Review

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Exploring the association between atrial fibrillation and celiac disease: a comprehensive review

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Objective: This paper aims to provide a comprehensive overview of the pathophysiology of atrial fibrillation (AF) and celiac disease (CD) individually while also exploring the emerging evidence of a potential association between the two conditions.
Methods: The pathophysiology of AF, the most prevalent arrhythmia globally, and CD, an autoimmune condition triggered by gluten consumption, is examined. Genetic, structural, electrophysiological, and inflammatory factors contributing to their development are explored.
Results: AF involves irregular atrial activity leading to electrical and structural remodeling of the atrium. CD is characterized by an immune response to gluten, primarily associated with HLA-DQ2 and HLA-DQ8 genetic mutations, resulting in damage to intestinal tissue. Emerging research suggests a link between AF and CD, possibly mediated through inflammation, fibrosis, and electromechanical delays in the atrium.
Conclusion: Understanding the association between AF and CD carries significant clinical implications. Recognition of this relationship can assist in identifying individuals at higher risk for AF and inform proactive management strategies. Additionally, it underscores the importance of comprehensive care for CD patients, considering potential cardiac implications. Further research is warranted to elucidate precise mechanisms and explore potential therapeutic interventions targeting common pathways, opening avenues for enhanced patient care and future investigations.

Keywords: atrial fibrillation, celiac disease

Introduction

Atrial fibrillation (AF) stands as the most prevalent arrhythmia addressed in medical care[1]. Its lifetime prevalence in adults hovers around 1 in 4[2], affecting an estimated 30 million individuals worldwide[3]. With the concurrent aging of our population, the incidence of atrial fibrillation is on the rise. Furthermore, both common and rare genetic variations, many of which encode for structural and electrical proteins in the heart, as well as more intricate hereditary factors such as height, obesity, and race, can

HIGHLIGHTS

- Atrial fibrillation (AF) and celiac disease (CD) association: The paper highlights the emerging association between AF and CD, revealing shared genetic predisposition, inflammation, and immune response as underlying factors. It emphasizes the increased risk of AF in CD patients and the importance of considering CD screening in AF patients, as well as monitoring CD individuals for AF.
- Prognosis and complications: The paper discusses the prognosis and complications associated with AF and CD. It highlights the significant risk of ischemic stroke and increased mortality in AF patients, emphasizing the importance of oral anticoagulation therapy. In CD, complications range from nutritional deficiencies and bone disease to cardiovascular risks and an increased risk of autoimmune diseases and cancer.
- Treatment challenges and considerations: The paper addresses the treatment challenges and considerations for AF and CD. It emphasizes the optimal intensity of anticoagulation therapy for AF patients, balancing the risk of stroke with bleeding complications. It also highlights the importance of a gluten-free diet (GFD) for CD patients and the need for an interdisciplinary approach involving gastroenterologists and cardiologists. The paper also discusses nutritional deficiencies in CD patients and the challenges in maintaining a well-rounded diet on a GFD.

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serve as predictive indicators for the onset of AF[4]. Atrial fibrillation is characterized by rapid, irregular, fibrillatory waves that fluctuate in size, shape, and timing. Typically, an irregular ventricular response is associated with this constellation of observations[5]. Among patients with atherosclerosis who also have AF, there is a heightened likelihood of experiencing heart failure, stroke, dementia, and mortality. Extensive research efforts have been devoted to AF, leading to the identification of numerous genetic loci linked to this condition[6]. Generally, atrial fibrillation initiates with a trigger, which may encompass alterations in autonomic tone, acute or long-term changes in atrial wall tension, atrial ectopic foci, and local variables, all capable of inciting the arrhythmia[5].

