Managing Elevated IgG-Antigen Immune Complexes

The presence of IgG antibodies to foods has been linked to a number of conditions such as irritable bowel syndrome\(^1\) and migraines.\(^2\) It is believed that the detrimental effect of IgG antibodies might be mediated through the formation of IgG-antigen complexes which deposit in various tissues, giving rise to type III hypersensitivity reactions.\(^3\)

Elevated IgG-antigen complexes should generally be managed by supporting the integrity of the intestinal mucosa. This is because a dysfunctional mucosal barrier can be a key event in the pathophysiology of elevated IgG-antigen complexes. Several clear therapeutic targets exist to support the integrity of the intestinal mucosa.

**The Four Aims in Managing Elevated IgG-antigen Complexes and Symptoms of Intestinal Permeability**

1. **Remove exposure to dietary antigens**
   - Temporarily avoid foods that cause an IgG response

2. **Replace with low allergenic foods**
   - Low allergenic food list

3. **Reduce intestinal inflammation and support digestion and immunity**
   - Consider supplementing with Slippery elm, *Saccharomyces boulardii* and Glutamine
   - High quality Norwegian Omega-3 or
   - Zinc, Vitamin A, Selenium and flavonoids such as Quercetin and Bromelain

4. **Support the normal health and function of the mucosal barrier**
   - Consider supplementing with high-quality strain-specific probiotic with *Lactobacillus rhamnosus* HN001

*This information is for healthcare professionals only*

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The pathophysiology of elevated IgG-antigen complexes

Under normal circumstances, IgG antibodies are generated as part of the normal function of the mucosa-associated lymphatic tissue (MALT)—the collection of immune cells within the intestinal wall and the underlying lamina propria. Since the intestinal mucosa acts as a defensive barrier to a multitude of pathogens, the MALT is replete with immune cells prepared to respond to foreign antigens including dietary antigens. However, to prevent the MALT from responding to commonly consumed dietary antigens, a state of immunotolerance to these dietary antigens is developed. In part, this immunotolerance is mediated through IgG antibodies. When a dietary antigen is consumed, IgG-secreting B cells release IgG antibodies which compete with IgE antibodies, reducing the likelihood that dietary antigens will initiate an IgE-mediated anaphylactic response. Once formed, the IgG-dietary antigen complexes are cleared by the reticuloendothelial system.

Although the MALT is an effective barrier to the entry of pathogens and foreign dietary antigens, it relies on the strong selective permeability of the intestinal mucosa. This selective permeability is of critical importance, as it restricts the passage of foreign and excessive dietary antigens into the MALT. Maintaining the integrity of this mucosa is specialised epithelial cells and intercellular proteins termed tight junctions. The epithelial cells selectively absorb particular molecules, while the tight junctions, present in the gaps between the specialised epithelial cells, only permit the diffusion of molecules of a particular size and electrical charge.

A small defect in the intestinal lining, such as caused by stress, can initiate a catastrophic chain of events. First, the increased permeability of the intestinal mucosa permits the passage of large, foreign and excessive dietary antigens, as well as pathogens. These dietary antigens and pathogens may cause the MALT to initiate a pro-inflammatory response. In turn, this pro-inflammatory response relaxes the tight junctions, rendering them more permeable to pathogens and dietary antigens. Thus a vicious cycle is established, where increases in intestinal permeability elevates intestinal inflammation, and intestinal inflammation elevates intestinal permeability.

While this is happening, it is believed that the elevated exposure to dietary antigens to which tolerance has been developed may result in an overabundance of IgG-antigen complexes, as the IgG-secreting B cells work to respond to these commonly consumed antigens. This overabundance may overwhelm the ability of the reticuloendothelial system to clear them, ultimately resulting in their passage to the systemic circulation. Once in the systemic circulation, it is believed that they may deposit in various organs, eliciting a type III hypersensitivity reaction.

Thus, re-estabishing the integrity of the intestinal mucosa may be essential to halting and reversing the development of elevated IgG-antigen complexes. This can be achieved in four ways:

1. Reducing exposure to commonly consumed dietary antigens;
2. Supporting digestion and intestinal immunity;
3. Reducing exposure to foreign dietary antigens and pathogens; and
4. Reducing intestinal inflammation and supporting the normal health and function of the mucosal barrier.

The management of elevated IgG-dietary antigen complexes

Saccharomyces boulardii improves intestinal permeability

Investigating the influence of Saccharomyces boulardii on intestinal permeability, 34 patients with Crohn’s disease in remission were given either 400 million CFUs of Saccharomyces boulardii or placebo. Over three months, the Saccharomyces boulardii group experienced a significant improvement in intestinal permeability compared to placebo as measured by the urinary lactulose/mannitol ratio.

Reduce exposure to dietary antigens

Regular consumption of dietary antigens generates dietary antigen-specific IgG-secreting B cells. Thus, when the integrity of the mucosal barrier is impaired, increases in the exposure of the MALT to these known dietary antigens may stimulate an upregulation of the IgG response. This upregulation may result in the formation of elevated IgG-antigen complexes, as the reticuloendothelial system struggles to clear the extra IgG-antigen complexes. Thus, minimising the extent to which such antigens penetrate into the MALT is of critical importance.

