



IgG-food allergies and the treatment of depression

Depression is a widespread disease, affecting 350 million people worldwide according to recent WHO data¹. Statistics from 2015 showed, that about 3% of the world's population is affected by severe depressive disorders².

Various factors seem to increase the risk and neuroprogression of depressions, such as psychosocial stress, poor diet, physical inactivity, overweight, smoking, altered intestinal permeability, sleep, vitamin D deficiency. Most of these factors are plastic, and can therefore be modified by therapeutic and preventive measures. They also play a role in other psychiatric disorders such as bipolar disorders, schizophrenia, autism and post-traumatic stress disorders³⁻⁵. But also a lack of neurotransmitters, especially 5-hydroxytryptamine (5-HT), is causally involved in depression⁶. Increased inflammation and immunity markers, oxidative and nitrosative stress are characteristic for depressive patients^{5,7}. At least 30% of patients have increased CRP concentrations^{8,9}. Other proinflammatory

cytokines, such as the tumour necrosis factor- α (TNF- α) are also higher in patients with depression¹⁰. Diseases associated with chronic inflammation, such as cardiovascular disease, inflammatory bowel disease or rheumatoid diseases, are accompanied by an increased risk of comorbid severe depression¹¹. Systemic inflammation and depressive symptoms can be triggered by food. Proteins or protein-derived compounds that occur in food may modulate the immune response of the body.

A recent publication by the International Society of Nutrition and Psychiatry in the journal "Lancet Psychiatry" suggests that nutrition is as important in psychiatry as it is in cardiology, endocrinology and gastroenterology¹²:

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- » Epidemiological studies have shown the link between healthy eating habits and a reduced prevalence or risk of depression^{13,14} and suicides¹⁵.
- » Dietary habits modulate the function of the immune system, thereby reducing the risk of depression⁴.
- » In children and adolescents, a link between an unhealthy diet and poor mental health was demonstrated¹⁶.
- » Within the European PREDIMED study, a strong trend was demonstrated towards a reduced incidence of depression in subjects following a Mediterranean diet enriched with nuts. This protective effect was particularly observed in patients with type 2 diabetes¹⁷.

The immune system takes food proteins or derived compounds as immunogens that generate food specific IgG antibodies, which are combined with food particles and then induce inflammatory responses, presented as symptoms or diseases. Continuous and repeated consumption of the same foods that trigger IgG-mediated hypersensitivity reactions may thus promote and maintain silent inflammations, being a cause for the development of numerous diseases.

In recent years, an increasing amount of evidence showed links between depression, inflammation and leaky gut syndrome¹⁸⁻²¹. The gliadin-mediated overproduction of zonulin causes a loosening of the tight junction connections in the intestinal epithelium, which is accompanied by an increased permeability of the intestinal wall (leaky gut). This allows larger molecules, which are normally retained in the intestine, to enter the bloodstream and induce IgG-mediated food intolerances. The resulting immune response associated with the release of pro-inflammatory cytokines can lead to the development of depressive symptoms^{19,22}. This new paradigm for the pathogenesis of depressive disorders combines IgG-dependent food sensitivity, systemic inflammatory processes and leaky gut. It is in agreement with the success

that many therapists worldwide observed, when IgG reactive food was eliminated. However, more in-depth studies are still required to confirm this hypothesis.

As mentioned before, depression can be a comorbidity of other inflammatory diseases, such as inflammatory bowel disease. The aim of a recent study was to compare levels of serum IgG against 39 selected food antigens between three groups of participants: patients with major depressive disorder (MDD group; 22 patients), patients with irritable bowel syndrome (IBS group; 22 patients) and healthy controls (HC group; 21 healthy volunteers)¹⁹. IgG food hyperreactivity was assumed if the average IgG concentration was above 7.5 µg/ml. The following values were determined for the 3 groups:

- » **MDD group:** 64% of patients had average IgG titre above 7.5 µg/ml
- » **IBS group:** 46% of patients had an average IgG titre above 7.5 µg/ml
- » **HC group:** 19% of patients had an average IgG titre above 7.5 µg/ml

Gluten intolerances were significantly higher in depressed patients than in patients with IBS. The results suggest that food-specific IgG-mediated intolerance of food or food proteins may be an important mechanism leading to immune activation and chronic inflammation, characteristic of severe depression.

In another study with 184 adolescent patients who experienced their first episode of depressive disorder, it was investigated whether there was a link between IgG-specific hypersensitivity to 14 foods, total IgE and different inflammation markers such as C-reactive protein (hs-CRP), food-specific IgG antibodies (14 foods), tumour necrosis factor- α (TNF- α), diamine oxidase, histamine, homocysteine and S100 calcium-binding protein B

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(which is expressed mainly in the astrocytes of the CNS and is regarded as a biomarker for a leaking blood-brain barrier). The results showed that depressed adolescents had far more pronounced IgG-mediated food intolerances than healthy adolescents. At the same time, a substantially higher histamine concentration in the blood was also observed in the depressed young people, histamine is one of the few central nervous system neurotransmitters found to cause consistent blood-brain barrier opening²³. In this way, proinflammatory cytokines reach the brain and contribute to inflammatory dysbalance and the emergence of depressive symptoms.