Celiac disease, an autoimmune condition triggered by the consumption of gluten, primarily affects the small intestine and is influenced by hereditary susceptibility. Its prevalence in the general population ranges from 0.5 to 2%, with an average of 1%[7,8]. Formerly known as celiac sprue, gluten-sensitive enteropathy, or non-tropical sprue[9], clinical manifestations can vary from malabsorption to asymptomatic individuals identified through high-risk screening groups. A definitive response to a gluten-free diet (GFD) and/or evidence of small intestine villous atrophy are requisite for the diagnosis of celiac disease[10]. The presence of human leukocyte antigen (HLA) risk alleles is a necessary but insufficient condition for CD formation. HLA haplotypes alone account for about 35–40% of the genetic risk for CD, underscoring their essential role in its pathophysiology[9]. The morbidity associated with celiac disease is often underestimated, creating a gap in the market for improved patient management strategies[11].

Pathophysiology of AF

AF overview

In 1628, William Harvey initially referred to atrial fibrillation as "auricular fibrillation." It was believed to represent a dissociation between the peripheral pulse and heartbeat[12]. Over the past decade, our understanding of the pathophysiology of atrial fibrillation has significantly advanced.

Theories of AF

Initially, two theories were postulated:

- Multiple wavelet hypothesis: This posited that right and left atria generate numerous wavelets of electrical activity that initiate and sustain irregular atrial rhythms[13].
- Focal theory: According to this theory, AF arises from fibrillatory conduction spreading across the atria following a rapid discharge from one or more foci, with the pulmonary veins being the most common focus[14,15]. Haïssaguerre *et al.*[16] concluded that the pulmonary veins play a pivotal role as a source of ectopic beats. The mechanism encompasses multiple micro re-entries, involving various regions like the superior vena cava, coronary sinus, the walls of both atria, and the interatrial septum[17]. Aberrant automation or after-depolarization may be primary mechanisms.

Remodeling processes in AF

In the presence of atrial fibrillation, remodeling processes occur, involving electrical, contractile, and structural changes within the atrium. This leads to a reduction in action potential duration and wavelength due to electrical remodeling. These alterations also result in decreased cytosolic calcium levels, reduced contractility, dilatation, and ultimately atrial stretching, contributing to contractile remodeling. Connexins have been implicated in structural remodeling, causing fibrosis, which leads to anisotropy, zigzag conduction, and ultimately many micro re-entries. This phase is characterized by fibroblast activation and collagen buildup[18–22].

Clinical manifestations of AF

Clinical manifestations of atrial fibrillation can vary widely and may include symptoms such as palpitations, fatigue, shortness of breath, chest discomfort, and dizziness. Some individuals, however, may be asymptomatic and identified through screening efforts, particularly those in high-risk groups.

Prevalence and risk factors

Less than 1% of individuals between the ages of 60 and 65, and 8–10% of those over 80, experience atrial fibrillation. It is more prevalent in men than in women, and white individuals are at higher risk compared to black individuals. Aging and the severity of underlying heart disease, particularly congestive heart failure and valve dysfunction, increase the risk of atrial fibrillation. Hypertension and sleep-disordered breathing are common comorbidities. The risk of developing AF can be assessed using the HATCH scoring system, which allows for the evaluation of the risk of progression to persistent or permanent AF. The scoring is based on various factors including hypertension (1 point), age 75 years or older (1 point), history of transient ischemic attack or stroke (2 points), and the presence of chronic obstructive pulmonary disease or heart failure (2 points). Individuals with a score greater than 5 are considered to be at high risk for progression of AF[23–25].

Genetic component

Additionally, there is a substantial genetic component to AF. Research indicates that having a parent with AF roughly doubles an individual's likelihood of developing AF within the next four years. The KCNQ1 gene, responsible for encoding the pore-forming subunit of the Kv7.1 voltage-gated potassium channel, and specifically the S140G mutation, is the most frequent genetic mutation associated with AF. Subsequent studies have identified numerous additional candidate genes and risk loci for AF, including genes related to ion channels, fibrosis, extracellular matrix remodeling, cardiogenesis, cell-cell coupling, nuclear structure, as well as loci discovered through genome-wide association studies[25–28].

