizing avoidable procedures and unnecessary diet restriction. The 2022 ISPAD consensus chapter on associated conditions in youth with T1D supports systematic screening for CD and provides an international framework for when to test and how to interpret results in pediatric diabetes care [5]. However, more recent analyses sharpen unresolved issues: transient or fluctuating tTG positivity can occur in children with T1D, raising concern that early testing or single time-point positivity especially near diabetes onset may prompt endoscopy or GFD without histologic CD [9, 10]. This is clinically consequential because the GFD's benefits in T1D populations are not uniformly demonstrated across all outcomes; a 2022 systematic review summarizing youth with T1D and CD reported discordant findings across studies, while suggesting that GFD adherence can support normal growth without worsening HbA1c or insulin dose, yet may affect post-prandial glycemia exactly the type of nuanced evidence that complicates "one-size-fits-all" counseling [4]. Therefore, the current literature supports the importance of screening and treatment, but simultaneously signals the need for tighter diagnostic pathways, clearer thresholds for biopsy decisions, and better outcome-focused evidence that reflects modern diabetes technologies and dietary environments.

This paper aimed to: (i) summarize contemporary estimates of CD prevalence in T1D across settings and screening paradigms, (ii) integrate current understanding of shared pathogenesis, emphasizing genetic susceptibility and emerging mucosal immunology; and (iii) critically evaluate clinical implications screening strategies, diagnostic confirmation challenges (including transient seropositivity), and practical consequences of GFD initiation in people living with T1D. The motivating gap is that, despite updated international guidance and new mechanistic and epidemiologic work, day-to-day clinical decisions still face uncertainty about optimal screening timing/intervals, interpretation of borderline or early antibody results, and which patient-important outcomes are most likely to improve with diagnosis and treatment of CD in the context of contemporary T1D care.

1. Genetic Susceptibility and Shared Autoimmune Pathways

We may learn a great deal about the common autoimmune pathophysiology of CD and T1DM from their molecular foundations. With over 30 genetic loci implicated in susceptibility, both illnesses are acknowledged as complex polygenic syndromes. High concordance rates among monozygotic twins and persistent evidence of family aggregation imply a considerable genetic susceptibility to both illnesses, highlighting the important role of heredity [16, 28]. Most researchers agree that the HLA class II region is the single most important genetic component in determining the likelihood of developing type 1diabetes and coronary heart disease (CHD). Chromosome 6p21 includes the DR, DQ, and DP loci, as well as high-risk haplotypes as DR3-DQA10501-DQB102:01 and DR4-DQA103:01-DQB103:02, the main factors that increase the likelihood of type 1 diabetes [29, 30]. People with the DR3/DR4 genotype are much more likely to acquire type 1 diabetes, particularly if they have a first-degree relative who has the disease. The fact that anti-tissue transglutaminase (tTG) antibodies are present in a large percentage of type 1 diabetic patients who are homozygous for DR3/DQ2 further supports the idea that the two diseases have a same genetic architecture.

Two of the most common T1DM susceptibility genes, DQB103:02 and DQB102:01, are also major CD susceptibility genes. In cases of severe or refractory CD, the most important risk molecules are HLA-DQ2 and HLA-DQ8 [31, 32, 33]. When it comes to HLA risk, linkage disequilibrium has a bigger role, especially when it comes to DR3 and DQ2. While DR3 is inherited in a hereditary fashion, there is speculation that DQ2 has a direct role in the presentation of autoantigens in both disorders. In CD, particular interactions at β-chain residues explain the mechanism by which negatively charged gliadin peptides, whether they are native or deamidated by tTG, attach with a high affinity to DQ2 and DQ8 molecules [34, 35]. A similar process has been proposed for type 1 diabetes, whereby diabetogenic peptides may have a preference for binding to DQ2, suggesting a shared antigen presentation route that may initiate the illness. However, the exact triggering antigen for type 1 diabetes is yet unknown [16].

Though there is a significant risk associated with HLA, it does not completely explain how type 1 diabetes or chronic kidney disease (CD) begin. Additional non-HLA loci involved in immune modulation have been discovered by genome-wide association studies. These include genes involved in T-cell differentiation, survival, and activation (e.g., RUNX3, ETS2, FASL, TNFSF18, RGS1, CTLA4, ICOS, CD28, CD247, SH2B3), as well as loci associated with B-cell maturation (ICOSLG, RGS1) and cytokine signaling (IL18R1, IL1R1, IL1RL2). Despite having very small impact sizes, these loci add to the overall picture of autoimmune vulnerability [16] (Figure 1). Noting shared variations in a considerable number of susceptibility loci, there is genetic overlap between type 1 diabetes and chronic kidney disease. Crucially, a number of these sites have been linked to other autoimmune diseases, lending credence to the idea that there may be a shared genetic fingerprint underpinning a variety of immune-mediated illnesses.

