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## Review

## Q4 Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease

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## ABSTRACT

The incidence of autoimmune diseases is increasing along with the expansion of industrial food processing and food additive consumption.

The intestinal epithelial barrier, with its intercellular tight junction, controls the equilibrium between tolerance and immunity to non-self-antigens. As a result, particular attention is being placed on the role of tight junction dysfunction in the pathogenesis of AD. Tight junction leakage is enhanced by many luminal components, commonly used industrial food additives being some of them.

Glucose, salt, emulsifiers, organic solvents, gluten, microbial transglutaminase, and nanoparticles are extensively and increasingly used by the food industry, claim the manufacturers, to improve the qualities of food. However, all of the aforementioned additives increase intestinal permeability by breaching the integrity of tight junction paracellular transfer. In fact, tight junction dysfunction is common in multiple autoimmune diseases and the central part played by the tight junction in autoimmune diseases pathogenesis is extensively described. It is hypothesized that commonly used industrial food additives abrogate human epithelial barrier function, thus, increasing intestinal permeability through the opened tight junction, resulting in entry of foreign immunogenic antigens and activation of the autoimmune cascade. Future research on food additives exposure-intestinal permeability–autoimmunity interplay will enhance our knowledge of the common mechanisms associated with autoimmune progression.

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68

69 **1. Introduction**

70 The incidence of autoimmune diseases (AD) is increasing world-wide,  
 71 mainly in western countries and the role of the environment in AD devel-  
 72 opment is gradually becoming clear [1]. Similarly, industrial food process-  
 73 ing and food additive consumption is expanding. The recent increased  
 74 knowledge on the functions, mechanisms and abnormalities of intestinal  
 75 permeability and the specific relationship between some common food  
 76 additives and their deleterious effects on the tight-junction, prompted  
 77 us to review these observations and put forward the hypothesis that in-  
 78 creased intestinal permeability induced by the industrial food additives  
 79 explains the observed surge in autoimmune disease.

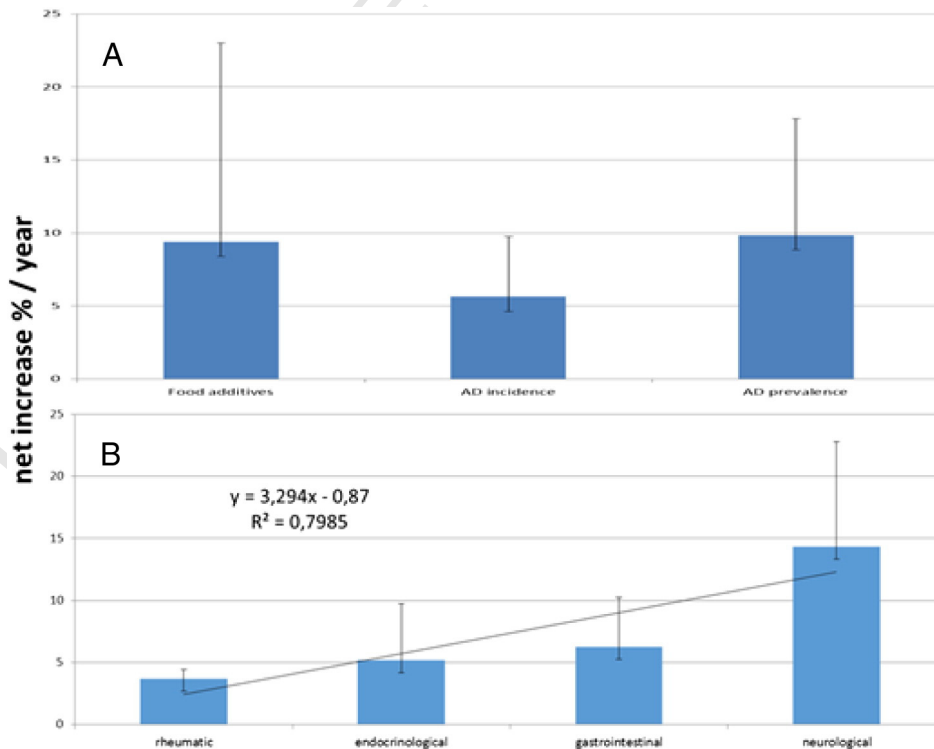
80 **2. Autoimmune diseases are on the increase**

81 Epidemiological data provide strong evidence of a steady rise in  
 82 AD throughout westernized societies over the last three decades  
 83 [2]. Multiple sclerosis, type 1 diabetes, inflammatory bowel diseases  
 84 (mainly Crohn's disease), systemic lupus erythematosus, primary bili-  
 85 ary cirrhosis, myasthenia gravis, autoimmune thyroiditis, hepatitis and  
 86 rheumatic diseases, bullous pemphigoid, and celiac disease are several  
 87 examples [2–6, Fig. 1, Ref.: 4,7–24]. Fig. 1A shows the cumulative net  
 88 fold increases in AD incidence/prevalence worldwide in those countries  
 89 where it was reported. Increased folds/year of type 1 diabetes, bullous

90 pemphigoid, and autoimmune thyroiditis, of 0.77, 0.35 and 0.24, respec- 90  
 91 tively, were noted [14,18,20]. Type 1 diabetes increased 3–4% per 91  
 92 annum and undiagnosed celiac disease mortality increased 4 fold in 92  
 93 the USA [21,25]. Grouping the ADs to major disease classes, the highest 93  
 94 net increase % per year was noted in the neurological followed by gas- 94  
 95 trointestinal, endocrine, and rheumatic diseases (Fig. 1B). The 95  
 96 geoepidemiological distribution of AD, the world-wide North–south 96  
 97 and West–east gradients in Europe, their relationship to socioeconomic 97  
 98 status, their rapid increase in developed countries and observations in 98  
 99 migrant populations all indicate some form of environmental impact, 99  
 100 rather genetic factors, driving these recent and rapid evolutionary pro- 100  
 101 cesses [1–3]. Among many others, two major environmental factors, 101  
 102 strongly related to socioeconomic status are suspected to driver 102  
 103 these phenomena: infections and nutrition. The present review will 103  
 104 not expand on the debate of the interrelationship between AD and in- 104  
 105 fections [26]. A survey of the recent changes in industrial food additives 105  
 106 processing and the effect of food additives on intestinal permeability, 106  
 107 resulting in increased tight junction leakage, local and systemic immune 107  
 108 stimulation and potentiating AD induction, is presented here. 108

109 **3. Increased usage of industrial and consumer food additives**

110 The changes in agricultural and industrial practices over the past 110  
 111 decades have increased the world's capacity to provide food through 111



Q1

Fig. 1. A. The mean net % increase per year of industrial food additives usage and AD incidences and prevalences. B. The mean net % increases of different classes of ADs. Adapted from: Ref.: [4,7–24].

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