Inflammatory mechanisms

The underlying cause of the disease lies in structural and electrophysiological changes in the atrium induced by inflammation. Conen *et al.*[29] conducted a study suggesting that median plasma levels of biomarkers are independently associated with disease progression in patients, highlighting inflammation as a potent predictor of AF occurrence. Additionally, levels of high-sensitivity C-reactive protein (hs-CRP) are directly correlated with AF recurrence in response to inflammatory stress.[30] The role of Angiotensin II has also been established in the fibrosis and structural remodeling of cardiac tissue and has been linked to the activation of NOX and subsequent irregularities in calcium handling caused by oxidation, leading to electrical remodeling of

the atria[31,32]. Innate immune cell activation and inflammatory ligand release are enhanced during an inflammatory state. Activated immune cells lead to increased production of tissue factor (TF), von Willebrand factor (vWF), and P-selectin, resulting in the production of IL-2, IL-6, IL-8, TNF-alpha, and MCP-1. These molecules mediate both monocyte-endothelial cell attachment and platelet agglutination. This incident significantly elevates the likelihood of thrombus development and exacerbates endothelial damage caused by AF in the patient's heart[33–35].

Pathophysiology of celiac disease

Celiac disease (CD) overview

Celiac disease is a chronic, immune-mediated enteropathy triggered by dietary gluten in individuals with specific genetic mutations[36]. Gluten, found in wheat, barley, and rye, constitutes the protein fraction[37]. Over ninety percent of celiac disease patients exhibit DQ2 positivity, with the remaining majority showing DQ8 positivity, both encoded by the HLA class II genes, HLA-DQA1 and HLA-DQB1. These genes produce the celiac-associated heterodimer proteins DQ2 and DQ8, expressed on the surface of antigen-presenting cells[8].

In CD, a robust, pro-inflammatory immune response targets the intestinal tissue and specific gluten components, leading to structural alterations[37].

Transglutaminase 2 (tTG2) and Antibodies

tTG2, an enzyme converting glutamine to glutamate, plays a pivotal role.[38] Normally, tTG2 is rapidly inactivated by oxidation. However, in a persistent inflammatory state, tTG2 remains active extracellularly, potentially perpetuating ongoing tTG2 activity. Additionally, specific glutamine residues, known as toxic epitopes, exhibit a higher affinity for tTG2 deamidation in the small intestine. This inflammation promotes the activation of tTG2 in the extracellular environment[39–41].

Anti-tTG2 antibodies, especially IgA, prove highly sensitive and specific for diagnosing celiac disease[42]. Research suggests that these autoantibodies may alter the biology of the small intestine, influencing the transit of gliadin peptides, suppressing angiogenesis, or modulating tTG2 activity[43].

Adaptive immune response in celiac disease

The adaptive immune system plays a critical role in the pathogenesis of celiac disease. It involves a lymphocyte-mediated response to gluten in the small intestine, resulting in distinctive pathological alterations, notably villous atrophy[44]. HLA-DQ2 or HLA-DQ8 molecules on antigen-presenting cells in the lamina propria present gluten peptides, which are then recognized by T cells[45]. Although gluten-specific CD4 + T lymphocytes are crucial in celiac disease, they alone are insufficient to induce the characteristic epithelial destruction and villous atrophy. This damage is primarily orchestrated by intraepithelial lymphocytes (IELs) in response to innate immunological signals[46].

Clinical manifestations of CD

- In children (under three and in the pediatric population):
  - Characterized by diarrhea, loss of appetite, abdominal distention, and failure to thrive[47].
- In adults and older children:
  - May include weight loss, bloating, constipation, or diarrhea. Malabsorption symptoms are less common in adults[48]. They may present with cachexia, sarcopenia, significant hypoalbuminemia, and electrolyte abnormalities.
- Other common presentations:
  - May resemble irritable bowel syndrome (IBS) with constipation, alternating bowel symptoms, and/or dyspepsia-like symptoms like nausea and occasional vomiting[49].