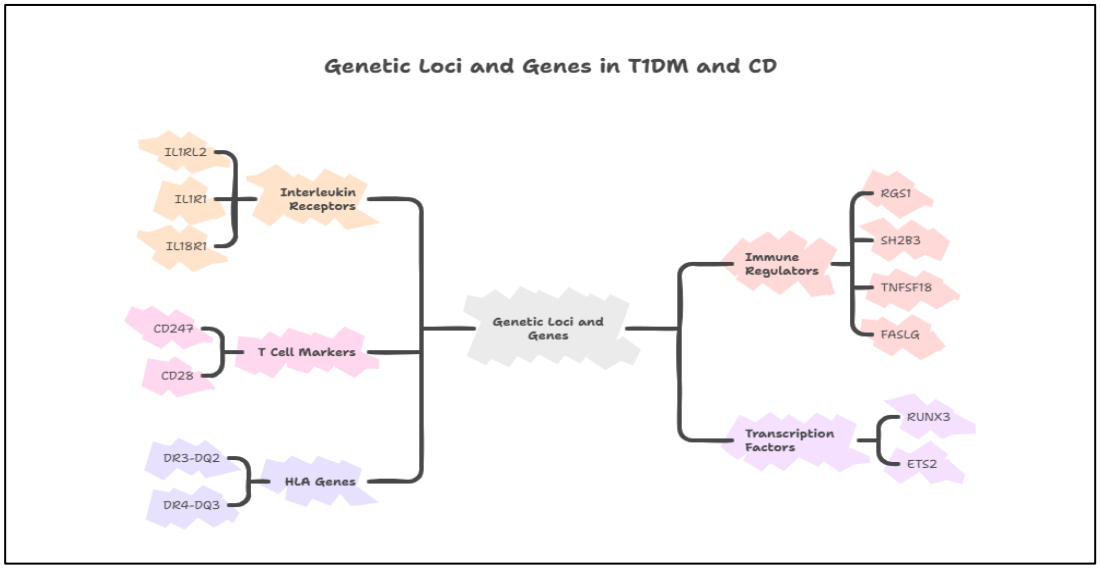

Fig (1): Genetic loci concerned in vulnerability to coexistence of CD and T1DM. Interleukin 1 receptor ligand 2: IL1RL2; Human leucocyte antigen class II genes: DR3-DQ2 and DR4-DQ3; Interleukin 1 receptor: IL1R1; Interleukin 18 receptor: IL18R1; Regulator of G protein Signaling: RGS1; SH2B adaptor family: SH2B3; T cell surface glycoprotein: CD247; Runt-related transcription factor 3: RUNX3, ETS2 ; ETS2; Costimulatory molecule: CD28; Tumor necrosis factor superfamily member 18: TNFSF18; Fas ligand: FASLG.

2. Immunopathogenesis and Mechanistic Insights

In type 1 diabetes mellitus (T1DM), the immune system destroys particular cells inside the body; in type 2 diabetes mellitus (CD), this damage targets the cells lining the intestines (enterocytes). Wheat gluten is the principal beginning antigen in CD, which helps to clarify its pathogenic processes, but the environmental trigger for type 1 diabetes is still unknown [36, 37]. Some viral agents, such rotavirus, hepatitis C virus, and adenovirus type 12, have also been suggested as possible environmental causes for CD, alongside gluten [38]. Similarly, enteroviruses and herpesviruses have been suggested as candidate triggers for T1DM [39, 40]. Considering that T1DM often precedes CD in autoimmune polyglandular syndrome type 4 (APS-4) [41], the cascade of events is frequently described in this order (Figure 2).

