

Diet and Autoimmunity: What is the connection?

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Abstract

Autoimmune disorders are characterized by complex multi-factorial etiology. The influence of environmental factors on their etiology is being investigated. Dietary factors that may have possible effect on development of autoimmunity are also being scrutinized. Modern diets are rich in foods which are processed at high temperatures and under conditions of dry heat. These processes are believed to result in formation of toxins with deleterious health effects. Advanced glycation end products are heterogeneous toxins formed in foods subjected to high temperatures while cooking or processing. Although they add to taste and appearance of food their excess has been linked to variety of diseases including autoimmunity. It is important to completely understand their effect on different autoimmune disorders as they are modifiable and can thus help in treatment or prevention of above disorders.

Keywords: Advanced glycation end products; Diet; Autoimmunity; RAGE

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Autoimmune diseases are multi-factorial in nature. Role of genetic factors in autoimmunity is well-established, however, environmental and lifestyle factors which may predispose to autoimmunity have not been properly characterized. In view of increasing incidence of autoimmunity it becomes relevant to investigate the effect of environment including dietary factors in etiology of autoimmune disorders. In this context dietary factors have generated interest as potential triggers for autoimmunity [1]. Modern diets include a large number of foodstuffs which are cooked at high temperatures to give them added flavour and texture. However, this leads to enhanced formation of advanced glycation end products (AGEs) the excess of which has been associated with different lifestyle and age related diseases [2].

AGEs are a group of heterogeneous compounds which are formed as a result of glycation reaction. Glycation is basically non-enzymatic attachment of glucose to the amino group of proteins and other biomolecules like DNA and lipids. Maillard reaction occurs that includes the formation of reversible Schiff's base intermediates, Amadori rearrangement products which ultimately form AGEs by further chemical modifications. The AGEs can be derived either from outside sources (Exogenous) or formed inside the body as a result of normal metabolism (Endogenous). Exogenous AGEs are usually food derived and are known as dietary AGEs (dAGEs). Total body AGE pool comprises of sum total of exogenous and endogenous AGEs [3]. Nε-(1-

Carboxymethyl)-L-lysine, Pentosidine and Methylglyoxal are some of the AGEs which have been assessed more commonly in diet.

AGEs have been linked to autoimmunity in several studies conducted on patients as well as experimental animals. Most of the work on AGEs has been done on type 1 diabetes where their presence has been linked to enhanced propensity to develop microvascular complications [4]. Chen et al. noted that interaction of receptor for AGEs (RAGE) with its ligand led to maturation of T cells to pathogenic phenotype in advanced stages of diabetes [5]. In rheumatoid arthritis, serum levels of pentosidine, a fluorescent AGE, have been correlated with the disease activity [6]. Dong et al. in their study on autoimmune uveitis found elevated serum levels of glyceraldehyde-AGEs in patients and treatment with pyridoxamine, an AGE inhibitor, was found to result in reduction in clinical severity of the disease [7]. The possibility of involvement of AGE-RAGE axis in pathophysiology of myasthenia gravis has also been highlighted in some studies [8]. Bayoumy et al. demonstrated decreased soluble RAGE levels in patients with Systemic lupus erythematosus thus suggesting the involvement of RAGE pathway in its pathogenesis [9]. However, RAGE is a multiligand protein and whether or not AGEs are majorly responsible as ligands is not well studied. AGEs have also been implicated in pathogenesis of multiple sclerosis

(MS) and methylglyoxal derived AGEs have been isolated from brain as well as plasma of MS patients [10].

One of the possible mechanisms responsible for triggering of AGE induced autoimmunity is believed to be the enhanced immunogenicity of AGE modified proteins. Previous studies have shown that AGE modification of proteins like albumin, IgG, LDL, and factor VIII may contribute to their enhanced immunogenicity and formation of antibodies against them [11,12]. The binding of AGEs to RAGE is believed to exhibit pro-inflammatory effects mediated via NFκB and cytokines like IL-6 may further be responsible for pro-autoimmunity immune modulation [13,14]. AGEs have been shown to activate monocytes, thereby leading to increased expression of adhesion molecules, enhanced cytokine production and T-cell proliferation in patients of diabetes mellitus post organ transplantation [15]. Han et al. in their study on incubation of lymphocytes with BSA-glucose derived AGEs found higher differentiation of naive CD4+ T-cells towards Th1/Th17 phenotype and elimination of suppressive function of T regulatory cells [16]. Indirect effects of AGEs like alteration of gut microbiota may further serve to divert body's immune milieu towards autoimmunity [17,18].

Although the potential role of AGEs in different autoimmune conditions has been highlighted in several studies a direct link between AGE intake in diet and autoimmunity has not been well explored. Approximately 10-30% of dAGEs may be absorbed. Plasma AGE levels have been found to increase in response to dAGE intake. Studies show that consumption of an AGE rich diet promotes their accumulation in the tissues. Further, dAGEs akin to the endogenous AGEs have also been shown to act as RAGE ligands thereby contributing to the activation of RAGE signalling

pathways [19]. Thus, suggesting a direct connection between dietary uptake of AGEs and propensity to develop autoimmunity is not far-fetched. A reduction in dAGEs has been found to be associated with improvement in insulin sensitivity in both animal and human diabetics [20]. Abate et al. in their study showed overcooking of Pasta led to an increase in ROS production and activation of immune response due to IL-8 release. The above factors are known to be involved in etiopathology of autoimmune diseases [21]. The above observations merit further studies to prove the contribution of dAGEs in different autoimmune disorders. Further, intake of which type of AGEs is more deleterious and in what concentration needs to be sorted out. Despite several studies on dAGEs and aging and lifestyle related disorders no threshold/safety limit for AGE intake in diet has been defined! Also one should make an attempt to find out whether the effect of AGEs on immune system is temporary or long lasting. Whether AGEs predispose to autoimmunity in all individuals or only in those with a suitable genetic background? Addressing above questions will help to provide a factor which can be targeted easily to prevent autoimmunity or check its progress.

The concept of possible etiological role of dAGEs in autoimmunity, though, not new, remains in its infancy due to lack of adequate number of studies. Such studies though limited by heterogenous nature of dAGEs are however feasible. Large scale studies characterizing the dAGEs which influence T and B-cell profiles favouring autoimmunity are warranted. Proving the causal or promotional role of dAGEs in autoimmune diseases may pave the way for using anti-AGE molecules for treatment or prevention of autoimmunity.

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