Extraintestinal manifestations

- Iron deficiency microcytic anemia:
  - Due to malabsorption[50].
- Changes in bone mineral density:
  - Including osteopenia or osteoporosis[51].
- In children:
  - Growth retardation and short stature can raise suspicion of underlying CD[52].
- Other signs:
  - Tooth enamel defects, aphthous stomatitis[53], hypertransaminasemia[54].
- Neurological symptoms:
  - Such as headaches, paresthesia, neuroinflammation, anxiety, and depression[55].
- Reproductive function alterations:
  - Including delayed menarche, amenorrhea, recurrent miscarriages, premature delivery, early menopause, and changes in spermatozoa quantity and motility[49].
- Subclinical cases:
  - Identified in patients undergoing antibody screening due to being relatives of CD patients or cases identified through screening in the general population[56].

Association between AF and CD

Multiple studies have discovered a significant link between celiac disease and various cardiac symptoms. Among the most prevalent arrhythmias associated with considerable morbidity is AF. Hidalgo *et al.*[57] conducted a meta-analysis and systematic review, providing robust evidence for the strong association of AF with CD (95% CI: 1.01–1.88). They found a 38% increased risk of atrial fibrillation in individuals with CD.

Kucukseymen and colleagues conducted a prospective study, demonstrating that atrial electromagnetic delay serves as a substantial biomarker for AF in patients with CD. While the inflammatory pathway plays a role in this delay, both fibrosis and the inflammatory process may contribute. This study represents the first to elucidate how fibrosis impacts the vulnerability to AF in patients with CD[58].

Bayar and colleagues conducted a prospective study involving 52 age-matched healthy controls and 71 patients with biopsy-proven, antibody-positive CD. Using surface electrocardiography, they assessed P-wave dispersion (PWD) to evaluate the electrical capabilities of the left atrium. Additionally, tissue Doppler echocardiography was employed to measure electromechanical delay (EMD) time and atrial conduction. Results indicate that while atrial mechanical functions are preserved in patients with CD, a slower electrical conduction rate was observed, suggesting a heightened risk of AF in this population[58].

Furthermore, a cohort study conducted by Emilsson and colleagues further supports the association of AF and CD. The absolute risk of AF in CD was 321 per 100 000 person-years, with an excess risk of 81 per 100 000. Additionally, a prior AF diagnosis was associated with an increased risk of subsequent CD (odds ratio = 1.45, 95% CI = 1.31–1.62)[59].

West and colleagues conducted a study concluding that adults with celiac disease are somewhat more likely to experience atrial fibrillation compared to the general population. Given that vascular disease accounts for 40% of all deaths in people with celiac disease, it emerges as the leading cause of death in this condition[60]. Celiac disease serves as a risk factor for developing AF later in life (HR = 1.34; 95% CI = 1.24–1.44). Even after accounting for type 1 diabetes, autoimmune thyroid disease, and rheumatoid arthritis, risk estimations remained consistent, showing no significant alterations in estimates after controlling for education level or country of birth[59].

Pattanshetty *et al.* utilized electronic health records from 13 different healthcare systems, revealing that patients with celiac disease had a twofold higher prevalence of AF than those in the control group. This elevation in risk may be attributed to the autoimmune nature of the illness and its role in systemic inflammation[61].

As an autoimmune condition, celiac disease induces inflammation, consequently putting individuals at risk for developing AF[57]. Numerous molecular processes associated with CD, including the activation of immune cells like macrophages, T and B cells, neutrophils, and inflammatory cytokines (IL-6, TNF-), have been directly linked to inflammation and oxidative stress. These activated cytokines and immune cells may impact the electrical stability and contractility of myocytes, ultimately leading to the activation of fibroblasts and cellular fibrosis[62,63]. These atrial changes, as confirmed clinically and by electrocardiogram, contribute to reentrant arrhythmias.[64] This observation aligns with prior research indicating that elevated inflammatory markers serve as predictors of atrial fibrillation[59] (Fig. 1, Table 1).