In T1DM, exposure to an unidentified triggering factor induces pancreatic β-cells to major histocompatibility complex (MHC) class I molecules and upregulate interferon (IFN)-α, promoting their recognition and targeting by autoreactive $CD8^+$ cytotoxic T lymphocytes [42]. Type I interferons activate dendritic cells (DCs), which subsequently present antigens of β-cell to naïve $CD4^+$ T cells. These $CD4^+$ T cells help macrophage-mediated destruction via pro-inflammatory cytokines and reactive oxygen species, while also activating antigen-specific B cells to generate autoantibodies. These antibodies participate in complement-mediated β-cell injury and further amplify antigen presentation. Antigen-specific $CD4^+$ T cells facilitate DC licensing for cross-presentation, causing cytolytic $CD8^+$ T lymphocytes to activate and undergo β-cell apoptosis via the perforin-granzyme pathways and Fas-FasL signaling system. This response is controlled by regulatory immune cells, such as $FoxP3^+$ regulatory T (Treg) cells and IL-4-producing natural killer T cells. However, Treg cell function may be impaired in the presence of cytokines such as IL-21, resulting in a relapsing–remitting disease pattern often described as the "honeymoon phase," with temporary reduction in exogenous insulin requirements, before progressive β-cell loss leads to overt T1DM [14, 16, 43].

After type1 diabetes begins, autoreactive T and B cell responses remain, in contrast to temporary immunological remission. This might be due to the persistent presence of autoantigens or continuous exposure to an unknown trigger. Treg dysfunction and a pro-inflammatory systemic environment may have a role in the future development of CD in certain people [44, 45]. The autoimmune interaction may now reach the gut as a result of neuropathy and immunological disturbance caused by hyperglycemia, which raise intestinal permeability. The gut-associated lymphoid tissue may prime diabetogenic T cells first, then regional lymph nodes activate them further [46].

There are three traditional steps in the development of CD: (1) events in the lumen and early mucosa, (2) the activation of harmful $CD4^+$ T cells, and (3) inflammatory tissue damage caused by innate and adaptive immunity. The complex combination of wheat proteins known as gluten consists mostly of gliadins and glutenins [47, 48]. Incompletely digested proline- and glutamine-rich peptides derived from wheat, barley, or rye traverse the intestinal epithelium due to increased permeability [49]. These peptides are deamidated by tissue transglutaminase (tTG), generating negatively charged epitopes with high affinity for HLA-DQ2 and DQ8 molecules, which are then presented to $CD4^+$ T cells in the lamina propria [50]. Shorter gluten-derived peptides, such as the 19-mer, also induce innate immune activation via IL-15, promoting epithelial barrier disruption and driving IFN-γ production and cytotoxic activity by intraepithelial lymphocytes. Subsequent access of longer immunodominant peptides, such as the 33-mer, to the lamina propria leads to expansion of gluten-specific T cells and cytokine-mediated villous atrophy, further amplified by metalloproteinase release from stromal and inflammatory cells. In addition to impeding tTG function and epithelial differentiation, activated T cells promote B cell-mediated production of anti-tTG antibodies and anti-gluten [48, 51].

Emerging data highlight the prominent role of the gut microbiome in shaping autoimmune susceptibility in T1DM and CD. Although it remains unclear whether microbial dysbiosis is a cause or consequence of disease, priming of autoreactive effector T cells in the gut has been documented in both conditions. Toll-like receptor–mediated responses to bacterial and viral components may contribute to pathological T cell activation [52, 53]. Gram-positive bacteria are potent inducers of Th1-driven inflammation, and antibiotic suppression of these organisms reduces T1DM incidence in non-obese diabetic mice. Alterations in intestinal microbiota have been observed in individuals even during the prodromal phase of T1DM. A pathogenic strain of *Nesterenkonia jeotgali* has also been isolated from the duodenal mucosa of CD patients. While the precise contribution of the microbiome remains to be fully elucidated, these findings strongly suggest its modulatory role in autoimmune pathophysiology [14, 16].

