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# The Gut Feeling of the Heart: Pathophysiological Pathways in the Gut-heart Axis in Celiac Disease

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**Abstract** The chain of events, starting from nutrients that change microbiome/dysbiome ratio followed by their secreted mobilome and ending with the leaky gut syndrome, can be applied for cardiovascular diseases. The Gut-heart axis is only one avenue where intestinal luminal eco-events induce remote organ's pathology. The present editorial highlights the mechanisms and potential pathways in the nutrients-microbiota-endocrine-cardiovascular axis that might affect human heart morbidity and mortality in celiac disease.

***Keywords:*** *celiac disease, cardiovascular disease, microbiome, dysbiome, metabolome, nutrition, gut-heart axis, leaky gut, nutritional deficiency*

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## 1. Introduction

The epidemiology of celiac disease (CD) is changing constantly and its incidence is surging in the last decades [1,2,3]. Despite amelioration in cardiovascular diseases (CVD) therapy, their prevalence, morbidity and mortality are high [4]. In fact, CVDs are the leading cause of mortality, responsible for 46% of non-communicable disease deaths.

More and more data are accumulating relaying heart diseases to nutrition, enteric luminal and mucosal eco-events, thus reinforcing the gut-heart axis [5,6,7]. One of those axes is the gut-cardiovascular axis and with this regard, CD and CVDs are going to be the topic of the present editorial.

## 2. Potential Intestinal Mechanisms that Might Affect the Heart

### 2.1. Beneficial Nutrients vs. Harmful Nutrients or Diets

Understanding the basic mechanisms underlying specific nutrients' effects and the advances made in Nutrigenetics/Nutrigenomics allow the development of precision nutrition in various aspects of the metabolic syndrome and more specifically in CVDs [8]. Western diet, overnutrition, junk food, industrial process food, unsaturated and trans fatty acids, simple sugars, salts and other harmful food additives are associated with CVDs [8,9,10,11,12]. On the contrary, vegetarian, Mediterranean, high fiber and optimal omega 3/6 fatty acid diets are preventive and a better therapeutic option [13,14,15]. Coming back to CD, gluten consumption and withdrawal might have some effects on heart morbidity and even on mortality [7,11,16].

### 2.2. Microbiome/dysbiome in CD and Potential Mobilome that Affects the CVD

Alterations in the microbial composition and diversity increase the risk of autoimmune diseases, including celiac disease [5,6,7,17,18,19]. Autoimmune and non-autoimmune heart diseases are not an exception. Notably, CVDs are associated with a luminal microbial imprint and its metabolic repertoire might play a crucial role in the induction and evolvement of those conditions [20,21]. The gut microbial metabolites that play a role in CVDs induction were summarized recently [22].

### 2.3. Posttranslational Modification of Proteins

This is a well-established enzyme-operated phenomenon that is quite frequent in the enteric gut compartment. The luminal and the mucosal transglutaminases are essential in breaking the tolerance to gluten and gliadin peptides, turning them immunogenic in CD [19,23]. Nonetheless, CVDs are also dependent on luminal enzymatic activity and heart diseases are highly connected to the gut microbiota/dysbiota ratio and their performances [24]. It appears that some nutritional and microbial components that reside in the lumen, have cardiogenic,

diabetogenic, atherosclerotic, coagulatory or hypertensive capacities (ex: choline, trimethylamine, betaine, carnitine, lipopolysaccharides). The posttranslational enzymatic modification of those molecules might contribute to cardiovascular pathology. Since choline and carnitine are major dietary precursors of trimethylamine in the human gut lumen, their enzymatic modifications are pivotal in driving cardiovascular pathology [25]. The gut microbiota-dependent metabolite, namely, trimethylamine N-oxide, produced from choline and phosphatidylcholine, is a known detrimental molecule that enhances atherosclerosis and thrombosis and CVDs morbidity and outcome [26]. It can be summarized that both CD and CVDs are highly dependent on nutrition, microbiome abnormalities and luminal enzymatic modification of foreign proteins.

### 2.4. Luminal Horizontal Gene Transfer

This is a very conserved prokaryotic genetic mechanism for microbial survival in the environment, including in the human gastrointestinal tract [27]. In several minutes, adjacent bacteria can laterally transfer genetic material, helping them to overcome antibacterial drugs or to suppress local human immune systems. Antibiotic resistant genes and various additional hostile genes are some examples [27,28]. The potential connection to CVDs is the dysbiosis associated with CD and cardiovascular conditions.

In addition to the trimethylamine/trimethylamine N-oxide, short-chain fatty acids primary and secondary bile acids pathways and metabolism independent processes, horizontal gene transfer of detrimental "cardiogenic" genes might drive or contribute to CVD pathogenesis [5,6,29].

### 2.5. Intestinal Permeability and the Leaky Gut

In many human chronic conditions, including metabolic, autoimmune, allergic, infectious, cancerous and geriatric diseases, intestinal tight junction functional integrity is compromised [30]. Gluten/gliadins are known to enhance intestinal permeability in CD and in non-CD conditions and the permeability is increased in various CVDs, as well [5,6,7,11,31,32,33]. The CD associate leaky gut can potentially irradiate microbial constituents and mobilome toward the cardiovascular organs [5,6,7,31,32,33,34]. The following diets and nutrients were associated with enhanced enteric permeability: High fat diet, High carbohydrate/sugar diet, fructose, gluten, process food additives like salt, sugar, organic acids, emulsifiers and nanoparticles, medium chain fatty acids; capric acid, lauric acid, Acyl carnitines, Chitosan, Ethanol and Capsianoside [7,11,35,36].