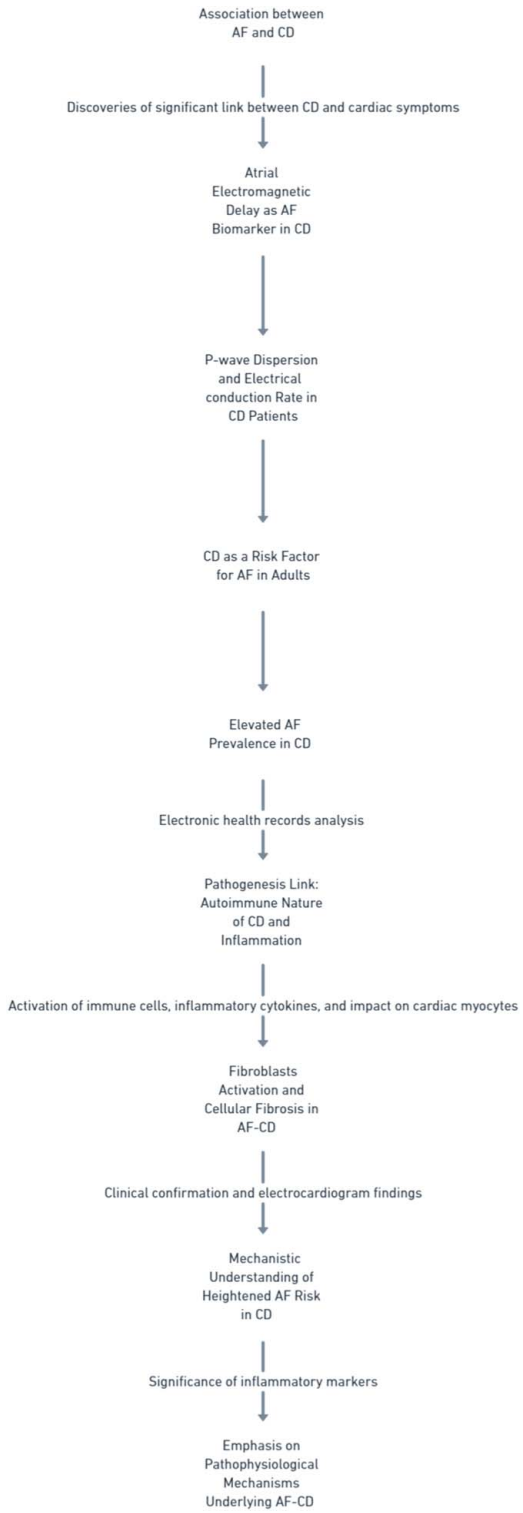

Figure 1. This mind map illustrates the pathogenesis link between AF and CD. AF, atrial fibrillation; CD, celiac disease.

Clinical presentation and diagnosis

In Atrial fibrillation symptoms include palpitations, shortness of breath, inability to exercise, chest pain, and lethargy are more noticeable in some patients[65]. Asymptomatic (silent) atrial fibrillation is more common in the elderly, especially, although some individuals with this condition experience significant symptoms during other episodes[66]. Asymptomatic individuals are diagnosed on routine investigations for pacemaker regulation[67]. A normal result on one ECG does not rule out atrial fibrillation because it is frequently paroxysmal[68]. When atrial fibrillation is suspected but the initial ECG is normal, longer-term monitoring may be beneficial. 24- or 48-h continuous Holter monitoring is typically sufficient for diagnosing patients with everyday symptoms[69]. Modern patch monitors are a good substitute for conventional Holter monitors since they provide 7–10 days of continuous monitoring without attached leads[68]. Both symptomatic and asymptomatic atrial fibrillation are recognized and recorded by implanted pacemakers and implantable cardioverter-defibrillators with atrial leads[70]. Diagnosis of CD can be challenging and it is estimated that ~83% of Americans are undiagnosed or misdiagnosed[71]. Tests for CD are reliant on gluten consumption, and beginning a gluten-free diet (GFD) before testing can cause a false negative as mucosal tissue heals and serological markers return to normal[72]. Serologic testing is the first thing to do if CD is suspected. The tissue transglutaminase (tTG)-IgA antibody, which has shown to have good specificity and sensitivity, should be used for routine initial testing[73].