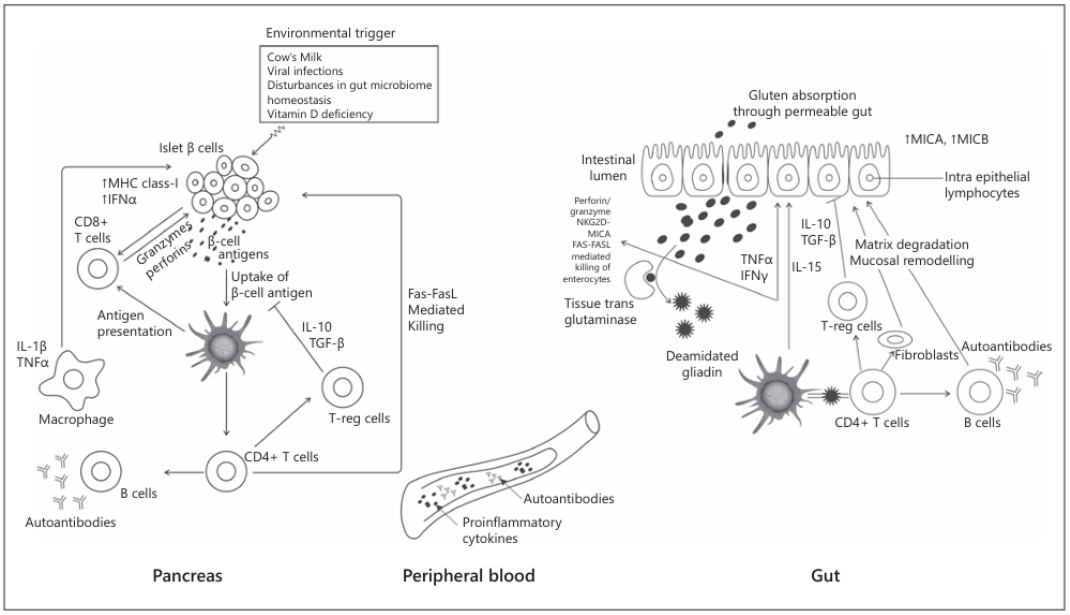

Fig (2): Pathophysiological mechanisms in celiac disease and type 1 diabetes leading to immune-mediated destruction of intestinal enterocytes and pancreatic β-cells [16].

3. Clinical Spectrum, Diagnostic Markers, and Screening Protocols

In majority of patients with this subtype of APS-4, T1DM precedes the onset of celiac disease (CD), whereas the rest of them exhibit the reverse or simultaneous presentation. The reason for this pattern remains unclear, although it has been postulated that the extended prodromal phase of T1DM may facilitate progressive epitope spreading, eventually leading to the development of celiac-specific autoantibodies [54, 55].

Prolonged hyperglycemia is the main clinical feature of type1 diabetes, which manifests itself clinically as traditional osmotic symptoms such as extreme weight loss, increased thirst, increased hunger, and increased urine production. Diabetes may be diagnosed or ruled out with the help of nonspecific symptoms including nausea,

vomiting, stomach pain, constipation, and headaches, in addition to these telltale signs. Other concerning signs include secondary enuresis in a previously recurrent pyogenic skin infections, nocturia, toilet-trained child, and candidal diaper rash. The detection of urinary ketones also supports the diagnosis of T1DM [56, 57, 58, 59].

According to the American Diabetes Association (ADA) guidelines, type 1 diabetes may be diagnosed when plasma glucose levels are either 11.1% or higher at random, 7.0 mmol/L while fasting, 11.1% or higher after a 2-hour oral glucose tolerance test, or 6.5% or higher with HbA1c [47, 48]. Type 1 diabetes mellitus (T1DM) is distinct from other forms of diabetes because individuals with it need insulin injections continuously throughout their lives. Other forms of diabetes include type2 diabetes in children and adolescents (LADY), slowly progressive insulin-dependent diabetes mellitus (SPI-DM), and latent autoimmune diabetes in adults (LADA) [60]. Although hyperglycemic hyperosmolar condition is uncommon in type 1 diabetes, it is linked with a high mortality rate, and around 30% of patients first present with diabetic ketoacidosis [16].

At disease onset, majority of patients with T1DM test positive for one or more pancreatic autoantibodies, including insulin autoantibodies (IAA), islet cell antibodies, glutamic acid decarboxylase 65 (GAD65) antibodies, and zinc transporter 8 (ZnT8) antibodies [61]. IAA is frequently the earliest detectable antibody, often present years prior to clinical onset [62]. GAD65 antibodies are widely recognized as general markers of autoimmunity and have been correlated with CD- and autoimmune thyroid disease-related antibodies [63].

In T1DM patients, CD may present with classical, atypical, or silent manifestations. Therefore, routine screening is essential, as early detection and implementation of a gluten-free diet (GFD) improves glycemic control and metabolic outcomes [64]. Infertility, mild gastrointestinal symptoms (such as abdominal bloating or discomfort), growth failure, fatigue and unexplained weight loss, that mimics constitutional delay, recurrent aphthous ulcers, osteopenia, osteoporosis, and, in rare cases, enteropathy-associated T-cell lymphoma raise clinical suspicion [65, 66]. Iron and folate deficiency with or without anemia is one of the most frequent laboratory outcomes [67]. Patients with type 1 diabetes who also have chronic kidney disease are at a higher risk of developing microvascular complications such diabetic retinopathy and nephropathy, and they are more likely to have hypoglycemia episodes [68]. T1D and coronary heart disease (both conventional and non-conventional) symptoms are reviewed in Table 1.