### 2.6. Cardiogenic Nutritional Deficiencies

An additional mechanism that can affect cardiovascular performances is a specific nutritional deficiency. vitamin A, C, D and E, creatine, coenzyme Q, potassium, calcium, magnesium, selenium, zinc, taurine, folic acid, B6 and B12 and iron are important for heart and vessels functionalities. Intriguingly, vitamin A, D and zinc deficiency and Glutamine deprivation were reported to increase intestinal permeability. However, despite their popular routine consumption as multi-vitamins and multi-minerals, no scientific evidence exists for their intake to prevent or treat CVDs, unless a specific deficiency is detected [37,38,39,40,41]. In the present journal, Bohra and Shah reported on cardiomyopathy as a cardiac manifestation of CD [42] and Boutrid et al, in a corresponding editorial, highlighted carnitine deficiency as a potential contributor to the heart dysfunction [43]. The interrelations between carnitine, cardiomyopathy and CD are well documented in the literature [44]. Despite the endogenous synthesis, exogenous carnitine supply and absorption is pivotal for the body energy homeostasis and cardiac performances .

## 3. Potential Intestinal Pathways that Might Irradiate to the Heart

### 3.1. The Enteric-luminal Sensing Cells

The separation between commensal or pathogenic microorganisms and distinguishing between self and foreign luminal contents are essential for avoiding unnecessary immune stimulations and induce tolerance. In order to accomplish those tasks, sensing the luminal constituents and reporting on eco-events' consequences is indispensable, in order to transmit the messages to efferent systems, for adequate responses. Those enteric epithelial and subepithelial cells are: enterocytes, colonocytes, goblet, M, dendritic, enteroendocrine, enteric glial and Tuft cells. Following sensing and processing, several pathways exist to deliver the signals to remote organs, heart included [5,6,45,46].

### 3.2. Gut-heart Blood Vasculature

Most probably the gut-originated blood vessels are the main avenue for systemic sharing of the informative luminal cargo. Mucosal committed immune cells, proinflammatory cytokines and lymphokines, post translation modified peptides, microbial processed constituents and mobilome, autoantibodies, antigen presenting cells and finally gluten/gliadin peptides can circulate via the blood vessels, to negatively impact the cardio-vascular domains [5,6,7].

### 3.3. Gut-heart Lymphatic Vessels

The lymphatic vasculature is a unidirectional conductive compartment that returns filtered interstitial fluid and peripheral tissue-originated molecules to the systemic blood circulation. The lymph is important for immune cell trafficking and surveillance, protective antibodies and lipid absorption [47]. Recently, the role of lymphatics in organ regeneration and injury repair was unraveled, adding some new aspect for cardiac growth and regeneration and repair [48]. The gut lymphatic vasculature might represent an additional door to door pathway in the gut -heart axis.

### 3.4. Enteric Nervous Inter-connections

The two intestinal mucosal neuronal plexuses and their close connections to the neuroendocrine, the vagal and autonomic nervous system were extensively described [45]. Adding the sub-epithelial glial cells adjacent to the basement membrane, enterocyte mono layer, entero-chromatin and sub-epithelial dendritic cells and blood/ lymphatic vessels, those mucosal glial networks can potentially participate in gut lumen sensing and trafficking the messages and signals to the heart. Such an enteric mucosal-brain route was reported for alpha synuclein in Parkinson's disease [49]. The question that arises if such a pathway can't operate between the gut and the heart? In summary, enteric nervous pathways in the gut-heart axis are presently suggested.

## 4. Conclusions

Collectively, through both nutrient metabolic processing and metabolism-independent mechanisms, the gut microbiome forms a largely overlooked dynamic yet resilient genetic, metabolic and endocrine organ that uptake nutritional hints, process and integrate them with the host, thus participating in the pathogenesis of CVDs and associated metabolic disorders [50]. By secreting SCFAs and converting primary bile acids to secondary ones, the microbiota can increase energy expenditure and insulin sensitivity and suppress inflammation. On the contrary, by assisting trimethylamine-n-oxide liver production, they can enhance atherosclerotic changes and hypercoagulability, thus enhancing cardiac morbidity, inducing myocardial infarction, stroke and death [50]. It seems that the nutrients-microbiota-endocrine-cardiovascular axis is a major pathway that determines human heart morbidity and mortality. Molecular mimicry between shared antigen present in both the myocardium and the small bowel may be responsible for cardiac injury. Interestingly, some reports on dilated cardiomyopathy, autoimmune myocarditis and recurrent pericarditis associated with CD were shown to improve to gluten withdrawal [51,52,53,54]. It is foreseeable that the CD cardiac manifestations like heart Failure, dilated cardiomyopathy, autoimmune myocarditis, recurrent pericarditis or arrhythmias can be prevented or improved by nutritional manipulations, microbiome rehabilitation, tight junction functional strengthening or quelling the leaky gut. Their exploration might bring new nutritional, microbial and metabolic therapeutic strategies to combat those prevalent heart diseases.

## Abbreviations

CD- celiac disease, CVD-cardiovascular disease.

## Conflicts of Interest

No conflict of interest and the manuscript was not granted.

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