Table 1

Presents a summary the main results of studies about the shared pathogenesis of atrial fibrillation and celiac disease

Study	Association strength (CI)	Key findings
Hidalgo *et al.*[57]	Strong (95% CI: 1.01–1.88)	CD associated with 38% increased risk of AF
Kucukseymen *et al.*[58]	Significant biomarker	Atrial electromagnetic delay as biomarker for AF in CD
Bayar *et al.*[59]	Electrical conduction	Slower electrical conduction in CD patients, higher AF risk
Emilsson *et al.*[60]	Excess risk	CD associated with absolute AF risk of 321 per 100 000 person-years
West *et al.*[61]	Elevated risk	CD patients somewhat more likely to experience AF
Pattanshetty *et al.*[62]	Twofold higher prevalence	CD patients show twofold higher AF prevalence

AF, atrial fibrillation; CD, celiac disease.

In children younger than 2 years, the tTg-IgA test should be combined with define DGP-IGA (first use) DGP-IgG to improve the accuracy of testing[74]. A positive serology patient should undergo intestinal biopsy[75]. The gold standard of CD diagnosis is intestinal biopsy of the proximal duodenum[76]. Genetic testing, HLA, can be an additional screening strategy; however, they should not be used as an initial diagnostic test. The two HLA genetic markers for CD, DQ2 and DQ8, are not specific to CD and occur in 40% of the population[77].

Management strategies for AF and CD

Atrial fibrillation is associated with an increase in morbidity and mortality. A rise in morbidity and mortality is linked to atrial fibrillation[78]. When treating a patient with AF, the medical doctor must decide between two options. The first step is to determine whether the patient needs anticoagulation and to assess the thromboembolic risk. The next choice is between implementing a rhythm control technique and a primary rate control strategy[79]. The latest ESC recommendations include aiming for a resting heart rate of less than 110 bpm and modifying therapy if the patient still experiences symptoms. They stress how crucial it is to attempt to prevent persistent bradycardia[79]. As far as the pharmacological therapy is concerned it includes Beta-blockers, non-dihydropyridine Calcium channel blockers, and digoxin as the major substances used to regulate rate[80]. Antiarrhythmic drugs exert their predominant effects via blockade of one or more ion channels or by modulation of adrenoreceptors[81].

Patients with symptomatic AF seeking a rhythm control strategy to improve quality of life, as well as those with heart failure and a low ejection fraction, should consider catheter ablation (using radiofrequency ablation or cryotherapy), as it may reduce mortality, heart failure hospitalization rates, and maintain sinus rhythm for a longer period of time than cardioversion[82]. The pathogenetic mechanism behind CD's increased hypercoagulability is complex and includes hyperhomocysteinemia brought on by vitamin B12, B6, and folic acid malabsorption, endothelial dysfunction, atherosclerosis acceleration, chronic inflammation, thrombocytosis, and thrombophilia[83].

It is hypothesized that the increased exposure of phospholipids or new epitopes representing autoantigens is caused by the intestinal damage, endothelial dysfunction, platelet abnormalities, and accelerated apoptosis recently identified in celiac disease. These autoantibodies may serve as markers for prospective anticoagulant preventative therapy and may contribute to the thrombophilia caused by celiac disease. In order to evaluate the risks and advantages of anticoagulants, more research is required on the role of its therapy in CD, particularly in terms of prevention[84]. In a research conducted by Pantic and colleagues, vitamin K antagonists were most frequently started while anticoagulant medication was given to 69% of the patients. According to this review, anticoagulation medication is very significant since patients who got anticoagulants had a 100% survival rate. Accordingly, unless there are specific contraindications, anticoagulant therapy should be begun in all CD patients who have thrombosis. The length of therapy still needs to be determined[85]. All patients with AF, but with low risk of stroke (nonvalvular AF and CHA2DS2-VASc score = 0 in males or 1 in females), require treatment with oral anticoagulants (OACs) unless they are contraindicated. On the other hand VKA, like warfarin, reduces vitamin K in the liver, which prevents the manufacture of the vitamin K-dependent coagulation factors II, VII, IX, and X[87]. Up to 60% of the AF population classified with the CHADS2 score (congestive heart failure, hypertension, age 75, diabetes mellitus, stroke/TIA) have previously been thought of as candidates for aspirin (acetylsalicylic acid) as an alternative to OAC[87].