Table (1): Classical and non-classical symptoms of CD and T1DM

Type 1 diabetes mellitus [56], [57], [58], [59]	**Celiac disease [16], [69]**
Urine ketones Recurrent candida rash Polyphagia Pyogenic skin infections Nocturia Headache Constipation Abdominal discomfort Vomiting Polydipsia Osmotic symptoms-polyuria Hyperglycemia	Dental hypoplasia Dermatitis herpetiformis Compensatory hyperthyroidism Low bone mineralization Recurrent aphtous stomatitis hypogonadism Infertility Growth abnormalities Fatigue Weight loss Abdominal discomfort/ bloating

CD diagnosis follows a widely accepted two-step protocol involving serological testing followed by histopathological confirmation [70]. As a first step in the screening process, we check for antibodies that target tissue transglutaminase (tTG) and endomysial antibodies (EMA). In seronegative cases with high clinical suspicion, total serum IgA is measured to assess for selective deficiency of IgA, if present, EMA IgG and tTG IgG are evaluated. An extra set of antibodies, such IgA/IgG antibodies against gliadin and IgA antibodies against deamidated gliadin peptide, can be useful for identifying unusual instances [71, 72].

Seropositive people must have a small intestine biopsy for histological confirmation. Symptoms such as crypt hyperplasia, partial to complete villous atrophy, and elevated intraepithelial lymphocytes (>25 per 100 enterocytes) may be used as diagnostic tools [73]. Periodic screening is highly advised irrespective of symptomatology, even if

developing data has prevented current recommendations from key organizations, such as the ADA, ISPAD, CDA, and NASPGHAN, from consistently specifying CD screening procedures in type1 diabetes [74].

4. Therapeutics Strategies and Clinical Outcomes

An exogenous insulin pump is the mainstay of type 1 diabetes treatment, whereas a gluten-free diet (GFD) that completely cuts out wheat, rye, and barley is the only effective intervention for celiac disease (CD). There is no widely agreed-upon safe level of gluten consumption per day; therefore it is best to stay away from it altogether. Consequently, both illnesses rely heavily on proper nutrition [75].

To maximize postprandial glycemic control in type1 diabetes, a diet rich in foods with a low glycemic index (GI) is advised. When type1 diabetes and celiac disease coexist, dietary management might be more challenging since many gluten-free goods on the market have a higher GI [76, 77]. Both disorders have metabolic effects, which might impact the development of both diseases and their symptoms.

Poor glycemic control, reduced total and high-density lipoprotein (HDL) cholesterol levels, lower diastolic blood pressure, and an increased prevalence of microvascular complications such as diabetic nephropathy and retinopathy are common in type 1 diabetic patients with newly diagnosed or undiagnosed CD, according to several studies. Also, this subgroup often has inferior development markers, such as a lower body mass index (BMI), less bone mineral density, and shorter stature. The good news is that there is new research that shows how many metabolic and clinical abnormalities improve after a year of following a GFD religiously. The fact that GFD has a positive impact on inflammatory immune responses demonstrates that it has therapeutic value beyond just alleviating symptoms [16, 78].

2- CONCLUSION

The co-existence of type 1 diabetes mellitus (T1DM) and celiac disease (CD) is a significant subtype of autoimmune polyendocrine syndrome, as it has common genetic factors, immunological mechanisms, and complexities in management. The evidence that is emerging in this field highlights the importance of early screening, holistic metabolic and nutritional strategies, and long-term follow-up to prevent complications and achieve optimal outcomes. There is a need for a multidisciplinary approach involving endocrinologists, gastroenterologists, dietitians, and immunologists. However, some existing limitations are still present in the current literature. The majority of the literature is observational, regional, or retrospective in nature. Some differences in the screening practices, diagnostic criteria, and follow-up times make it difficult to compare the studies. Furthermore, although the genetic overlap of HLA-DQ2/DQ8 is well established, the precise environmental factors and immunological mechanisms of coexistence of the disease are not well understood. The data available on the long-term cardiovascular, microvascular, and bone disease in patients with both diseases is still limited.

Future research should aim at conducting large-scale prospective cohort studies to better elucidate the temporal relationship between T1DM and the development of CD. Moreover, research studies that aim to elucidate the underlying mechanisms of immune regulation, microbiota alterations, and environmental factors would also aid in better understanding the shared pathogenesis. In addition, interventional studies that aim at optimized dietary management and personalized screening intervals could also aid in better managing the disease. The key to better managing the disease may lie in the development of precision medicine strategies that integrate genetic, immune, and metabolic profiling.

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