The comparison of the laboratory values between diseased and healthy adolescents revealed the following findings:

- » Significantly higher prevalence of food-specific IgG antibodies in depressed (165 of 184 patients) compared to healthy adolescents (24 of 184 subjects)
- » Slightly increased prevalence of IgE antibodies (total IgE) in depressed (66 of 184 patients) compared to healthy adolescents (42 of 184 subjects)
- » Significantly higher histamine level in depressed adolescents (average: 12.35 ng/ml) compared to healthy patients (average: 9.73 ng/ml)
- » Significantly higher homocysteine levels in depressed adolescents (average: 24 µM) compared to healthy patients (average: 9.55 µM)
- » Higher S100 levels in depressed adolescents (average: 902 ng/l) compared to healthy patients (average: 725 ng/l)
- » No differences in serum values from hs-CRP or TNF-α

The authors believe that the concept of IgG-mediated food hypersensitivity plays a more important role in depression than chronic inflammatory processes. Therefore IgG-positive food as well as histamine-food should be avoided²⁴.

References

1. Marcus, M., Yasamy, M. T., van Ommeren, M. & Chisholm, D. Depression, a global public health concern. WHO Dep. Ment. Heal. Subst. Abus. 1–8 (2012).
2. Vos, T. et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. (2016).
3. Sforzini, L., Nettis, M. A., Mondelli, V. & Pariante, C. M. Inflammation in cancer and depression: a starring role for the kynurenine pathway. *Psychopharmacology (Berl)*. (2019).
4. Berk, M. et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med*. 11, 200 (2013).
5. Moylan, S. et al. Oxidative & nitrosative stress in depression: Why so much stress? *Neurosci. Biobehav. Rev*. 45, 46–62 (2014).
6. Yohn, C. N., Gergues, M. M. & Samuels, B. A. The role of 5-HT receptors in depression. *Mol. Brain* 10, 28 (2017).
7. Maes, M. Evidence for an immune response in major depression: a review and hypothesis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 19, 11–38 (1995).
8. Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H. & Kivimäki, M. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain. Behav. Immun*. 49, 206–15 (2015).
9. Howren, M. B., Lamkin, D. M. & Suls, J. Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. *Psychosom. Med*. 71, 171–186 (2009).
10. Dowlati, Y. et al. A Meta-Analysis of Cytokines in Major Depression. *Biol. Psychiatry* 67, 446–457 (2010).
11. Barton, G. M. A calculated response: control of inflammation by the innate immune system. *J. Clin. Invest*. 118, 413–20 (2008).

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12. Sarris, J. et al. Nutritional medicine as mainstream in psychiatry. *Lancet Psychiatry* 0366, 1–4 (2015).
13. Lai, J. et al. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *Am. J. Clin. Nutr.* 99, 181–197 (2014).
14. Psaltopoulou, T. et al. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Ann. Neurol.* 74, 580–91 (2013).
15. Nanri, A. et al. Dietary patterns and suicide in Japanese adults: the Japan Public Health Center-based Prospective Study. *Br. J. Psychiatry* 203, 422–7 (2013).
16. O'Neil, A. et al. Relationship Between Diet and Mental Health in Children and Adolescents: A Systematic Review. *Am. J. Public Health* 104, e31–e42 (2014).
17. Sánchez-Villegas, A. et al. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. *BMC Med.* 11, 208 (2013).
18. Karakula-Juchnowicz, H. et al. The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders. *Nutr. Neurosci.* 20, 110–118 (2017).
19. Karakula-Juchnowicz, H. et al. The food-specific serum IgG reactivity in major depressive disorder patients, irritable bowel syndrome patients and healthy controls. *Nutrients* 10, 548 (2018).
20. Karakula, H. et al. Psychobiotics : new possibilities for treatment of affective disorders? (2016). doi:10.17393/fpn.2016.01.005
21. Kelly, J. R. et al. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front. Cell. Neurosci.* 9, 392 (2015).
22. Karakula-Juchnowicz, H., Szachta, P. & Opolska, A. The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders. *Nutr. Neurosci.* 0, 1–9 (2015).
23. Abbott, N. J. Inflammatory mediators and modulation of blood-brain barrier permeability. *Cell. Mol. Neurobiol.* 20, 131–47 (2000).
24. Tao, R., Fu, Z. & Xiao, L. Chronic Food Antigen-specific IgG-mediated Hypersensitivity Reaction as A Risk Factor for Adolescent Depressive Disorder. *Genomics. Proteomics Bioinformatics* 17, 183–189 (2019).

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