The gluten-free diet (GFD) has gained popularity beyond its main medical indication as the treatment for gluten-induced immune-mediated disorders[88]. Early detection, lifestyle changes, and adherence to a gluten-free diet may reduce the incidence of AF in individuals with CD[57]. Before any screening programs, the impact of therapy with a gluten-free diet on these risk variables should be evaluated for celiac disease[4].

Prognosis and complications of AF and CD

AF is an important risk factor for ischemic stroke resulting in a fivefold increased stroke risk and a twofold increased mortality. The CHA2DS2-VASc score, which is advised by national and international society standards, is the most used risk score for assessing the incidence of ischemic stroke in AF[82]. AF contributes to the rising mortality and morbidity in individuals with cardiovascular disorders by elevating the risk of heart failure, thromboembolism, and stroke[89]. In patients with non-rheumatic atrial fibrillation, oral anticoagulation can reduce the risk of stroke by over 70%. The primary objective of anticoagulation must be evaluated against the danger of bleeding complications, which are mostly extracranial. The degree of anticoagulation has a direct relationship with bleeding problems. An INR between 2.0 and 3.0 has been demonstrated to be efficient and secure in patients with non-rheumatic atrial fibrillation. Without an extra protective effect, the bleeding risk is significantly higher above an INR level of 4.0[90].

Celiac disease is a benign disorder with a good prognosis in those who adhere to a gluten-free diet[91]. Numerous complications can occur in celiac disease, nutritional (growth failure in children, malnutrition, vitamin deficiencies), hematologic (anemia), bone disease(osteoporosis, fracture), gynecologic (hypo fertility), cardiovascular (coronaropathy, venous thrombosis), neurological (peripheral neuropathy), hepatic (cytolysis, cirrhosis) and with an increased risk of autoimmune diseases (type 1 diabetes, thyroiditis), and cancer (upper digestive tract, hepatocellular carcinoma, lymphoma). The main digestive complications are microscopic colitis and refractory sprue, (resistant to gluten-free diet)[92]. Another commonly observed association of CD is with Dermatitis herpetiformis (DH), which is a cutaneous manifestation of CD, causing an itching and blistering rash, typically on the elbows, knees and buttocks CD has been associated with abnormal liver function tests at diagnosis that usually[93] resolve with a gluten-free diet[94]. The risk of ischemic stroke, myocardial infarction, and thromboembolism, such as deep vein thrombosis and pulmonary embolism, is higher in patients with CD, while there is accumulating evidence that gluten-free diet in CD patients decreases the risk of these complications[83]. With the right care, including a GFD, CD appears to mostly or totally resolved. However, damage to the heart may not completely be reversed if CD is not identified until a late stage[95].

Treatment challenges and considerations

Oral anticoagulant therapy in reducing the risk of stroke and systemic embolism in patients with non-rheumatic atrial fibrillation. The optimal intensity of anticoagulation was found to lie between an INR of 2.0 and an INR of 3.9[96]. One of the most crucial factors in determining treatment efficacy and lowering hemorrhagic risk is the intensity of therapy. The INR should ideally be maintained in the therapeutic range for the most of the time; however, achieving this aim depends on a variety of circumstances. These include physiological and pharmacologic factors, such as concomitant conditions or medications that affect the pharmacokinetics or pharmacodynamics of warfarin, dietary or gastrointestinal (GI) factors that affect the availability of vitamin K1, or physiological factors that affect the synthesis or metabolic fate of vitamin K-dependent coagulation factors[97]. Short-term OAC treatment is often applied after deep venous thrombosis, whereas long-term treatment may be required for atrial fibrillation or after prosthetic heart valve implantation and Short-term OAC treatment is often applied after deep venous thrombosis, whereas long-term treatment may be required for atrial fibrillation or after prosthetic heart valve implantation[98]. The role of anticoagulation in CD, especially in terms of prophylaxis, has not been investigated, and further studies are needed to assess the risk and benefits of this therapy[83].

