

Celiac Disease and Ischemic Heart Disease: What is the Link?

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In a recent publication by De Marchi et al. [1], coeliac disease (CD) in young adults was linked to a potential increase in risk for early atherosclerosis [1]. Of note, it has been previously reported a positive association between CD and ischemic heart disease (IHD) [2,3]. Concordantly, it has been found that subclinical cardiac involvement and cardiovascular disease risk factors are quite frequent in celiac children when compared to healthy subjects [4,5]. Until today, it is not well-defined whether a cause-and-effect relationship can be inferred from the association between CD and IHD or if these conditions occur as consequences of a common underlying cause. CD patients may suffer primarily from gastrointestinal symptoms, even if the disease may be related to lots of extraintestinal disorders [6,7]. CD has been described as a chronic systemic immune-mediated condition triggered by dietary gluten in genetically susceptible individuals [4]. Gluten-sensitive enteropathy is characterized by villous atrophy, various degrees of crypt cell hyperplasia and increased numbers of intraepithelial lymphocytes of the proximal small intestine [6-9]. It has been assessed that the cytokine expression pattern in response to gluten is strongly dominated by Interferon- γ (IFN- γ) and that celiac patients show an increased expression of IFN- γ and a high number of TCD4⁺IFN- γ -producing cells [7]. IFN- γ has been illustrated as a key determinant in gut permeability as well as in inflammation in CD [8,9]. It has been found that IFN- γ secreted by gluten-activated celiac patient T cells, represents the primary effector of increased gluten peptide translocation during active disease [9]. Toxic gluten peptides have been reported to elicit an important immune response in the celiac intestine after regiospecific deamidation by an endogenous extracellular enzyme, transglutaminase 2 (TG2) [10]. It has been recognized that IFN- γ is the most potent inducer of TG2 [8]. It has been detected that IFN- γ mediated activation of TG2 requires phosphatidylinositol-3-kinases (PI3Ks) activity [10]. It is now accepted that chronic inflammation is considered as a major pathogenic factor in atherosclerosis and cardiovascular accidents [11]. Atherosclerosis has been linked to heart attack and ischemic stroke representing its major clinical consequences [11-13]. The atherosclerotic vascular remodelling and pathophysiology involve multiple cell types and a wide range of mediators and cascades [12]. Inflammatory factors, such as cytokines and adhesion molecules, have been connected with the onset and propagation of the atherosclerotic lesion [11,12]. Among the cytokines, IFN- γ has been shown to be a critical player in atherogenesis and in the development and progression of cardiovascular disease [12,13]. IFN- γ has been found to be expressed at high levels in atherosclerotic lesions [12,13]. Interestingly, it has been provided evidence that IFN- γ regulates the function and properties of all the cell types in the vessel [12]. Moreover, it has been suggested that serum concentrations of IFN- γ correlate with severe left ventricular dysfunction in patients affected by acute myocardial infarction [14]. The basic pathophysiological mechanisms underlying cardiovascular events are mediated via a number of factors and signaling pathways including PI3Ks in a variety of a different cell types, such as endothelial cells, smooth muscle cells, platelets, monocytes and cardiomyocytes [12]. It has been shown that PI3K-related signaling pathways are crucial in the pathogenesis of

cardiovascular diseases [12]. PI3Ks have also been revealed to dominate the inflammatory aspects of atherosclerosis [12]. With respect to the above, we advance the hypothesis that patients suffering from CD may be at increased risk of IHD. We suppose that CD and IHD may share a common underlying link. The autoimmune etiology of CD and the potential role of inflammation in the development of atherosclerosis and IHD, point to inflammation and the immune system as target areas for research. We postulate that aberrant expression of IFN- γ may be responsible for susceptibility to IHD in CD patients through upregulation of PI3K-related signalling pathways. For that reason, celiac patients should be screened for other factors that also increase the chance that existing IHD will worsen such as high blood pressure, high cholesterol, obesity, diabetes, hyperhomocysteinemia, smoking and physical inactivity both at the time of diagnosis and during follow-up considering the possible coexistence of these conditions. Identification of the mechanisms that trigger early development of atherosclerosis in CD is important for development of interventions to prevent and treat CVD in this population given that there is increasing incidence of CD in the world. Large prospective trials are needed to verify the possible role of IFN- γ in the positive association between latent CD and IHD. Strict adherence to a gluten free is currently the only effective management of CD. However, cardiovascular disease screening and a dietary counseling targeting cardiovascular disease prevention may contribute significantly to improve or go away cardiac complications. PI3K inhibitors may represent a potential attractive therapeutic option for immunomodulatory intervention strategy to halt or even prevent IHD in CD patients slowing down the adverse effects of IFN- γ .

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