The simplest manner in which to avoid overstimulating the immune cells of the MALT and to avoid producing elevated IgG-antigen complexes is to reduce exposure to dietary antigens.
complexes, is to avoid consuming dietary antigens that are known to have active IgG antibodies. Thus, any food that a serum IgG test determines to have high levels of IgG antibodies is best to be avoided until it is believed that the dysfunction in intestinal permeability is resolved. It is essential, however, to consider the possible nutritional deficiencies that such an exclusion diet might bring about, and to design the diet to mitigate any such deficiency.

At the same time, the MALT naturally produces an antibody, termed secretory IgA, that functions in part to bind to and remove dietary antigens within the intestinal lumen, thus preventing their passage to the mucosal surface. Several studies have found that Saccharomyces boulardii appears to elevate secretory IgA secretion; further, a study of 398 children aged one to five years, a daily dose of 10 billion CFUs of Lactobacillus rhamnosus HN001 for three months was found to significantly raise secretory IgA levels compared to controls. Finally, Glutamine is understood to elevate secretory IgA production, however its mechanism is unknown.

Support digestion and intestinal immunity
Elevated intestinal permeability may also permit partially digested food components and pathogens through to the MALT where, being foreign, they may incite additional inflammation. Thus, supporting adequate digestion and intestinal immunity is essential. Saccharomyces boulardii has been shown to increase the activity of the brush border enzymes lactase, α-glucosidase, and intestinal alkaline phosphatase; as well as interfere with the colonisation of pathogens which would otherwise destabilise the function of the mucosal barrier through their production of noxious stimuli.

Reduce intestinal inflammation
Intestinal permeability and intestinal inflammation exist in a balance. Reducing intestinal inflammation may halt the relaxation of tight junctions, allowing the intestinal mucosa to regenerate. A range of nutrients may be of assistance.

Slippery elm, a demulcent and emollient, provides soothing protection to the mucous membranes of the intestinal tract. Specifically, it is the inner bark of mature Slippery elm, rich in mucilage, which is used to coat the intestinal mucosa and decrease inflammation.

Flavonoids such as Quercetin and Bromelain possess anti-inflammatory properties. A range of mechanisms have been attributed to these flavonoids, largely involving interactions with cells and pathways associated with inflammation and immunity, including some of the body’s common responses to inflammation. Like flavonoids, Saccharomyces boulardii possesses a range of anti-inflammatory activities, including decreasing pro-inflammatory cytokines and modulating T cell behaviour. In addition, antioxidant vitamins and dietary lipids such as Vitamins A and D and omega-3 fatty acids play an important role in the regulation of the intestinal immune system. Vitamins C and E, along with Selenium and Zinc, are able to influence various aspects of innate immunity by reversing the Th2 cell-mediated immune response to pro-inflammatory Th1 cytokines and by supporting immune cell function. They also mediate the production of pro-inflammatory cytokines and prostaglandins.

Support the normal health and function of the mucosal barrier
While the factors that undermine the integrity of the mucosal barrier are avoided and the intestinal inflammation is dampened, therapy should concentrate on providing ingredients that help the mucosal barrier return to its normal state.

Butyrate is a short chain fatty acid normally produced from the metabolism of various carbohydrates. This important fatty acid both supports the normal growth of intestinal cells, as well as supports the production of tight junction proteins. In a study of patients on total enteral nutrition, 500mg Saccharomyces boulardii for six days was found to significantly elevate faecal butyrate concentrations compared to fifteen healthy controls. Also supporting the integrity of tight junctions, flavonoids such as Quercetin appear to have a beneficial effect on tight junction proteins.

Finally, the non-essential amino acid Glutamine is needed for the synthesis of proteins, neurotransmitters, glycoproteins and glycans. A significant body of evidence indicates that Glutamine preserves the integrity of the intestinal mucosa and prevents its permeability to toxins and pathogens, restricting their movement from the gut lumen into the mucosal tissue and then into the circulation. Recent studies have demonstrated that Glutamine exerts protective effects on the gut mucosa by preserving epithelial tight junction integrity, enhancing microcirculation in the colon wall, improving barrier function of the colon lining, preventing nutrient and water loss and inhibiting the migration of endotoxins. Additionally, Glutamine maintains the structural integrity of the intestinal lining, supporting its quick turnover.

References available upon request
Bacteria adhere to Sb; Sb decreases invasion and preserves tight junctions and therefore the function of the mucosal barrier.

Modulation of intestinal flora increases short chain fatty acid function (butyrate).

Sb increases IgA levels which supports immune defenses.

Regulates inflammatory cytokines:
- COX-2
- TNF-α
- IL-2
- IL-6
- IL-8
- IL-12
- IL-1β

Sb improves intestinal permeability.

Figure 1: Managing elevated IgG-antigen complexes with Saccharomyces boulardii