An interdisciplinary approach with skilled dietitians involved in GFD is quite beneficial as initial GFD adherence at diagnosis predicts long-term dietary compliance[99]. In cases of patients with preexisting CD complicated with AF a multidisciplinary approach is required involving gastroenterologist and cardiologists[95].

CD is characterized by the atrophy of the intestinal villi that leads to altered nutrient absorption. Deficiencies will be corrected throughout the first year of therapy when the intestinal mucosa heals. Biochemical evidence will thus demonstrate this trend together with the abatement of symptoms. Analyzing nutritional intake, however, makes more sense over the long run, once a rigorous GFD is adhered to and mucosal repair is accomplished[100]. The GF diet was shown to be low in dietary fiber, particularly as a result of the necessity of avoiding certain naturally high-fiber foods (such as grains) and the low fiber content of GF products, which are typically manufactured with starches and/or refined flours. Along with some minerals including iron, zinc, magnesium, and calcium, it has been observed that micronutrients are also lacking, particularly vitamin D, vitamin B12, and folate. In particular, it was discovered that the meal's glycemic index and glycemic load had increased, as well as its level of saturated and hydrogenated fatty acids in GFD[101].

Future directions and research gaps

The cardiac autonomic nervous system (ANS) plays a pivotal role in both maintaining healthy cardiac physiology and in conditions leading to cardiac arrhythmias. Various targeted therapies have emerged, including ganglionated plexus ablation, epicardial botulinum toxin injection, vagal nerve (tragus) stimulation, renal denervation, stellate ganglion block/resection, baroreceptor activation therapy, and spinal cord stimulation. Additionally, therapeutic focus on the multiple nexus points along the cardiac neuraxis has shown promise. Recent years have witnessed a surge of interest in cardiac neuraxis intervention for managing cardiac arrhythmias. While randomized controlled studies have displayed promise for treatments like renal denervation and LLTS, further research with larger sample sizes is imperative[102].

Catheter ablation (CA) has become the cornerstone therapy for maintaining sinus rhythm in patients with AF, with pulmonary vein isolation (PVI) being the most frequently employed treatment strategy. Pulsed field ablation (PFA) presents a novel energy source, demonstrating substantial efficacy in achieving lasting PVI without severe ablation-related complications, although large-scale clinical trials are still limited[103].

Advances in artificial intelligence (AI) are particularly well-suited for handling extensive data, making predictive analyses, and ultimately enhancing patient management plans. AI holds the potential to enhance early noninvasive diagnosis, develop more effective therapeutics, and forecast long-term clinical outcomes for patients with AF. It also aids in comprehending the anatomical and functional foundations of the disease[104]. Given the high prevalence of celiac disease, there is an urgent need for non-dietary therapies for this widespread yet under-treated condition. In essence, a deeper molecular understanding of the gluten-induced pathophysiology of celiac disease may yield valuable insights into mucosal immunology[105].

For the discovery of medication targets, establishing effective goals, and creating noninvasive biomarkers suitable for monitoring and potentially diagnosing celiac disease, a comprehensive understanding of the condition's etiology is indispensable. Sensitivity assessments of CD4+ T cells, specifically those targeting deamidated gluten, are anticipated to be pivotal for clinical management as well as for advancing research and drug development[106]. Moreover, the public health burden of untreated celiac disease might be alleviated through mass screening, although it remains a topic of debate, as it is yet to be determined whether the benefits of early detection outweigh any potential drawbacks[107].

Conclusion

Recent studies have highlighted a growing association between AF and CD, revealing shared genetic predisposition, inflammation, and immune response as underlying factors. While the exact mechanisms linking the two conditions are not fully understood, evidence suggests an increased risk of AF in CD patients. It is important for healthcare providers to consider CD screening in AF patients and monitor CD individuals for AF, as this knowledge can improve patient management and outcomes. Additionally, further research is needed to uncover precise mechanisms and develop targeted interventions for individuals with both AF and CD. Understanding this connection provides valuable insights into genetics, inflammation, immune response, and facilitates the development of more comprehensive treatment approaches for individuals with AF and CD.

Ethical approval

Not applicable.

Consent

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